Forgó / Kollek / Arning / Kruegel / Petersen

Ethical and Legal Requirements for Transnational Genetic Research

C. H. Beck · Hart · Nomos

Forgó/Kollek/Arning/Kruegel/Petersen
Ethical and Legal Requirements for Transnational Genetic Research

Ethical and Legal Requirements for Transnational Genetic Research

by

**Dr Nikolaus Forgó, Professor of Law,
University of Hanover**

**Dr Regine Kollek, Professor for Technology Assessment,
University of Hamburg**

**Dr Marian Arning, Senior Reseachr Fellow,
University of Hanover**

**Dr Tina Kruegel, Senior Research Fellow,
University of Hanover**

**Dr Imme Petersen, Senior Research Fellow,
University of Hamburg**

Verlag C. H. Beck München 2010

Published by
Verlag C. H. Beck oHG, Wilhelmstraße 9, 80801 München, Germany,
eMail: bestellung@beck.de

Co-published by
Hart Publishing, 16C Worcester Place, Oxford, OXI 2JW, United Kingdom,
online at: www.hartpub.co.uk

Published in North America (US and Canada) by Hart Publishing, c/o International Specialized Book Services, 930 NE 58th Avenue, Suite 300, Portland, OR 97213-3786, USA, eMail: orders@isbs.com

ISBN 978-3-406-61011-0 (Beck)
ISBN 978-1-84946-128-3 (Hart Publishing)

Printed in Germany by
fgb · freiburger graphische betriebe
Bebelstr. 11, 79108 Freiburg

Typeset by Reemers Publishing Services GmbH, Krefeld

Contents

List of abbreviations IX

1. Introduction 1

1.1. From clinical to clinico-genomic research: New ethical and legal challenges 1
1.2. The ACGT project: Developing an ICT infrastructure 3
1.3. Aim and structure of the book 4

2. Ethical requirements 7

2.1. Introduction 7
2.2. Informed consent 8
2.2.1. Ethical foundations of the doctrine of informed consent 8
2.2.1.1. Historical background 9
2.2.1.2. General aspects 10
2.2.1.3. Informed consent in tissue-based research 10
2.2.2. The scope of consent 12
2.2.2.1. Models of consent 12
2.2.2.1.1. Specified consent 13
2.2.2.1.2. Broad or blanket consent for future research 14
2.2.2.1.3. Tiered consent models 17
2.2.2.1.4. Patients' and donors' perspectives 18
2.2.2.1.5. Particularities of consent to research involving children 21
2.2.2.2. Informed consent and communication 25
2.2.2.2.1. The character of information 27
2.2.2.3. Issues to be consented to 29
2.2.2.3.1. General requirements 30
2.2.2.3.2. Sharing data and information 30
2.2.2.3.3. Re-contact 31
2.2.2.3.4. Commercial interests 31
2.2.2.3.5. The timeframe of consent 32
2.2.2.4. The right to withdraw consent 32
2.3. The right to know, the duty to inform, and the quality of feedback 33
2.3.1. Access to personal information: a donor driven inquiry process 34
2.3.2. Feedback of research results: an investigator driven disclosure process 35
2.3.2.1. Informing about general research results 36
2.3.2.1.1. Ethical foundations 36
2.3.2.1.2. Practical challenges of feedback processes regarding general research results 37
2.3.2.2. Information about individually relevant research results 38
2.3.2.2.1. Ethical foundations 39
2.3.2.2.2. What to feed back? 40
2.3.2.2.3. Characteristics of genetic research results in the context of cancer trials 44
2.3.2.2.4. To whom to feed back? 47
2.3.2.2.5. Practical challenges of feedback processes regarding individual research results 50
2.4. Summary of consolidated ethical requirements 55
2.4.1. Ethical requirements 56
2.4.1.1. Summary: The informed consent process 56

2.4.1.2. Conclusions: How to design the informed consent process ... 58
2.4.1.3. Summary: Donor driven inquiry processes and investigator driven individual feedback processes ... 60
2.4.1.4. Conclusion: How to organize donor driven inquiry processes and investigator driven individual feedback processes ... 63
2.5. Outlook: Ethical challenges in the european context ... 64
2.5.1.1. Revision of data protection and information flows ... 64
2.5.1.2. Community interests ... 65

3. Legal requirements ... 67

3.1. Introduction ... 67
3.2. Theoretical analysis ... 67
3.2.1. European Data Protection Directive 95/46/EC ... 67
3.2.1.1. Genesis ... 67
3.2.1.2. Scope of the Directive ... 68
3.2.1.2.1. Personal data ... 68
3.2.1.2.1.1. Anonymous data ... 69
3.2.1.2.1.2. Pseudonymous data ... 70
3.2.1.2.2. Territorial application ... 70
3.2.1.3. Fair and lawful data processing ... 70
3.2.1.3.1. General ... 70
3.2.1.3.1.1. Requirement of a legal basis ... 70
3.2.1.3.1.2. Technical and organisational measures ... 71
3.2.1.3.2. Sensitive data ... 72
3.2.1.3.2.1. Definition ... 72
3.2.1.3.2.2. Prohibition of data processing ... 73
3.2.1.3.2.3. Exceptions ... 73
3.2.1.4. Duties of the data controller ... 74
3.2.1.5. Rights of the data subject ... 75
3.2.1.5.1. Information duties regarding data collection from the data subject ... 75
3.2.1.5.2. Information duties regarding data which has not been obtained from the data subject ... 76
3.2.1.5.3 Right of access ... 77
3.2.1.5.4. Right to rectification, erasure or blocking ... 78
3.2.1.5.5. Exemptions and restrictions ... 79
3.2.1.5.6. Right to object ... 79
3.2.1.6. Transfer of personal data to third countries ... 80
3.3 Data protection within a trans-european research project – using the example of ACGT ... 82
3.3.1. Data flows ... 82
3.3.2. Legitimate processing of genetic data (Directive 95/46 EC) ... 84
3.3.2.1. Genetic data ... 84
3.3.2.1.1. Special characteristics of genetic data with regard to data protection ... 85
3.3.2.1.2. Anonymisation of genetic data ... 90
3.3.2.2. Relevance of the character of data processing for the distinction between personal data and anonymous data ... 95
3.4. Data protection framework within genetic research networks ... 101
3.4.1. Anonymisation of genetic data within research networks ... 102
3.4.2. Necessary legal agreements, contracts and informed consents ... 103
3.4.2.1. Contract between the Data Protection Authority and the data exporter (e.g. a hospital) ... 105
3.4.2.1.1. Guarantee of a "state-of- the-art" pseudonymisation ... 105
3.4.2.1.2. Technically and organisationally separated project database ... 105
3.4.2.2. Contract between Data Protection Authority and end users ... 106
3.4.2.2.1. Data controllers within genetic research networks ... 106

3.4.2.2.2. Data Protection Authority as central Data Protection Authority within the research network ... 108
3.4.2.2.3. Ensuring the context of anonymity ... 110
3.4.2.2.4. Separated database ... 111
3.4.2.2.5. No matching ... 111
3.4.2.3. Second pillar and first fallback scenario: Informed Consent ... 112
3.4.2.3.1. Regulatory framework ... 113
3.4.2.3.1.1. Definition ... 113
3.4.2.3.1.2. Declaration of intention ... 113
3.4.2.3.1.3. Freely given ... 113
3.4.2.3.1.4. For a specific case ... 113
3.4.2.3.1.5. Informed indication ... 114
3.4.2.3.2. Scope of the consent ... 114
3.4.2.3.2.1. Object of the consent/purpose specification/future research ... 114
3.4.2.3.2.2. Expected period of usage/temporal scope of the consent ... 115
3.4.2.3.2.3. Death of the patient ... 116
3.4.2.3.2.4. Data transfer to third parties/third countries ... 117
3.4.2.3.3. Consent of relatives needed? ... 117
3.4.2.3.3.1. Additional information of relatives is collected ... 117
3.4.2.3.3.2. No additional information of relatives is collected ... 118
3.4.2.3.4. Consent of the minor data subject or person with intellectual disabilities needed? ... 118
3.4.2.3.5. The right to withdraw and right to erasure ... 119
3.4.2.4. The right to know and the duty of notification ... 120
3.4.2.5. Third Pillar and second fallback scenario: Exceptions for genetic research in national legislations ... 122

4. Legal conclusion ... 125

5. References ... 127

6. Appendix 1– legal terminology ... 137

7. Appendix 2 – relevant regulation ... 141

List of abbreviations

AAP	American Academy of Paediatrics (USA)
ACGT	Advancing Clinico-Genomic Trials on Cancer
Art.	Article
ASCO	American Society of Clinical Oncology (USA)
AuthN	Authentication
AuthZ	Authorization
BDSG	(Deutsches) Bundesdatenschutzgesetz (Federal Data Protection Act of Germany)
BMB	(Deutsches) Bundesministerium für Bildung (German Ministry for Education)
BRCA1/BRCA2	Breast Cancer 1/Breast Cancer 2
BVerfG	(Deutsches) Bundesverfassungsgericht (German Federal Constitutional Court)
CAT	De facto anonymisation tool
CDP	Centre for Data Protection
cf.	confer/compare
CIOMS	Council for International Organisations of Medical Sciences (international)
CoE	Council of Europe
CR	Computer und Recht (German Law Journal: Computer and Law)
DHHS	Department of Health and Human Services (USA)
Dir.	Directive
DNA	Deoxyribonucleic Acid
DPA	Data Protection Authority
DSG	(Österreichisches) Datenschutzgesetz (Austrian Federal Act Concerning the Protection of Personal Data)
DuD	Datenschutz und Datensicherheit (German Law Journal: Data Protection and Data Security)
EC	European Community
ECJ	European Court of Justice
ed(s).	editor(s)
EEA	European Economic Area
e.g.	exempli gratia/for example
EPOF	European Privacy Officers Forum
EU	European Union
ff.	following pages
GCCR	German Childhood Cancer Registry
GEMSS	Grid-Enabled Medical Simulation Services
GMC	General Medical Council (UK)
HIV	Human Immunodeficiency Virus
HUGO	Human Genome Organization (international)
ibid.	ibidem
IC	Informed Consent

ICT	Information and Communication Technology
IT	Information Technology
lit.	litera/letter
MMR	Multimedia und Recht (German Law Journal: Multimedia and Law)
MPG	(Österreichisches) Medizinproduktegesetz (Austrian Medical Drugs Act)
MRC	Medical Research Council (UK)
MRI	Magnetic Resonance Tomography
MS	Member States of the European Union
NBAC	National Bioethics Advisory Commission (USA)
no.	number
OECD	Organisation for Economic Co-operation and Development
p./pp.	page/pages
para.	paragraph
PET	Positron Emission Tomography
RdM	Recht der Medizin (Austrian Law Journal: Medical Law)
SOA	Service Oriented Architecture
StGB	(Deutsches) Strafgesetzbuch (German Criminal Code)
TTP	Trusted Third Party
UNESCO	United Nations Educational, Scientific and Cultural Organization (international)
WHO	World Health Organization (international)
WMA	World Medical Association (international)
WS	Web Services

1. Introduction

1.1. From clinical to clinico-genomic research: New ethical and legal challenges

With the advancement of molecular technologies, cancer research has made 1
enormous progress over the last decade. Recent methodological and technological achievements have resulted in an explosion of information and knowledge about malignant diseases and their development. In order to not only understand and characterize such diseases better, but also to develop more efficient treatments, it has been postulated that a more individualized approach would be suitable, which takes into account more closely not only the clinical and biochemical markers of a patient, but also his or her genetic outfit and the pattern of the genes expressed in their tumours. This has lead to the design of a new type of clinical study: the clinico-genomic trial. In the context of such trials, molecular genetic data, e.g. germ line and gene expression patterns are collected in addition to clinical data. For this reason, biopsy samples taken from the tumour – and often also bloods samples – are subjected to gene-expression and protein analyses. Furthermore, new ways of scanning cancers and making them visible by imaging technologies, such as MRI and PET, are applied to improve the early detection of tumours and metastasis. The ultimate goal of the new strategy of a more individualized diagnosis and treatment is to include not only clinical information relating to tissues, organs or personal health into clinical decision making, but also information at the level of molecules and cells that is produced by genomics and proteomics research. The combination of these data derived from – what is also called post-genomic – research should enable doctors to classify patients into different groups according to their individual characteristics and choose the most appropriate treatment for them.

To facilitate clinico-genomic research, the collection, integration and exploitation 2
of data and information generated at different levels are required. On the one hand, this applies to the human body, starting from the molecular and biochemical level, via the cellular level to organ and whole body level. On the other hand, a large number of individuals needs to be diagnosed in order to find out small but significant effects of single genes or other factors that have an impact on the development and progress of cancer. Hence, data on larger populations are needed. One possible solution to this requirement is to link different databases together and share data collected in the context of different trials. Therefore, the ubiquitous access to data sources in an integrating and high-performing environment is necessary to enhance such cross-organizational data sharing.

However, up to now, the lack of a common infrastructure has prevented clinical 3
research institutions from being able to mine and analyze disparate data sources. As a result, very few cross-site studies and clinical trials are performed and in most cases it isn't possible to seamlessly integrate multi-level data. Moreover, clinicians or molecular biologists often find it difficult to exploit each other's expertise due to the absence of a cooperative environment that enables the sharing of data, resources

or tools for comparing results and experiments, and a uniform platform supporting the seamless integration and analysis of disease-related data at all levels.

4 Clinico-genomic research produces therefore new challenges from different angles. Medically, data of different levels have to be analyzed by using different techniques ranging from molecular analysis to diagnosis acquired of clinical parameters. Technically, these data have to be stored in a way that makes them accessible for different methods to integrate heterogeneous data sources, to select data, and to incorporate collaborative approaches to data analysis. However, technical safety, accessibility and integration are only the first of many challenges posed by clinico-genomic trials. From the ethical and legal perspectives, protection of personal rights, and especially data protection, has to be guaranteed at any time of research. However, common standards for collecting, storing, processing, and using clinico-genomic data are still missing. The last aspect is even more important, because biomaterials are extracted, stored and examined. Such biomaterials are, on the one hand, valuable resources for biomedical research. On the other hand, they are part of the donor's body. At least as long as such samples can be traced back to the donor, they are carriers of sensitive information and therefore are protected by personality rights in general.

5 Genetic data of a human being provides information not only about the person herself – such as genetic dispositions to diseases and response to treatments – but also about her family, parentage and eventually ethnic descent, just to mention some possibilities of use. The DNA can be procured easily (even without the affected person's knowledge), for example, of a lost hair or a cell of the oral mucosa in the toothbrush, and can be pulled up for the answer of any genetic question. Genetic data provides information about relatives of the data subject and therefore can have significant effect on the family over several generations and in certain cases on the whole group to which the data subject belongs.[1] As genetic information is unique and distinguishes the data subject from other individuals, concerns grow that genetic information could become a modern tool of discrimination. People worry that gene tests and genetic profiling could be used to put them on genetic risk for certain diseases or conditions and, as a consequence, to disqualify them from getting jobs and health insurance.[2] Therefore, ethics committees and data protection legislation on the international and European level and, in many cases, by national law, have created strict regulations for the processing of this sensitive data.

6 As will be shown in the following chapters in more detail, clinico-genomic research principally challenges established rules for research and clinical data protection. Hence legal and ethical requirements tailored to clinico-genomic research are necessary. Scientists are principally interested in unrestricted storage periods of genetic data, because they want to use them for future research projects, whose purposes are not – and can not be – known at the time of data collection and storage. In order to be in accordance with data protection legislation, the confidentiality of stored and processed genetic data has to be ensured in a sustainable and long-term way. To use a person's data and tissue in research, her informed consent is required. This requirement is considered to be a doctrine in the pursuit of

[1] Data Protection Working Party 2004

[2] See for example, Wellbrock 2003, 77; Lemke 2004, 2006; Nationaler Ethikrat 2005, 2007; Kollek and Lemke 2008, 191 ff; Stockter 2008

ethically responsible research. According to this doctrine, persons concerned have to be adequately informed about the purposes and consequences of research. The reason for this is that research in genetic data can achieve results that can change the view on information duties and/or information rights of the patient considerably. Since data could be – in certain cases – potentially important not only for the individual but also for groups of individuals sharing genetic features (e.g. family members or ethnic groups), the issue of who is the data subject and who needs to be informed about research outcomes arises, as well as the question of whether and which research results need to be returned to patients and their relatives.

Such fundamental problems of data protection, informed consent, and feedback 7
of data have to be addressed in order to ensure protection of personal rights of data subjects and tissue donors and compliance with data protection legislation within an environment for clinico-genomic research, which is shaped by and dependent upon information and communication technologies (ICT).

1.2. The ACGT project: Developing an ICT infrastructure

The research project "Advancing Clinico-Genomic Trials on cancer: Open Grid 8
Services for improving Medical Knowledge Discovery" (in short: ACGT),[3] aims to deliver to the cancer research community an integrated clinico-genomic information and communication technology (ICT) environment enabled by a powerful Grid infrastructure.[4] ACGT's vision is to become a pan-European voluntary network or Grid connecting individuals and institutions, to enable the sharing of data and tools.

To create the ICT infrastructure, ACGT focuses on the following considerations: 9
(1) how to design experiments for obtaining coherent and consistent medical and biological data, while avoiding various types of biases and errors; (2) how to develop methods for heterogeneous (e.g. genomic, medical) data source integration, including the use of ontologies that facilitate mapping and information retrieval; (3) how to develop methods for data selection, checking, cleaning, and pre-processing of combined genomic/medical data, and (4) how to incorporate collaborative approaches to data analysis, since biomedical statisticians and data miners in genomics and medicine have been following different methodologies, and dedicated, often proprietary, tools.

The ICT infrastructure will be validated in concrete settings of advanced clinical 10
trials on cancer, raising the need to integrate multiple data from the patients (mainly clinical, biological, and genomic data). Hence, pilot trials have been selected. At the moment two clinical trials targeting two major cancer diseases, namely breast cancer and paediatric nephroblastoma, use the ACGT platform. The breast cancer trials running at Jules Bordet Institute (Belgium), University of Crete

[3] The ACGT project is funded in the 6th Framework Program of the European Commission under the Action Line "Integrated biomedical information for better health". The ACGT research consortium consists of 25 cancer hospitals and institutions located in different European countries and working in a variety of disciplines, mainly medical- and bio-informatics, molecular biology, medicine, law, and ethics (www.eu-acgt.org).

[4] A Grid-infrastructure is a collection of severs and communication protocols that allow highly complex and compute-intensive tasks to be shared by the computers in the Grid in a safe and efficient manner.

(Greece), and University of Oxford aim to identify biological markers associated with pathological complete response to anthracycline therapy (epirubicin), one of the most active drugs used in breast cancer treatment. To identify these predictive markers, the trial mainly uses gene-expression profiling based on microarrays, as well as on genotyping technology. The nephroblastoma trial running at the University of the Saarland (Germany) is a randomized trial to evaluate the necessity of anthracyclines (doxorubicin, a cytostatic drug with the potential risk of heart disease as a side effect) in the treatment of unilateral non-metastasized kidney cancer. Patients enrolled in the trial – usually children aged from a few months up to ten years – will receive preoperative chemotherapy followed by surgery of the tumour. Nephroblastoma is one of the success stories in cancer, where clinical trials did help to reverse prognosis during the last decades.

11 Generally speaking, the objective of ACGT is to obtain a better understanding of the optimal adjuvant therapy for the individual patient through translational research. In the area of adjuvant systemic therapy for cancer the three most important tasks can be defined as follows: 1) assessment of risk for metastasis (prognosis); 2) assignment of differential risk to different groups of patients (patient stratification); and 3) selection of treatment for the individual patient (individualized therapy).

12 The large-scale collection and comparison of body materials and the data derived from them make it possible to establish correlations that may in the long term yield a valuable diagnostic and therapeutic return. However, there is a risk that the data and samples could be used for purposes other than those to which the donor has consented or be passed on to third parties. One of the essential preconditions for establishing an integrated clinico-genomic ICT environment employing data extracted from human tissues therefore, is that all research done in this context involving human subjects conforms to existing legal and ethical requirements. However, there is no special European legislation governing Europe-wide research in genetic data. Existing national legislation has to be taken into account to ensure compliance of clinico-genomic research with all relevant legal and ethical provisions. But in-depth knowledge of existing EU-legislation is not sufficient. In addition, it is necessary to analyse clinico-genomic research from the ethical perspective in order to identify new ethical issues emerging in the context of such research. Finally, conclusions have to be drawn with respect to the design of an ICT environment that conforms to the ethical and legal requirements, which in turn have to take into account the features, goals and processes specific for transnational and future oriented clinico-genomic research, ■

1.3. Aim and structure of the book

13 In clinico-genomic research, vast amounts of all kinds of data need to be processed. Referring to this, it has been shown to be beneficial to share data and computer power, in order to improve therapies and meet the increasing demand for personalized health care. However, genetic data are of an extremely sensitive nature, giving information not only about the person herself but also about relatives who might not even be born yet. Insurance companies, employers or state prosecutors therefore may have an interest in using such data for their own purposes.

Several issues arise here according to different perspectives involved. From the 14
legal and ethical perspective, the right to privacy is a fundamental human right that has to be protected. From the scientific perspective, if patients suspect that the personal data they agreed to share for medical care and research may be used for other purposes, they will simply refuse to allow access, creating an obstacle for further research projects. From a medical perspective, simply anonymizing data and processing it without linkage to the patient is not possible, because often data of the same patient have to be fed into the database several times, making it necessary to re-identify data or data files respectively. Furthermore, patients have a legally and ethically guaranteed right to be informed, especially if the research done with their data leads to a result with a possible impact on their disease, or to withdraw their data and/or donated tissue sample.

In order to meet the posted challenges and problems, this book aims to analyze 15
the relevant ethical and legal requirements for setting up the ACGT infrastructure to maintain clinico-genomic research within the European Union. Full compliance with all legal and ethical regulations is the first goal of the ACGT infrastructure and is reflected in the whole ACGT architecture itself. Accordingly, ACGT devotes special efforts towards the elaboration of a legal and ethical framework. Scientists, physicians and patients will therefore be able to base their co-operation and work on an infrastructure respecting current ethical standards and delivering high data protection and security. The elaboration of clearly defined guidelines is the second goal of the ACGT infrastructure. Therefore, this elaborated legal and ethical framework designed for ACGT will be adaptable and usable by many other ICT infrastructures. *The aim of this book,* therefore, is to (1) analyze the basic ethical and legal requirements of clinico-genomic trials, and (2) to develop practicable solutions for ACGT that can be assigned to other ICT infrastructures for health space as well.

In *the first part of this book,* the ethical requirements for clinico-genomic trials 16
are examined. It consists of five chapters. After an introduction regarding the ethical challenges for processing sensitive personal information in extended ICT infrastructures (chapter 2.1), ethical debate dealing with the involvement of patients in clinical and tissue based research is analyzed in the chapter 2.2. First, we depict the ethical principle of autonomy, which is generally recognized as one of the most basic principles in research involving human subjects. Derived from autonomy, the doctrine of informed consent has been widely acknowledged. However, clinico-genomic research poses new questions, because data are collected and used not only for a specific research project, but also for future research that is not known or cannot be defined at the time consent is requested. Furthermore, research results may be obtained which could be important for individual patients or their family. Facing these new demands, doubts have been raised concerning the applicability of the doctrine of informed consent in its current form in tissue-based and/or genomic research. In the second part of chapter 2, we therefore present the different models of consent that are currently discussed. At the end of this chapter, we will propose a model of how to seek informed consent for clinico-genomic research, which is within the limits of ethical, as well as legal considerations.

In the third chapter of part I we will discuss whether and under what circum- 17
stances that data should or must be fed back to patients. It is widely acknowledged that general study findings must be accessible for patients involved. Furthermore,

anybody has the right to access personal data stored about him or her. But the right to access such data, which is based on ethical principle as well as on legal provision, is a passive one. Therefore, the implementation of this right requires an organisational structure that is suitable to reply to donors' requests. Additionally, we discuss whether and under what circumstances this infrastructure may create an ethical obligation to feed back information to patients that may be relevant for them. One of the preconditions to enable an investigator driven feedback process is to pseudonymize data. Therefore, the process of feeding back individually relevant data requires technical mechanisms to guarantee data retrieval by those donors who ask for an individual feedback. Nevertheless, it is controversially discussed what kind of data should be fed back, since the relevance of data is not easy to define.

18 The fourth chapter of part I sums up the discussed ethical challenges and requirements and formulates practical solutions with regard to the design, the informed consent for clinico-genomic research and the disclosure of research results. Given that transnational research collaborations – like ACGT – are desirable to facilitate the integration of vast amounts of heterogeneous data, the last chapter of part I raises the issue of data interchange in the European context. Herewith, upcoming challenges are in focus that may be relevant in further ethical considerations regarding data flowing from one Member state to another.

19 *The second part of the book* analyses the legal requirements to be fulfilled for lawfully establishing an integrated clinico-genomic ICT environment employing data extracted from human tissues. This part has four chapters. After a short introduction regarding the legal challenges for ICT infrastructures, the starting point of the analysis in the second chapter of part II is the European Data Protection Directive 95/46 EC, which introduces rules applicable to every processing of personal data and sensitive data on a European level. As every EU Member State has to implement the regulations of the Data Protection Directive into national law, for an EU-wide project like ACGT, this Directive is the common legal basis for all participating states. For this reason, the relevant sections of the Directive on Electronic Commerce 2000/31/EC are analysed in detail in the second chapter of part II.

20 From a legal point of view, it has to be stressed that genetic data are very sensitive data, which holds information not only about the current and future life of the data subject but also of his or her relatives. The processing of this kind of data is therefore only possible under special requirements, which are broadly discussed in chapter three of part II. The trust and security services are therefore a fundamental part of an ICT infrastructure for clinico-genomic research. Nevertheless, the infrastructure has to find a balance between the two opponents: modern genetic research and the data protection needs of the participating patients. The fourth chapter of part II presents therefore a practical solution of how to meet both requirements, by simultaneously complying with current data protection legislation.

2. Ethical requirements

2.1. Introduction

In order to assemble and to prove an ICT infrastructure for clinico-genomic research, several preconditions have to be fulfilled beyond technical requirements. The first part of the book will discuss which aspects and principles have to be considered to allow and advance ethically justifiable research using such an infrastructure. One of the most basic points is the involvement of patients. Like clinical research, clinico-genomic research is not possible without participating patients. A second important feature of such trials is that genomic data is needed in addition to socio-demographic and clinical data of these patients. 21

Ethical debate concerned with the involvement of patients in clinical trials has a long tradition. Among the principles that have been identified as being applicable to clinical research, it is generally accepted that autonomy is one of the most basic principles to be respected. Furthermore, it is also applicable to research involving data and biological material (cells, tissues, DNA) collected from patients. 22

Derived from the principle of autonomy, is the doctrine of informed consent. Even though this doctrine is globally recognized as of up most importance for clinical practice, as well as biomedical research, it is – from a historical point of view – a relatively new phenomenon. It was only in 1964 that the General Assembly of the World Medical Association adopted the Declaration of Helsinki strongly emphasizing the need to obtain informed consent in medical treatment and research. But even today, considerable lack of clarity still exists when it comes to the question of how the doctrine can or should be applied in different medical, social and cultural contexts. Clinico-genomic research challenges the content of an informed consent that the involved patient is asked to give. Here the question arises, whether consent can be given in advance to future, still unknown research projects. It is therefore intensively discussed whether informed consent can be given for future and undefined research projects and which ethical requirements it has to fulfil. Thereby, the scope of consent and different aspects of the consent process as such are analysed. In this analysis, emphasis is placed on the patients' and donors' perspective including particularities of research involving children. 23

In general, clinico-genomic research yields raw statistical data, which are – as long as they are not verified – of no or only limited use for the individuals taking part in the trials. However, occasionally or in certain cases, such research may also yield individually relevant research results. Hence, the question whether and under what circumstances which data should or must be fed back to patients concerned, has to be addressed in the context of ethical requirements for clinico-genomic research. At least in the European context it is indisputable that everyone has the right to make inquiries about personal data that have been collected about him or her. Due to legal provisions, investigators are obliged to disclose such data on request. This is especially applicable if a research process yields information that enhances treatment or helps to avoid harm. But it is debatable whether it is ethically 24

required to feed back to patients information on genetic polymorphisms and gene expression, whose clinical significance has not been fully established yet. Therefore, in focus is the question whether or not researchers should actively approach patients to return study findings that might be or become important for him or her – or even for the patients' relatives.

25 The approach chosen here is not one of normative, but of empirical ethics. The outcome of normative reasoning depends to a great extent on the ethical framework chosen. Since the research project ACGT, for which the ethical requirements will be discussed and exemplified, is a pluralistic research network, it cannot be presumed that all partners share the same moral preferences and refer to the same ethical frameworks. Hence, referring to selected frameworks only would be an undue predefinition of ethical positions. For this reason, we concentrate on reviewing and summarizing the current ethical literature pertinent to clinico-genomic research, biobank-research and related activities. The aim of such an approach is to identify current positions on the questions outlined above and to find out on which issues consensus is reached and where dissent remains.

2.2. Informed consent

26 The doctrine of informed consent is one of the most well known elements of medical ethics and bioethics today. In the core of the doctrine stands the principle that any preventive, diagnostic or therapeutic medical intervention, is only acceptable with the prior, free and informed consent of the person concerned, based on adequate information. Furthermore, consent should, where appropriate, be expressed and may be withdrawn by the person concerned at any time and for any reason without disadvantage or prejudice.[5]

27 Since medical treatment or research may pose risks to patients or human subjects, they have to be protected from unwanted and unwarranted interventions. Individual consent therefore is an indispensable prerequisite for medical care or biomedical research. It is an expression of respect for autonomy and self-determination. The importance given to this doctrine today is reflected by the fact that virtually all international agreements on ethical and legal standards in medicine and biomedical research endorse the requirement of consent or informed consent.[6]

2.2.1. Ethical foundations of the doctrine of informed consent

28 Today, the doctrine of informed consent has been widely accepted in both clinical practice and (bio-)medical research. However, this global recognition of informed consent as a condition sine qua non for regular and experimental medical interventions is a relatively new phenomenon. Historically, it is by no means self-evident that a patient or research subject has to be informed about such interventions and to be asked for consent.

[5] Hansson et al 2006, 267; a lucid summary of theoretical background for informed consent is given by Alderson and Goodey 1998. For a brief outline of the history of informed consent, see Williams 2001 or, limited to the US, Press and Browner 1995. For a recent overview see Kollek 2009.

[6] Examples of international instruments that list informed consent as one of the key principles of biomedical research are: World Medical Association (WMA) 1964; Council of Europe 1997, 2005; Council for International Organizations of Medical Sciences (CIOMS) 2002; UNESCO 1997, 2003, 2005.

2.2.1.1. Historical background

The history of informed consent is manifold, culturally diverse, and rather controversial and cannot be "reduced to linear narration of social events and practices"[7]. What seems to be clear, however, is that the concept of informed consent and its evolution is tightly connected to the physician-patient-relationship and the way it developed through the centuries. The history of informed consent reflects these changes. Furthermore, the idea that patients should be asked for consent before any medical intervention is also closely linked to a secular conception of medicine, which did not develop before the sixth or fifth century of our time in ancient Greece. 29

In parallel, the first explicit conception of medical ethics can be located. It has been traced back to Hippocrates, one of the founders of this new secular and empirically based medicine. According to this "Hippocratic oath" physicians were obliged to act for the benefit of their patients and to avoid harm. However, this did not entail the obligation to tell the truth to their patients. On the contrary, sometimes it was considered harmful to be to outspoken about their disease, its treatment and prognosis. The physicians regard themselves as knowing best what is good for the patients. In Western countries, such paternalistic conceptions of the doctor-patient-relationship prevailed until the second half of the 20th century. In contrast to paternalism, modern conceptions of the physician-patient-relationship are characterized by individualism and self-determination. The physician acknowledges that it is the patient who finally authorizes interventions into his or her body. In Western countries, this change is at least in part, the result of the social emancipation movement of the 1960s and 1970s, with its strong rejection of authoritarian structures in all dimensions of societal life.[8] In addition to the strengthening of informed consent for treatment and clinical research, the requirement of informed consent for the use of stored tissue and patient data became a subject of ethical debate in the 1980s. 30

Obtaining consent for necessary treatment in case of painful and/or progressing illness is but one part of the history of consent. The other, much more recent and controversial part of this history is related to systematic medical research involving healthy volunteers or patients. Such research became an important part of medical practice in the second half of the 19th century, when scientific and experimental methodology was introduced into clinical medicine and large hospitals were established. Often, research was done "in the service of science and medical progress," without consent of the patients. After it became known that some people suffered injury and harm from non-therapeutic interventions, the ethics of human experimentation became a public and political issue. The first detailed regulations about non-therapeutic research, which set forth the legal basis for disclosure and unmistakable consent, were issued in Germany in 1900.[9] 31

However, it was not before the horrific crimes of the Nazi doctors became known, and the publication of the Nuremberg Code in 1947, that the moral duty of physicians and researchers to obtain consent became more widely recognized. In 1964, the "Ethical Principles for Medical Research Involving Human Subjects" 32

[7] Faden and Beauchamp 1986
[8] Fox 1990
[9] Vollmann and Winau 1996

strongly emphasizing the need to obtain informed consent for medical treatment and research, became adopted by the General Assembly of the World Medical Association in Helsinki.[10] Today, the doctrine of informed consent has been widely accepted in both clinical practice and biomedical research.

2.2.1.2. General aspects

33 The doctrine of informed consent represents an essential ethical and legal requirement for medical interventions, which protects patients and their fundamental rights to integrity and self-determination. These rights are part of human rights that have been affirmed by the majority of the countries in the world (Conference on Human Rights, Vienna 1993). In ethical terms, the requirement for informed consent is based on the principles of 'respect for persons' and 'respect for human dignity'. They denote that a human being must not be used merely as a means to an end. Instead, one should not act against their wishes, respect their autonomy, their capacity to consider options, make choices, and act without undue influence of others.

34 However, the fundamental rights to integrity and self-determination are not the only justifications for requirement of informed consent. For example, the duty to inform subjects about key aspects of a treatment, a clinical trial or research involving identifiable blood and/or tissue samples, can also be justified by the requirement of common decency or minimal respect which we owe other persons because they are human beings. Since most people do feel violated if others interfere with their bodily integrity without consent, it can also be argued that the necessity to obtain consent has anthropological roots, which are at least to a certain extent independent of social and cultural circumstances. These basic feelings extend – although to a lesser extent – to research on one's own tissue samples. The requirement of consent is therefore of fundamental importance for the protection of the most basic rights of a person in the context of medical treatment and research.

2.2.1.3. Informed consent in tissue-based research

35 Whereas ethical discourse focused on informed consent procedures concerning standard clinical research (e.g. drug trials) for a long time, current discussions concentrate on requirements for consent to tissue-based research. In this context, it is taken for granted that the potential donor has to consent to blood or tissue removal. The duty of the investigator to inform the potential donor and ask for consent is primarily based on the ethical principle of respect for the person and her/his autonomy. Thus, the doctrine of informed consent is closely connected to the physician-patient-relationship. Donors provide investigators with 'raw material' to produce knowledge and, thereby, to improve the treatment of diseases. As a result, seeking informed consent is seen as "one part of honouring the contribution that the person is making to advancement of knowledge".[11] At the same time, to obtain informed consent expresses the recognition of patients' autonomy and his right to choose.[12] Trouet, for instance, underlines that a "source can be opposed to certain

[10] WMA 1964
[11] Clayton 2005, 15
[12] Hansson et al 2006; Chen et al 2005; Clayton 2005; Pelias 2004

uses of his (anonymized) cells or tissues," and therefore, the donors need to be informed about intended uses of the tissue as well as asked for consent.[13]

The concept of personal autonomy in tissue-based research also comprises 36
control over information obtained from tissue samples.[14] "Autonomy encompasses not just the right to self-determination about our body and how it is treated, but also to information about ourselves, our lifestyle, and our health."[15] In his investigation of the Australian Law concerning questions of the human body and of privacy of personal information, Alston emphasizes that the issue of confidentiality is touched by using bodily samples, as well as by using the information obtained from it in research.[16] According to Alston the legal protection of the individual's right to have control over his or her bodily material is conditional on the "modern significance of bodily samples as direct sources of personal information". From that perspective, biological samples constitute "an immediate source of personal information", a "virtual medical record".[17]

Other scholars draw attention to the importance of informed consent procedures 37
to prioritize the interests of the present research subject, in relation to future patients or the society as a whole. "By insisting on informed consent, the medical researcher is forced to acknowledge that the present research subject has a greater ethical claim than do future treatment possibilities."[18]

The importance of informed consent for tissue-based research has not only been 38
emphasised in the context of the physician-patient-relationship, but also in a broader sense: Consistently, its importance to build-up trust is highlighted in the discussion.[19] Trouet points out that informed consent is necessary even if the biological material has been anonymized. For him, "[p]atients want to have confidence in their doctors and this trust is violated when they discover that their biological materials are stored and used for other purposes without their knowledge".[20]

Most authors underline the importance of informed consent, but quite a few 39
analyse and criticise how it is practiced in modern biomedical research. Although pretending to pay tribute to the principle of respect and autonomy, consent procedures in the research setting have become a "convenient means of transferring responsibility for risk from the clinician or researcher to the informed patient".[21] In practice, informed consent is often considered as paperwork to be done, mainly for legal reasons.[22] O'Neill draws attention to the fact that "institutions and professionals increasingly see obtaining informed consent as protection against accusa-

[13] Trouet 2004, 100

[14] Sass 1998

[15] O'Brien and Chantler 2003, 36

[16] Alston (2005, 434) emphasises the necessity to differentiate between the terms 'data' and 'information'; the distinction has been compared with that between 'raw material' and 'manufactured product' or between 'medium' and 'message'. The view of human biological samples as raw material is shared by various authors, as, for example, Reymond et al 2002, 257.

[17] Alston 2005, 431

[18] Banks 2000, 549

[19] See for example, Alston 2005; Trouet 2004; O'Brien and Chantler 2003; Clayton et al 1995

[20] Trouet 2004, 100

[21] Alderson and Goodey 1998, 1314; see also Kottow 2004 and Case 2003

[22] Especially in the US-debate it has been repeatedly underlined that obtained informed consent serves as a legal protection tool (O'Neill 2003; Alderson and Goodey 1998). Clayton et al (1995, 1787) underline that "obtaining informed consent also serves the interests of researchers by reducing the risk that subjects will pursue legal actions when their expectations about the research

tion, litigation, and compensation claims". She concludes that the growing importance of informed consent procedures is closely connected to formalisation processes in medical practice.[23] Informed consent, she cites a medical sociologist, has become "the modern clinical ritual of trust".[24]

40 Focusing on another aspect of practice, Sass criticises current informed consent procedures regarding their practicability. He states that the concept "has outlived its useful life in many areas of clinical research" and proposes that in the context of clinical trials and research the relationship between patient and clinician or researcher respectively, has to be understood as a contractual relationship.[25] Therefore, he wants to see the consent for tissue removal and usage as a contract between patient and clinician. Furthermore, according to Sass, "the best protection and implementation of principles of privacy and confidentiality is to play decisions back to the patients".[26] According to this reading, informed consent does not serve as an instrument to ensure patients' autonomy, but to avoid litigation and to solve questions of liability.

41 However, most scholars maintain the importance of informed consent as an instrument to implement the principle of autonomy in clinical and tissue-based research. Some authors explicitly reject the idea of embedding consent to research uses of tissue samples and data into a contractual framework. Especially O'Neill underlines that consent cannot be seen as sufficient justification for research activities: "Even if there is informed consent, we may judge surgery without medical purpose, medical practice by the unqualified, or unnecessarily risky treatment unacceptable and may think it wrong to use human tissues as commodities, as inputs to industrial processes, or as items for display."[27]

2.2.2. The scope of consent

42 According to international standards, informed consent is required for collecting, storing, and using human biological material such as tissue, blood, or DNA and data processed from tissue.[28] As discussed above, this requirement is based on the ethical principle of autonomy. In the European Union, a framework of data protection rules also obligates researchers to obtain consent to data processing and storage. However, these general requirements are far from clear instructions on how to deal with tissue collections or data processing in practice. Especially the issue of consent for future research purposes, which cannot be clearly defined at the time consent is sought, turns out to be difficult.

2.2.2.1. Models of consent

43 At stake are three different models of consent: 1) specified consent tailored to the aims and intentions of concrete research projects; 2) broad or blanket consent

are not met. The possibility of unhappiness and even litigation later on may be greatly reduced by early disclosure, discussion, and the opportunity to refuse to participate".

[23] O'Neill 2003, 4; see also O'Neill 2004, 1134

[24] Wolpe 1998

[25] Sass 1998, 295

[26] Ibid, 292

[27] O'Neill 2003, 5

[28] Council of Europe 2006, chapter III, article 10, 2 and EU 2004, Annex A. In the Declaration of Helsinki (WMA 2008) research on human biological material is not specified, however, informed consent of the participant is required for any research involving human beings.

containing no restrictions with regard to future research, and 3) tiered consent arranging different levels of authorisation in the consent procedure.

2.2.2.1.1. Specified consent. The model of specified consent emerged together with the reverse model of general consent for future research ('broad' or 'blanket' consent) in the context of collecting human biological material. Specified consent is similar to the original doctrine of informed consent, which is practiced in clinical trials, asking patients to consent to a specific clinical research project comprising a limited number of clearly defined therapeutic and diagnostic interventions and investigations. Basically, the concept of specified consent includes the obligation to inform potential study participants about the primary and secondary aims of the research project in question. They also have to be provided with information about potential risks and benefits of their participation, about processing data, measures taken to protect privacy and about their right to withdraw at any time. 44

Many scholars accept – at least in principle – the position proclaiming specified informed consent as an instrument to implement a patient's autonomy. But serious objections have been made regarding the practicability of this model as well as its ethical value with respect to research with tissue samples. Although the argument that specified consent expresses respect for the donor has been affirmed, it is usually accompanied by concerns that fully implemented, specified consent may be an impediment to research. "The argument would indeed be true if the process of obtaining specific consent did not jeopardise the amount and quality of research that can be done", conclude Hansen et al.[29] 45

Especially in biobank research and clinico-genomic research samples and data are usually collected and processed for a multiplicity of (future) research projects of unknown character. As a consequence, the efficiency of tissue-based research on the one hand, and respect for confidentiality, autonomy and patients' rights in general on the other hand, have been discussed as mutually exclusive. Other authors have criticised this distinction as a rather utilitarian view that does not recognise the principle of patients' autonomy appropriately and is "dangerously reductive".[30] However, as far as tissue-based research is concerned, there are some indications that 'amount and quality' of research could be seriously limited by a specified consent model. If operators of a tissue collection are requested to ask a multitude of tissue donors for specific consent for every new research project – possibly over a long period of time – the probability of losing a lot of volunteers and, thereby, data for research is high. In fact, as the practice has shown, requests for re-consent are usually characterised by low response rates.[31] Although, up to now, only limited experience with re-consent exists, it has been attended by the concern that "the need for renewed consent for use of biobank material would reduce the number of participants available, possibly introducing selection bias and decreasing the scientific importance of the studies".[32] Tissue donors simply might not be concerned with or interested in re-consenting, they might have changed their contact data, or 46

[29] Hansson et al 2006, 266

[30] O'Brien and Chantler 2003, 37; as outlined in paragraph 2.2.1/Ethical foundations of the doctrine of informed consent, O'Neill (2003, 4) also draws attention to this change in the understanding of informed consent in clinical practice

[31] Hansson et al 2006, 266 f

[32] Ibid

might be deceased.[33] Obtaining specified consent for every distinct protocol "would be contrary to the interest not only of society at large in medical progress but also to the interest of the individual research subject as well," De Montgolfier et al conclude.[34]

47 The model of specified consent is not only be regarded as impracticable with respect to future research, it is sometimes also impossible to achieve. If specified consent for future research is required, the potential donors have to be informed about conceivable research projects and also about imaginable possibilities and probabilities concerning the usage of the tissue, before tissue removal. But adequate informing is difficult, even in the context of standard clinical trials.[35] This applies even more for future, yet unknown research projects. Quite a few authors are additionally concerned that the request for specified consent might undermine the original idea of informed consent as a process that expresses respect for autonomy and enables the donor to exercise his or her right to self-determination. "Complex forms that request to consent to numerous, highly specific propositions may be reassuring for administrators (they protect against litigation), and may have their place in recruiting research subjects: yet they will backfire if patients or practitioners come to see requesting and giving consent as a matter of ticking boxes."[36] This appraisal is supported by the argument that the amount of issues regularly listed in consent forms may overstrain patients and, thereby, weaken the original meaning of informed consent.[37]

48 **2.2.2.1.2. Broad or blanket consent for future research.** Albeit the model of specified consent has not been clearly defined yet in the context of clinico-genomic or biobank research respectively, it has a long tradition in clinical research. In contrast, the model of broad or blanket consent has not been practiced in clinical research but emerged quite recently in practice with respect to systematic collections of biological samples and genetic data as well as in the bioethical discourse. The model refers to the argument that "in the presence of an informed consent, use of samples beyond purpose might be a violation of the subject's rights."[38] Since many investigators are generally interested in keeping the definition of the field of research as broad as possible, they do not share this view and try to establish an alternative model on informed consent, which is not limited to clearly defined research purposes.

49 Public opinion surveys have additionally shown that people highly accept, as of yet undefined, future research with already collected samples and data.[39] Hence, advocates of a blanket consent model emphasise its usefulness by referring to its efficiency in combining the interests of patients and investigators. Furthermore, it is often promoted by the argument that elaborate consent procedures are costly and time-consuming. Therefore, it would be more cost and time efficient to simplify the procedure.

---

[33] Referring to HIV-clinical research, De Montgolfier et al (2002, 668) call attention to "the possibility of a number of the participants in the cohort dying".

[34] Buchanan et al 2002

[35] O'Neill 2004, 1134

[36] O'Neill 2003, 6

[37] Fernandez et al (2003 a, 2906), for instance, examined consent forms of 235 US-institutions; the length of the forms was up to 50 pages.

[38] Reymond et al 2003, 353

[39] Chen et al 2005; Cousins et al 2005; Goodson and Vernon 2004; Hoyer et al 2004; McQuillan et al 2003; Stegmayr and Asplund 2002; Wendler and Emanuel 2002

Drawing on results of an empirical survey, Wendler et al argue that the consent for new research that differs from the initially consented project or trial can be assumed if donors already did consent to the use of their sample for research purposes. In the survey, the majority of respondents declared not to be in need of additional information to consent for further research with their samples.[40] The authors therefore conclude that "[t]hese data also suggest that individuals may not think it is necessary to specify which kind of research will be performed when obtaining biological samples initially."[41] Whereas this concept still relies on an initial informed consent based on its conventional understanding, other authors propose to completely replace consent procedures in the context of tissue donation by a model of simple binary choice. Chen et al, for example, do not see any problem to ask patients simply to consent to the use of their samples, for future research or not. Their survey results suggest that this would be sufficient to meet the needs of research participants.[42] 50

On the base of empirical data concerning attitudes of cancer patients, Pentz et al similarly recommend, "to offer individuals a one-time binary choice." Although the authors found a certain "level of mistrust", especially regarding possible breaches of confidentiality, "none of these concerns appeared to keep individuals from consenting to having their samples used for research purposes."[43] An empirical survey of 1200 tissue donors in Sweden underlines that potential donors do not mind the scope of consent. The majority (920 donors) agreed that the biobank and the regional research ethics committee decide on the use of their blood sample. Of those, 308 persons did affirm the phrase "I do not want any further information about new projects that involve my sample", whereas 446 patients "still appreciate information about projects involving my sample".[44] The recent qualitative US-study of 26 breast cancer patients supports the presumption that consent for future research projects is not a matter of concern in a patient's perspective.[45] According to the small and culturally unbalanced empirical base, patients apparently seem to have a lack of interest in the question regarding the scope of consent. 51

For tissue sampling in the clinical context, the British Medical Research Council even goes further. It recommends having only one box on the consent form, which should be ticked by the patient or the health professional respectively, if the patient does not want his or her tissue to be used for future research. In practice, this 'opt-out' model would lead to presumed consent for future research using the sample. The council argues that the practice would make it easier for researchers in any case to handle stored samples with no consent record attached to them. It would then be reasonable "to assume that consent had been given for its use in research".[46] 52

Beyond the rather functional arguments regarding the meaning of consent expressed above, proponents of broad consent also refer to the ethical principles of 53

[40] Wendler et al 2002 b, 1460

[41] Ibid

[42] More than 87 percent of the participants authorised future research on any condition, whereas only 1.2 percent of the participants authorised future research only if it is limited to the condition for which the sample actually was removed. Chen et al 2005, 634, 655

[43] Pentz et al 2006, 739

[44] Hoeyer et al 2005, 99

[45] Kaphingst et al 2006, 395

[46] MRC 2004, 3

autonomy, self-determination and doing no harm. To justify this model, the British Medical Research Council, for example, points out that those consent procedures could overstrain patients. Requesting blanket consent from tissue donors would spare patients as well as relatives with troublesome questions and decisions and prevent from psychological harm.[47] A different reference to the principle of doing-no-harm is made by Wertz, who regards obtaining blanket consent for future research as acceptable, as long as it is limited to diagnosis and treatment of diseases; it only should "exclude research related to reproduction, mental illness, violence, sexual orientation or other areas of behavioural genetics that are highly controversial", because research in these areas may produce greater than 'minimal' harm, especially to communities.[48]

54 Referring to patients' autonomy, Hansson et al bring forward the argument that "acceptance of broad consent and future consent implies a greater concern for autonomy than if such consents are prohibited".[49] The authors argue that full respect for patients' autonomy implies providing them with any possibility of decision-making, including broad consent. To deprive patients of one form of consent would "interfere with self-determination" and thereby "disrespect autonomy".[50] Opening that detailed informed consent, to all possible uses of stored tissue in the future, "is overprotective of people's autonomy interests", Merz et al support a broad consent model for future research.[51] Although neglecting the legitimacy of blanket consent as far as identified or identifiable tissue is concerned, in case of anonymized samples they consider it "acceptable".[52] O'Neill argues that broad consent complies with the ethical principles of autonomy and self-determination as long as patients "know they have access to extendable information and that they have given rescindable consent", because then they "have in effect a veto over what is done".[53]

55 A one-time consent could indeed undoubtedly simplify the research process. However, in the eyes of Caulfield et al blanket consent cannot be considered true consent "[B]ecause blanket consents are necessarily vague, they are, by definition, far too general to have much legal weight."[54] In that sense, the more or less pragmatic arguments brought forward to support blanket consent do hardly fulfil the demands and criteria of a legally acceptable, formal agreement to become involved in research projects.

56 Then again, it seems to be almost impossible to apply the original concept of specified informed consent to future, yet undefined research projects. As O'Brien and Chantler emphasise, "we cannot meaningfully give consent to the use of our data in future research projects which not yet have been identified."[55] From this

[47] Ibid
[48] Wertz 1999, 58
[49] Hansson et al 2006, 267
[50] Ibid; Hansson et al (2006, 268) also criticise that in clinical settings 'double standards' have been applied; "given that ethics-review boards might grant biobank research without consent, it seems odd that participants themselves should not be allowed to give broad consent to future biobank research."
[51] Merz et al 1997, 253
[52] Ibid, 254
[53] O'Neill 2003, 6
[54] Caulfield et al 2003, 3
[55] O'Brian and Chantler 2003, 39

point of view – especially in genetic and genomic research – future uses of donated tissue samples, as well as processed data scarcely may be anticipated. Because of "the speed of scientific development in the area of genetics and the vast spectrum of potential research hypothesis that may arise (…) there is no way to predict possible future uses of donated samples."[56] As Reymond et al conclude, "the traditional practice of obtaining consent for unspecified future use of biological samples and data generated from clinical trials is no longer adequate for genetic research".[57]

2.2.2.1.3. Tiered consent models. With regard to the limitations of the two consent models discussed above, some authors suggest abandoning the original doctrine of informed consent altogether and replacing it by the concept of authorisation instead.[58] However, O'Brien and Chantler emphasise that "moving away from 'consent' should not in any way be taken to imply a lesser need to give patients information and choices, and to respect their rights to privacy and autonomy".[59] 57

To overcome the apparently intractable problem of consent for future research, models of tiered consent have been proposed. Such models give patients the opportunity to choose between various alternatives on different levels and thus legitimize the utilization of their tissue in a more or less restricted manner. Such a practice seems to be more in accordance with the empirical findings mentioned above, as well as with the challenges of future tissue-based research. As one of the first authors, Wertz suggested a model of choice between at least two alternatives regarding the particular issues: "The fairest approach may be a 'line-item' informed consent that would allow people to express their wishes about alternatives."[60] 58

Similarly Reymond et al propose to provide patients with information about different options "to help them understand clearly the nature of the decision they are about to make".[61] Alternatives could be: 1) generally refusing the use of their biological material, 2) permitting only unidentified or unlinked use, 3) permitting coded or identified use for one particular study only with no further contact, so that further studies are impossible, 4) permitting coded or identified use for one particular study only with further contact permitted, so that further studies might be possible, 5) permitting coded or identified use for any study relating to the condition for which the sample was originally collected with further contact allowed to seek permission for other types of studies, or finally 6) permitting coded use for any kind of future study. 59

Williams suggests a model of tiered consent, which already has been exemplified by the US-National Heart Lung and Blood Institute.[62] According to his proposal, three levels of consent have to be recognised for 1) the current study, 2) goals broadly related to the area of the original study, and 3) goals unrelated to the area of the original study. In each level, consent should be obtained for the use of the samples by the investigators and collaborators, for the re-contact of donors and for the storage and reuse to accomplish the goals of further studies. 60

[56] Caulfield et al 2003, 2
[57] Reymond et al 2003, 351
[58] See O'Brien and Chantler 2003; Caulfield et al 2003
[59] O'Brien and Chantler 2003, 39
[60] Wertz 1999, 57
[61] Reymond et al 2003, 353
[62] Williams 2001, 454

61 A different model of tiered consent is the step-by-step model proposed by Caulfield et al.[63] Within this model, research participants choose at different moments the kind of consent they want to be asked for. As suggested above, an informed consent is obtained for the initial collection of patients' biological material and health information. For subsequent uses, participants have to give a 'pre-authorisation'; this means they have to pre-specify uses for which they do or do not wish to be asked for consent in the future. They may choose to be contacted, for example, only in case of clinically relevant findings or, for instance, only if potential commercial applications are being derived. In this model, participants are allowed to give blanket consent for future research, but a broad consent "can only occur by the choice of the participant".[64] Thus, "each individual can specify in advance the extent of involvement in decision-making that is desired. This preserves aspects of autonomy, but neither restricts future uses as much as a full consent model, nor is it as permissive as the proposed blanket consent models."[65] However, in this approach, the possibility of being informed about research results of clinical relevance is not taken into consideration. But Caulfield et al argue that biobank or genomic research often involves low penetrance genes. Therefore, "it is unlikely the research results will be of immediate clinical relevance to individual research participants."[66]

62 From a practical point of view, it is argued – similar to the discussion on specified consent – that re-consent is generally difficult to obtain.[67] Furthermore, bureaucratic obstacles are pointed out, especially the fact that participants have to be requested to inform the research institution or the sponsor respectively, about any change of contact data. Last but not least, the costs for obtaining re-consent are also mentioned in the discussion.[68] Nevertheless, tiered consent models seem to meet the demands of patients and future research and conform to ethical requirements at the same time. In contrast to the alternative models of specified and blanket consent, they therefore seem to be suitable for tissue-based biomedical research.

63 **2.2.2.1.4. Patients' and donors' perspectives.** The question, whether the requirement of informed consent and the relevant procedures could overstrain patients, is repeatedly addressed in the discussion. Concerns are not only expressed with respect to the extent of information given in the information sheets for patients or donors, but also with respect to the underlying concept of choice. Alderson and Goodey point out that the current focus on informed consent, which is promoted by the concept, may create severe problems in the clinical context. They ask if offering different options in medical and clinical settings, "although seeming to expand choice", rather "impose[s] a tyranny of choice".[69] They conclude that choice "can be more onerous when people are uncertain how to choose among values and rules for choice making".[70]

64 Beyond these general reflections there is empirical evidence to suggest that consent processes may overstrain patients. Presenting findings of an empirical

[63] Caulfield et al 2003
[64] Ibid, 3
[65] Ibid
[66] Ibid, 2
[67] Main arguments regarding the issue of re-consent are discussed in paragraph 2.2.2.1.1/ Specified consent. See also Hansson et al 2006; Case 2003; De Montgolfier et al 2002
[68] Wertz 1999, 57
[69] Alderson and Goodey 1998, 1315
[70] Ibid

study on participants of clinical drug trials, Corrigan alludes to differences between patients' reactions: Generally, for patients with conditions of a mild and chronic nature the informed consent process "can open up the field of choice", she concludes.[71] But for most of the patients who were seriously ill "the experience of being invited to take part in clinical drug trials was burdensome".[72] Similarly, Gotay refers to a limited ability of seriously ill participants, particularly of cancer patients: "The anxiety associated with cancer diagnosis may cloud patients' ability to process information such as that found in consent forms."[73] Other empirical studies have also shown that the decisions patients make in these situations cannot be called informed, competent, or free.[74] Therefore, overstraining patients undermines the original idea of informed consent, as Wertz highlighted: Patients who do not take up easily or absorb information – for whatever reason – are impeded to exercise their right to autonomy and self-determination.[75] At the same time some authors emphasize the actual setting in which consent is requested. Empirical studies on consent processes indicate that the time frame for the required decision on participation or non-participation in research – usually right after the first diagnosis – is emotionally experienced as an exceptional situation in such a way that the person concerned is hardly able to decide independently.[76] Retrospectively asked, many research participants are even unaware that they gave consent at all.[77] Wertz, for example, describes for the US, many patients do not realize that consent forms for surgery include that material left behind after the intervention becomes the property of the hospital, unless the individual objects within a certain time frame. Those "'opt-out' procedures are very general", she notes, "and do not specify who will use the samples or for what research purposes or how long they will be stored".[78] Many people, she assumes, "may not notice the statements about possible research uses of samples, because they have more urgent matters at hand".[79]

However, the argument frequently brought forward that research information and consent were "peripheral issues" in a moment when seriously ill patients have to consider "their own future with a serious disease" is also criticised as a pragmatic one; O'Brien and Chantler see it as a mere expression of a functionalist perspective on consent.[80] This view is supported by Case, who points out findings showing that researchers or medical professionals used the argument as a means to avoid informed consent becoming prescript in certain contexts.[81] 65

Nevertheless, to what extent consent procedures may be burdensome to patients is still unclear, since empirical data concerning the issue are very limited and partially contradictory. Results of a survey Kodish et al conducted provide an insight into differences that might exist between clinicians and parents of children 66

[71] Corrigan 2003, 788
[72] Ibid
[73] Gotay 2001, 1097; that "clouded ability" motivated her to survey healthy volunteers to assess participants' views on the adequacy of the consent process in clinical trials.
[74] Harth and Thong 1995; McCollum and Schwartz 1969
[75] Wertz 1999, 54
[76] See in particular, Corrigan 2003; Gotay 2001; Levi et al 2000
[77] See for example, Hoeyer et al 2005; Gotay 2001
[78] Wertz 1999, 54
[79] Ibid
[80] Ibid
[81] Case 2003, 225; see also the discussion in paragraph 2.5.1.2/Community interests

with cancer. The interviews with 23 parents and 23 clinical researchers about the information given, the consent process, and its effects resulted in obvious disparities between investigators and patients concerning the question of distress and harm potentially caused by informed consent processes: Whereas ten parents declared to feel less anxious, eight parents felt more anxious. In the investigators' sample, the relation was directly opposed: Whereas seven investigators believed that informed consent makes parents feel less anxious, eleven researchers thought the opposite would have been the case.[82] An even stronger disparity between the two interviewed groups can be noticed concerning the amount of information: Whereas eleven clinical researchers declared the amount of information given in the consent process being "too much", just three parents did so. A majority of fourteen parents found it "just right", five parents declared it to be "not enough", a statement which only two clinicians agreed to. As the authors conclude, clinicians "underestimate how much information parents want to be given."[83]

67 To sum up, in existing studies, possible situational, socio-demographical, and motivational factors relevant for the decision-making process have been analyzed. Yet, the numerous studies do not come to unambiguous results. According to these studies, possible factors that might influence consent or non-consent respectively are: recognized strains during decision-making, such as lack of privacy, time pressure, or missing care;[84] intensity of reading the information by the patient and how comprehensively it was written;[85] physician's consultation;[86] and the physician-patient-relationship in general.[87]

68 When asked for their motivation to consent, the majority of survey participants answered that patients' participation in clinical research would increase medical and scientific knowledge and other patients would benefit.[88] According to the US-survey of Cassileth et al (1982), asking patients with cancer, cardiology patients and members of the general public, most respondents believed that patients with any disease should serve as research subjects and that such patients make an important contribution to society. But a different motivation emerged when the same people were asked about their own potential participation: Over half of all respondents are primarily motivated by their belief that they would get better treatment by taking part in research.

69 Socio-demographical factors, such as education or sex apparently do not play an important role in decision-making. However, Pope et al (2003) demonstrated that subjects' educational level corresponds with the understanding of more complex issues, including the concept of placebo use.[89] Another interesting socio-demographic factor discussed in the US-literature is ethnicity.[90] It is assumed that ethnic

[82] Kodish et al 1998, 2471, 2476, 2478. See also paragraph 2.2.2.2.3/Particularities of consent to research involving children

[83] Kodish et al 1998, 2478

[84] Burgess et al 2003; Tait et al 2003a

[85] Burgess et al 2003; Maede and Howser 1992; Gallet et al 1994; Kruse et al 2000; Pope et al 2003; Tait et al 2003a

[86] Burgess et al 2003; Mason and Allmark 2000; Olechnowicz et al 2002

[87] Corrigan 2003; Harth and Thong 1995

[88] Cassileth et al 1982; Harth and Thong 1990; Kaphingst et al 2006; Mason and Allmark 2000; Pope et al 2003; Van Stuijvenberg et al 1998; Wendler and Emanuel 2002

[89] See also Bjorn et al 1999; Byrne et al 1988; Kjaergaard et al 1998

[90] See for example, McQuillan et al 2003; Pentz et al 2006

minorities generally have more mistrust in the research enterprise than members of the ethnic majority, suggesting that ethnic minorities may be less willing to contribute biological samples for research purposes. Even if Pentz et al (2006) conclude from their survey asking cancer patients of two ethnic/racial groups (African Americans and White Americans) that almost all respondents, regardless of race/ethnicity or socio-economic status, were willing to provide a biological sample for unspecified future research on all conditions, the results document at the same time a continued higher level of mistrust in the African American community. African Americans were more concerned than White Americans that more tissue would be taken for research than was needed for patient care and that researchers might discover genetic information about their ethnic or racial group. But the authors link the level of mistrust not only to ethnicity, but also to locality. According to their survey, participants are more willing to authorize research conducted with only local use of their samples in their home country and less willing to authorize research use of their samples in a country of another continent.

Empirical studies on the subjective assessment of the informed consent process 70
come to a totally different conclusion: It is reported that the majority of surveyed patients feel satisfied with their involvement in a clinical trial, their understanding of the given information, the information provided, and the consent process in general.[91] Normally they do not regret their decision to take part – but this assertion is often based on the (erroneous) assumption that the attending doctor would know privately which one of the investigated treatments is best and that they therefore would get better treatment by participating in clinical research.[92] It seems that an intrinsic element of the doctor-patient-relationship involves the trust that a patient has in the physician's ability and the certainty that the doctor will act in the patient's best interest. In conclusion, the confidence in the attending doctor, or in the health-care-system in general, is again a crucial factor in the decision-making process.[93]

2.2.2.1.5. Particularities of consent to research involving children. The required 71
decision on taking part or not taking part in research is even more difficult for parents who have to decide on behalf of their child. Children are – depending on age – either de facto or de jure not competent to give consent to research participation. Confronted with the diagnosis of their child, parents normally feel emotionally stressed and often helpless in this situation. The decision about study participation of a minor produces a special kind of responsibility for parents to deal with. However, empirical studies indicate that in principle, parents do want to make this decision by themselves and therefore do not accept that someone else – an ethics committee for example – would decide instead.[94] Hence, the investigator must obtain informed consent from the parents or legally authorized representatives respectively.

In addition, research involving children requires specific medical considerations. 72
Because of different bodily conditions, the risks of invasive clinical research might be more severe and might last longer for children and young persons than for

[91] Ferguson 2002; Gotay 2001; Hoeyer et al 2005; Pope et al 2003; see also Olver et al 1995

[92] Cassileth et al 1982. This phenomenon has also been termed "therapeutic misconception", see for example, De Melo-Martin and Ho 2008; Bamberg and Budwig 1992.

[93] Corrigan 2003; Pope et al 2003

[94] See for example, Burgess et al 2003

adults. For the latter reason, the World Medical Association Declaration of Helsinki on ethical principles for medical research involving human subjects,[95] first adopted in 1964, differentiates between research involving (legally or mentally) incompetent persons with and without therapeutic benefit. Research involving minors is ethically permitted only if the minors involved have direct (therapeutic) benefit and if the authorized representatives have given consent. The EU-directive on the implementation of good clinical practice in the conduct of clinical trials expands the permission for clinical trials on minors if "some direct benefit for *the group of patients* is obtained from the clinical trial".[96] Furthermore, the EU-directive states that the consent of the legal representatives must represent the minor's presumed will.[97]

73 The child's assent is increasingly regarded as necessary, if possible. The World Medical Association, for instance, states a duty to gain assent: "When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative."[98] In order to form his/her own opinion, the minor needs according to his or her capacity of understanding, information about the purpose and course of the trial, the possible risks and benefits, and implications of participation.[99]

74 According to empirical data[100] suggesting an unexpected capacity of children to participate in the process of informed consent, their involvement in decision-making has been growing within the last years. Guidelines in the United Kingdom even state: "The application of general principles indicates that, where children have sufficient understanding and intelligence to understand what is proposed, it is they and not their parents whose consent is required by law. (…) If the child is insufficiently mature to consent, then valid parental consent must be obtained."[101] Dawson and Spencer call attention to a possible disagreement between parents and child and conclude that "a parent cannot overrule a competent child's decision, but a clinician is unlikely to go ahead with research if either the child or the parent is reluctant".[102] From this follows that the investigator has to obey the minor's expressed will to refuse participation in, or to be withdrawn from, the clinical trial at any time.

75 However, the restrictions of research involving children have been criticised from different directions. At first, the distinction between basic research and therapeutic (or applied) research according to the World Medical Association Declaration of Helsinki, which demarcates ethically allowed from ethically prohibited research, is not always clear. As a result, minors are often excluded from clinical trials and, therefore, are generally discriminated against regarding medical improvement in therapy. For example 80 percent of the drugs currently given in paediatric therapy

[95] WMA 2008

[96] EU 2001, Article 4(e), "Clinical trials on minors" (underline added)

[97] EU 2001, Article 4(a), "Clinical trials on minors"

[98] WMA 2008, paragraph 25; see also EU 2001 (Directive 2001/20/EC, Article 4(c), "Clinical trials on minors")

[99] Dawson and Spencer (2005, 234) discuss suitable formats for children, e.g. multimedia shows; see also Kurz 2003, 1280

[100] See for example, Lohaus et al 2002; Alderson 1993

[101] Royal College of Paediatrics 2000, 5

[102] Dawson and Spencer 2005, 233

are not tested for children.[103] Accordingly, children generally have a higher risk in therapy, because they are treated with drugs that are not sufficiently tested for this patient group.[104]

In the US, the discussion is more focused on the evaluation of risks posed by clinical trials involving children. According to the guidelines of the US-Department of Health and Human Services (US-DHHS), which are implemented in the Food and Drug Act, "research not involving greater than minimal risk" is generally allowed[105], provided that parents have given consent. Minimal risks are present when "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests".[106] Accordingly, the American Academy of Paediatrics (AAP) describes minimal risks in research involving children for activities such as physical examinations, venipunctures, or urine sample collections.[107] 76

Nevertheless, empirical data reveals that this approach does not prevent minors from risk and harm. Janofsky and Starfield published an US-survey in 1981asking heads of paediatric clinics to assess the risks of different clinical routines. In regard to distinct age groups, the clinicians were supposed to assess the risk of measures – for example venipunctures, intramuscular placebo injections, or skin biopsies – according to three risk categories: no risk or minimal risk, a minor increase over minimal risk, or greater than a minor increase over minimal risk.[108] The results of the survey have shown that clinicians haven't found a general consensus of how risks are supposed to be rated.[109] Therefore, risks of distinct measures are assessed differently by practitioners, according to their personal perception, empathy and experience. 77

The second major criticism against restrictions of research involving children is concerning the minor's assent. Though it is widely accepted that children have to be involved in the informed consent process according to their capacity of understanding, it remains unclear how to approach the capacity of minors appropriately.[110] Possible criteria discussed in the literature are age, maturity, or psychological conditions of the child. Referring to empirical data, Leikin proposes that the capacity of understanding has two dimensions: understanding of their role within the research process as well as reasoning about research,[111] the latter requiring 78

[103] Dahl and Wiesemann 2001, 88

[104] Clinical trials to get medical drugs for children approved are very costly. Additionally, paediatrics will prescribe medicines regardless of their status, because they do not have any alternative. As a result, pharmaceutical companies are generally not very ambitious in testing drugs on children (Levine 1996).

[105] US-DHHS 2005, § 46.404, "Research not involving greater than minimal risk"

[106] Ibid, § 46.102 (i), "Definitions"

[107] AAP 1995, 286

[108] Janofsky and Starfield 1981; the categories are based on the definition of minimal risk according to the US-DHHS.

[109] Arteriepunctures for 12-18-year-old, for example, were assessed by 24 percent of the interviewees as no risk or minimal risk, by 55 percent as a minor increase over minimal risk, and by 21 percent as greater than a minor increase over minimal risk (Janofsky and Starfield 1981, 844).

[110] See for example, the wording of the Convention on Human Rights and Biomedicine: "The opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to his or her age and degree of maturity (Council of Europe 1997, Article 6 (2), "Protection of persons not able to consent").

[111] Leikin 1993

abstract thinking beyond personal experiences. In order to be classified as competent, the child needs to have the capacity of understanding, the purposes and course of research, the possible risks and benefits, and implications of participation.[112] In this context, Kuther (2003) discusses two main challenges for child's capacity: 1) Children have an unspecific concept of disease, because they do not distinguish between symptom and cause of a disease. Their reasoning is rather different from that of an adult. They assume that diseases are caused by magical forces or are effects of moral misconduct. 2) Especially small children tend to not defy authorities such as parents or attending physicians.[113]

79 Many authors speculate about the general stages of a child's development. The ages recommended as level of attained maturity range from seven to 15 years.[114] Leikin, for instance, states that only children from nine years on can reason about research,[115] whereas Lohaus et al conclude that children at the age of 12 are mature enough to give full assent.[116] In their German survey, the authors assess the capacity to consent of 140 children in third to eighth grade by approaching their concepts of illness. Other authors even claim that seven-year-old children are able to decide competently, especially if they have experience with chronic illness.[117] Nevertheless, psychologists after the Piaget-era assume that no clear defined stages of development exist.[118] The child's development is rather seen as an ongoing process. Since up to now, it is not possible to demonstrate how cognitive capacity grows and why individuals differ, age classification on its own is not accepted as an appropriate criterion.[119]

80 Even a consensus on maturity or psychological conditions – both discussed as having an important influence on the capacity to assent – is still missing. An anxious child, for example, might approach the informed assent procedure differently from a self-confident child that is not afraid of posing questions at any time.[120] Therefore, it finally remains to the judgement of the doctor to assess the child's capacity and to decide if his or her assent to participate in research is necessary.

81 However, as Dawson and Spencer highlight, "paediatrics is usually acute",[121] especially, in the context of clinical trials, if the child is ill or was recently confronted with a more or less serious diagnosis. Therefore, he or she may neither be capable of retaining information, nor of giving consent to research activities. Consequently, consent to participation of children in research in clinical trials usually will be given by the parents, and not by the research subjects themselves. Besides parental consent, research involving children creates some additional ethical questions to be taken into consideration, especially if it relates to genetic data or tissue samples. In this context, neither blanket consent nor consent to unlimited

[112] Kuther 2003

[113] With respect to parents' influence see also Abramovitch et al 1995; Scherer 1991; Susman et al 1992

[114] Abramovitch et al 1995; Kuther 2003; Leikin 1993; Lohaus et al 2002; Ondrusek et al 1998; Tait et al 2003b

[115] Ibid, see also Ondrusek et al 1998

[116] Lohaus et al 2002, 1503

[117] See for example, Alderson 1993; Nicholson 1991

[118] See for example, Koocher and De Maso 1990; Tait et al 2003b

[119] Kuther 2003

[120] Dorn et al 1995

[121] Ibid

future use of data and samples are regarded as acceptable. At least when the child who donated the tissue matures and reaches legal capacity to consent, the principle of respect for the autonomy demands that the donor himself has to be informed and asked for consent.[122] For similar reasons Clayton et al underline that "genetic research involving children should also be structured in a way that allows the children to retain as many choices and opportunities as possible once they reach adulthood".[123]

In this context, some authors explicitly discuss a re-consent. Burke and Diekema, for instance, recommend inviting paediatric participants to re-consent when they become mature. "Without such re-consent, participants enrolled as children will be denied the opportunity for an independent decision regarding research participation based on the participant's own review of information about study procedures and goals."[124] The authors emphasise a moral obligation of researchers to provide participants within the process of re-consent not only with sufficient information about storing procedures and confidentiality protections, but also about future possibilities and potential risks of storing and processing genetic data.[125] Even though Burke and Diekema state that it is "cumbersome and costly", the authors propose to ask periodically for re-consent. This allows paediatric patients "to participate more fully in the assent and consent process as they grow older, and to provide a legally valid consent upon reaching the age of consent".[126] 82

2.2.2.2. Informed consent and communication

Communication of information is an important aspect of informed consent. According to Beauchamp and Childress, communication is crucial for understanding.[127] Therefore, *informed* consent is not a single act. In fact, it comprises at least four main elements: 1) provision of information (content, timing, setting, and the way it is communicated); 2) comprehension; 3) willingness; 4) explicit declaration (written or oral). 83

Thus, a sensitive issue in the context of informed consent is the question of how to provide adequate information for decision-making, especially in tissue-based research, and, in particular, if children are involved. Approaching this problem, two crucial arguments will be discussed: how to design consent to research as an ongoing process and how to deliver comprehensive and understandable information. 84

Consent as a process 85

Quite a few authors insist on understanding consent to research as "a process rather than an event".[128] But in practice, the idea of consent as an ongoing process has not gained much acceptance.[129] "The process model is clearly an ideal, requiring 86

[122] Burke and Diekema 2006, 35
[123] Clayton et al 1995, 1792
[124] Burke and Diekema 2006, 36
[125] Ibid
[126] Ibid, 35
[127] Beauchamp and Childress 2001, 57 ff
[128] Kodish et al 1998, 2479
[129] In the drafting of the Universal Declaration on Bioethics and Human Rights, the International Bioethics Committee of UNESCO proposed the requirement for ongoing participation of the person in the provision of consent for medical diagnosis and treatment. This underlines the idea that giving consent is an interactive process in which the subject should take an active role from the beginning to the end of the research project. However, this procedural conception of informed

great psychological and pedagogical skills from the physician", Press and Browner state.[130] Therefore, usually "the event model" is realised.[131]

87 Nevertheless, a "need to see informed consent as an on-going process rather than a discrete act of choice that takes place in a given moment of time" is still postulated in the discussion.[132] Corrigan, for example, emphasises that the understanding of consent as a process facilitates the participants' right to withdraw consent. It "can open up the process of the trial itself, permitting the patient or healthy volunteer subjects to withdraw at any point during the study".[133] In this context, Kodish highlights that attitudes of participants can change over time.[134] Referring to genetic research, Knoppers et al underline that ongoing communication with research participants is necessary "to recognise the importance of their altruistic contribution to the progress of research in the field of genetics".[135]

88 Furthermore, some arguments support the idea of informed consent as an ongoing process concerning the handling of information. Criticising the often ritualised understanding of informed consent, O'Neill proposes to give just some initial information concerning the general purposes of a trial and offer at the same time an easy access to further, more specified information instead of providing research subjects with all information available before they consent.[136] Although her first intention is "to give patients control over the amount of information they choose to receive", she also underlines that research participants need time "to absorb further information".[137]

89 Accordingly, the issue of communication between health professionals and research subjects has been considered to be important. The meaning of verbal reflections and explications for an informed participation in clinical trials is underlined by various authors. "Verbal interaction with the researchers is a vital part of the consent process, especially as many people do not read the documents carefully".[138]

90 By interpreting the findings of her survey on healthy volunteers in cancer clinical trials, Gotay concludes that, "continued communication also can enhance commitment to the study and ensure that the participants are full partners in the research process".[139] She states that compliance over a period of years can only be achieved by continued information about the study and its potential side effects and by the opportunity to ask questions on an ongoing basis. "Even the best consent form and intensive patient counselling at the beginning of the study are inadequate to accomplish this goal", she concludes.[140] Although these consequences are drawn from the analysis of survey results related to long-term prevention studies and to

consent was not fully supported by other bodies involved in the process and hence does not appear in the declaration endorsed by the General Assembly (Kollek 2006, 2009).

[130] Press and Browner 1995, 10

[131] Ibid

[132] Corrigan 2003, 787

[133] Ibid, 788; for the issue of withdrawal see also paragraph 2.2.2.4/The right to withdraw consent

[134] Kodish et al 1998, 2479

[135] Knoppers et al 2006, 1

[136] O'Neill 2003

[137] Ibid, 6

[138] Wertz 1999, 58; see also O'Brien and Chantler 2003; Kodish et al 1998

[139] Gotay 2001, 1099

[140] Ibid

healthy volunteers, they are valuable hints for the organization of the process of informed consent in general and therefore in clinico-genomic trials as well.

In this context, the general trust-building character of consent procedures is emphasised. In biomedical research, co-operation with patients is indispensable; participation can only be achieved by a trust-based relationship between researchers, medical staff and potential research subjects.[141] As Williams expresses, an appropriate consent procedure, "protects both research participants and the enterprise of research itself".[142] Alderson and Goodey strengthen the argument by underlining that, especially from critical theory's point of view, consent is basically seen as a protection tool for patients as well as an "essential constraint on the most powerful profession".[143] In this perception, informed consent is "not regarded as simple, one way medical information giving, but as an exchange of knowledge between doctor and patient so that together they can make more informed decisions".[144] 91

O'Brien and Chantler conclude: "People want to feel involved, not just in their care, but also in decisions about research and in helping others (…). Communications with patients about what is to happen to them, how information about them will be used, or even what will be done with samples taken from them, seem to be of universal benefit in the provision of care. Its value lies in fostering relationships of trust between doctors and those they care for."[145] Thus, "the focus must be in giving information, providing choice, and respecting patients' autonomy – not on completing the paperwork".[146] 92

2.2.2.2.1. The character of information. Referring to the principle of autonomy and respect for participants, authors regularly stress the importance of comprehensive and understandable information provided in the consent process. Jepson et al, for instance, underline that information has to be comprehensive, because its purpose is to enable a person "to choose freely between different options".[147] Similarly, Kottow highlights that information has to be complete. "The idea of informed decision-making is incompatible with incomplete knowledge."[148] De Montgolfier et al emphasise the coherence between comprehensive and understandable information and conscious decision-making: "Not only must the information be truthful, clear, appropriate, complete and up to date", but the aim has to be "that the patient has as complete an understanding as possible of the consequences of his or her decisions".[149] 93

In practice however, this concept of information is faced by a number of obstacles. For instance, Wertz points to an intrinsic inconsistency of the approach towards information. According to her, there is a "trade-off between accuracy and completeness of information on the one hand, and the likelihood that people will read and understand it, on the other".[150] Indeed, empirical findings 94

[141] Hansson 2005; Williams 2001
[142] Williams 2001, 451
[143] Alderson and Goodey 1998, 1314
[144] Ibid
[145] O'Brien and Chantler 2003, 38
[146] Ibid, 39
[147] Jepson et al 2005, 193
[148] Kottow 2004, 568
[149] De Montgolfier et al 2002, 668
[150] Wertz 1999, 58

suggest that patients usually lose sight rapidly of the information given in the consent process.[151] Wendler et al, for instance, found in their survey of 130 participants of longitudinal studies, that a lot of information was forgotten after consent was given.[152] Similarly, a recent survey of 1200 tissue donors in Sweden shows that 37 per cent of participants could not remember whether they had received any information at all.[153] In addition, a number of empirical studies demonstrate that the information given to patients usually is not easy to read. Patient information is written in many cases at a reading level appropriate for college graduates.[154] Hence, a lot of patients (with no college degree) are supposed to often have problems understanding patient information and consent forms. Presumably, decisions are, for the most part, based on the oral explanations of the physicians – and therefore, highly dependent on the quality of the physician-patient-relationship.

95 Understanding informed consent as an ongoing process is seen as a possibility to reduce the loss of information as well as the lack of understanding. If participants have the opportunity to ask again and get information repeatedly, the problem might ease. Furthermore, as Gotay points out, "novel attempts to make the informed consent process more interactive (e.g. use of new technologies such as videodisks) may result in important information being retained longer".[155] However, since these proposals refer to trials with healthy volunteers, it remains debatable whether the approach would be efficient in clinical trials with patients. As discussed above, in clinical research consent procedures generally have the potential to overstrain patients, in particular if severely ill patients have to understand complex information in critical situations. As Bernstein summarises, "patients who have just been told they have a devastating condition (…) can hardly be expected to be in a psychological state of mind compatible with understanding all of the additional information the clinician investigator is about to tell them concerning a clinical trial".[156] Although his paper deals with informed consent in clinical trials in surgery, his conclusion can be referred to the situation of severely ill patients in general: "Given all the forces at play, some obvious and some not, it is exceedingly difficult to achieve full disclosure to surgical trial subjects, to ensure they are at full capacity to comprehend all the material important information, and to obtain a state of complete and unconditional voluntariness. It must simply be accepted that fully informed consent is rare and generally unattainable in most surgical clinical trials."[157]

96 To cope with this inconsistency, some authors entirely waive the demand for complete and comprehensive information. They rather address the criterion of appropriateness. For Hansson et al, for example, the content of information given depends on its relevance for the decision: "If the information covers all issues that are relevant for a person's choice, then that person's consent is appropriately

[151] Hoeyer et al 2005; Dawson and Spencer 2005; Wendler et al 2002a
[152] Wendler et al 2002a
[153] Hoeyer et al 2005
[154] Grossman et al 1994; Maede and Howser 1992; Tarnowski et al 1990, see also Agard et al 2001; Yuval et al 2000
[155] Gotay 2001, 1099
[156] Bernstein 2005, 271
[157] Ibid, 272

informed."[158] However, the authors do not explain how to assess in clinical practice the relevance of particular information for patients' decisions. They only mention several studies assuming that "general information on these studies might be sufficient for the donor of the sample to make an informed decision."[159] More generally, they believe that quality and content of information depend on the nature of research and the level of risk. "When there are more risks and high risks, information must be more detailed and the consent procedure more strict. For research that involves less risk for research participants, less strict information and consent procedures are appropriate."[160] Again, practical aspects of that approach, for example, the question of who defines, under what conditions, the levels of risk, remain open to discussion.

However, in this context it is crucial to refer to possible paternalistic attitudes and **97** their influence on the provision of information. Concerning the doctor-patient-relationship, Satin emphasises that consent might be given by patients as "an expression of blind faith in their physician's recommendations".[161] Similarly, Jepson et al see the danger of an "informed *compliance* rather than an informed *choice*".[162] The authors underline that the "provision of information may not be value free and may be used to direct choice".[163]

This point of view is supported by empirical findings. In the survey conducted by **98** Bevan et al 38 percent of patients who had consented to participate in clinical trials stated that their motivation was to comply with the doctors' request.[164] Interpreting her findings of a qualitative study on participants of clinical drug trials, Corrigan states that patients are looking for advice about the best treatment option and trying to get reassurance about their condition from the doctor.[165] "In such a context, the request to consent can be interpreted as guidance to consent."[166] She underlines that the current model of informed consent calls for an equitable doctor-patient-relationship based on mutual participation, but this is very seldom found in practice. Contrarily, "patients and doctors bring pre-existing norms and values to the clinical trial setting that shape their expectations and direct their behaviour".[167] Corrigan concludes that there is a need for more socially nuanced concepts of freedom, autonomy and consent, and sees "a necessity to open up the debate about consent beyond the current polar opposition of autonomous decision-making and autocratic paternalism".[168]

2.2.2.3. Issues to be consented to

Informed consent procedures consist of several steps. The first is to ask the **99** potential donor for participation and to provide him/her with information; the last is to receive the signed consent form. In most cases, patient information is provided in a written form. This information is distinct from the consent form, which has to

[158] Hansson et al 2006, 266; see also Jepson et al 2005
[159] Hansson et al 2006, 266
[160] Ibid
[161] Satin 2005, 293
[162] Jepson et al 2005, 193
[163] Ibid
[164] Bevan et al 1993
[165] Corrigan 2003
[166] Ibid, 782
[167] Ibid, 780
[168] Ibid, 771 f

be signed by the patient, the donor or the parent respectively. Patient information and consent forms for tissue-based research have to include general requirements that are always part of the patient information. However, to collect, store, and process data from tissue-based research, further considerations beyond the ones relevant for clinical trials have to be taken into account, in order to protect personal rights and to guarantee confidentiality appropriately.

100 **2.2.2.3.1. General requirements.** Some issues can be regarded as standards of informed consent because they are widely accepted and always part of the patient information. These issues require consent and have to be mentioned and explained to the potential donor. Although most of the following points have been discussed already in more detail, they are listed here to give a brief summary:

- The patient information has to include details of the main intentions of the tissue collection and the range of uses of data as well as the time frame of their storage.
- As far as interventions are necessary in order to obtain blood or tissue samples, it is important to provide the participant with information about the possible risks regarding such interventions.
- Potential participants have to be informed about measures taken to protect their personal rights and to guarantee confidentiality. Duties to disclose information to third parties (as insurers or public authorities) have to be explained. Institutions or other third parties that might have access to data have to be mentioned, as well as the extent of the access.
- Potential participants have to be informed about their legal rights to withdraw consent at any time and to access stored personal data.[169]

101 **2.2.2.3.2. Sharing data and information.** Biomedical research is increasingly realised on a global level, but is at the same time subject to a variety of local and national – in part conflicting – regulations. The lack of clearly established international frameworks for the protection of security, privacy, and confidentiality of tissue and data collections is intensely discussed by Reymond et al.[170] They conclude that consent to sample sharing might resolve the conflict of responsibility in regard to legal regulations.[171]

102 In addition to this practical argument, the need for consent to share data and information is stressed by a variety of authors referring to personal rights such as privacy and self-determination.[172] Following Alston, a "baseline privacy protection" requires an explanation of foreseeable or planned transfers of data to other institutions or organisations.[173] Clayton et al demand that consent for future research should include the possibility for potential tissue donors to select between different options concerning data sharing: They should be able to determine whether data will be shared with other researchers or not and, if affirmed, whether it may be shared with researchers inside or outside the institution that removes the sample.[174] The proposal corresponds with findings of a survey in the US enrolled by

[169] Knoppers et al 2006; Fernandez 2003 a; Merz et al 1997; Pelias 2004. The issue of feedback is discussed in detail in section 2.3/The right to know, the duty to inform, and the quality of feedback.

[170] Raymond et al 2002; for the European level see EU 2001, 2004.

[171] Reymond et al 2002, 264; they especially refer to the problem of intellectual property rights, which are regularly defined by national laws.

[172] Merz et al 1997; Wertz 1999; Ashcroft 2000; Reymond et al 2002

[173] Alston 2005, 439

[174] Clayton et al 1995, 1794

Pentz et al: Patients' willingness to donate their sample is slightly affected by the location where future research might occur. While a big majority broadly consents to the local use of their sample for research purposes, the consent is less likely to the use in the wider US, and least likely to the use in Europe.[175] However, conclusions concerning the scope of consent to data sharing in European research institutions can hardly be drawn from this study as long as patients' attitudes towards data sharing have not been studied yet in the context of the European health care systems.

2.2.2.3.3. Re-contact. Connected to the issue of data sharing, the problem of re-contact has been discussed in the context of tissue-based research. Authors suggest addressing this topic always in the initial consent form, and not only in the context of tiered consent models.[176] Most of them agree that the issue has to be mentioned at least if the need for re-contact is foreseeable. "Circumstances under which this will and will not occur should be carefully delineated at the time consent for the use of the samples is obtained", say for example Clayton et al.[177] This concern is stressed, because research subjects must be provided with the opportunity to refuse re-contact. Furthermore, consent for re-contact is needed in order to open the possibility to feed back individual research results to patients. Therefore, the question of re-contact should usually be part of the consent form.[178] 103

2.2.2.3.4. Commercial interests. It is supposed that the economic potential of research involving tissue samples has at least some implications for the consent procedure. Ashcroft even considers the issue so important, that he suggests separating consent for research purposes from consent for commercial use.[179] Since usually commercial uses can hardly be put in concrete terms at the moment the tissue is removed, this proposal makes little sense. However, quite a few authors underline that potential donors have to be provided with information about possible commercial interests.[180] Reymond et al, for instance, recommend that the issues of validation and patenting should be solved within the framework of the informed consent.[181] They emphasise the fact that "the subject – as provider of raw material – is the only member of the value chain who acts on an altruistic basis". 104

On the other hand, Reymond et al underline that the "transaction value" of the particular sample "that would have been trashed anyway" is considered – at least in Europe – as minimal".[182] Generally, in current biomedical research the limits between economic and medical interests are becoming increasingly blurred. Furthermore, the way a particular sample contributes to a publication, a patent, or a product, can hardly be assessed. Hence, it is logically consistent that Reymond et al propose to inform the subject that he or she will not participate in potential commercial benefits arising from the research projects in question. 105

[175] Pentz et al 2006, 736

[176] Reymond et al 2003; Merz et al 1997; in paragraph 2.2.2.1.3/Tiered consent, the issue is discussed in the context of tiered consent models.

[177] Clayton et al 1995, 1792

[178] Issues concerning the feedback of research results are discussed in section 2.3/The right to know, the duty to inform, and the quality of feedback.

[179] Ashcroft 2000, 410

[180] Clayton et al 1995; Reymond et al 2003

[181] Reymond et al 2003, 354

[182] Ibid

106 **2.2.2.3.5. The timeframe of consent.** Concerning future research involving tissue samples, the timeframe of consent is still an important issue in the bioethical debate. The question of how long a given consent might be considered as valid has been discussed controversially. Sass underlines, as far as genetic research is concerned, the "sheer limitlessness of information which can be gathered".[183] In addition, in genetic research the availability of research material is basically unlimited as well. Wertz recalls another aspect of timeframe: Researchers might move and research subjects may die.[184]

107 Nevertheless, only a few authors address the issue explicitly. Hansson et al state that, "consent should be regarded as valid until further notice".[185] Although recognising that, "it would be regrettable to destroy material as precious as DNA, which could be useful in the light of new discoveries in the future", De Montgolfier et al argue for a restricted timeframe of consent.[186] "It appears desirable to limit the period of commitment, given the changing and uncertain nature of the consequences of patient's choices."[187] The authors refer to a DNA-databank project of HIV-infected patients, where samples will be stored for ten years after the closure of the cohort. For an extension of the storage period, a new consent is required in this project; otherwise (if for any reasons consent is not accomplishable) the sample will be destroyed or completely anonymized. But information about timeframe cannot be regarded as standard of informed consent today in sample collection for biobank research.

2.2.2.4. The right to withdraw consent

108 The right to withdraw a given consent to research at any time is an inalienable right of individuals. Therefore, in bioethical discourse, the right to withdraw consent is evaluated as a fundamental right of research participants or tissue donors respectively.[188] Referring to the generally accepted prediction, Hansson et al state that, "there should be a realistic opportunity for withdrawal of consent for those who have donated identifiable samples and data".[189]

109 However, concerning tissue samples, the definition of what is meant by a right to withdrawal differs significantly in the discussion. Hansson et al, for example, propose that the withdrawal of consent should be tantamount to the termination of processing personal data. It "does not imply a right to withdraw results that have already accumulated, rather it implies that new data cannot be obtained and that existing data must be maintained in an impersonalised form".[190]

110 To respond to the withdrawal of consent merely with the anonymization of the respective sample and data is criticised by Eriksson and Helgesson. They state that donors who withdraw their consent to research expect that their sample will be destroyed and both, sample and data, not be used anymore for research. Thus, anonymization is "hardly satisfactory", regarding the concept of autonomy; "the

[183] Sass 1998, 290
[184] Wertz 1999, 55
[185] Hansson et al 2006, 269
[186] De Montgolfier et al 2002, 668
[187] Ibid
[188] See for example, Hansson et al 2006; O'Neill 2003
[189] Hansson et al 2006, 269
[190] Ibid

'anonymization tool' does not do much moral work", they conclude.[191] On the other hand Eriksson and Helgesson argue that research subjects who wish to withdraw their consent have to provide "valid reasons" for changing their mind.[192] According to this perspective, the moral obligation to participate in biomedical research should not at all result in "mandatory inclusions" of data or samples, but "no one should take withdrawal from biobank research lightly".[193] The decision whether the reasons to withdraw are sufficient should be made primarily by the researchers or biobank holders, the authors suggest. Concerns are supposed to be generally accepted if they are reasonable and not based on misconceptions.[194] However, this suggestion is inherently paternalistic and raises the question of how to assess reasonability of concerns.

Empirical findings show that participants are not very conscious about with- 111
drawal at all. Hoeyer et al, for example, published study findings showing that the majority of the 1200 tissue donors who participated in their survey either was not aware of the possibility to withdraw consent (55,7 per cent) or even did not realise having consented at all (12,7 per cent).[195] However, Eriksson and Helgesson pose some practical reasons for a review of participants' reasons to withdraw. This would permit to avoid misconceptions insofar as they could be identified and subsequently cleared up. Furthermore, Eriksson and Helgesson propose to invite participants to be part of the review process. Thereby, they can learn about different options, for example, anonymization, further research on existing identifiable material and/or data, or destruction of the sample.[196]

The majority of scholars involved in the debate on withdrawal in tissue-based 112
research demands respect for decisions made by tissue donors without reservation. Given that participation in research is a voluntary act, the right to refuse consent is, from this perspective, indispensable. "Research subjects' reasons not to want their biological materials or information used in a study may be plausible or implausible, reasonable or unreasonable, in the view of the investigators. Nevertheless, the long established ethical principle of personal self-determination demands that every research subject be given an opportunity to decline to participate in any research project."[197] Sade underlines that this principle is of critical importance: "[I]t should be sustained no matter how great the value (as perceived by the investigator or the research review committee) of the new knowledge [is] that might be obtained from such a study".[198]

2.3. The right to know, the duty to inform, and the quality of feedback

The research project ACGT focuses on clinico-genomic research in cancer. It 113
aims to identify genetic and other molecular components that are involved in cancer development and reaction to cancer treatment. Though genetic factors may

[191] Eriksson and Helgesson 2005, 1074
[192] Ibid, 1075
[193] Ibid, 1071
[194] Ibid
[195] Hoeyer et al 2005, 98
[196] Eriksson and Helgesson 2005, 1075
[197] Sade 2002, 1440
[198] Ibid

increase the probability of disease development or adverse drug reactions, they do not cause them in the narrow sense of the term. Since the influence of single risk factors is often small, large numbers of tissue samples and data have to be collected, stored and statistically analyzed. This general research condition determines and structures ethical considerations regarding the disclosure of data and information generated in research, since tissue donors may want to get access to data stored about him or her, general research findings, or research results that are of individual significance for him or her.

114 Important ethical questions that emerge from this research setting and which are not covered by specific legal provisions, yet have to be addressed, include the following: Under what circumstances are researchers required to actively give access to information? If at all, what kind of information do they have to feed back to patients or tissue donors respectively? In the following part of this chapter issues and arguments raised in bioethical discourse regarding these guiding questions will be identified, analyzed, and evaluated in their relevance for an ICT environment maintaining clinico-genomic research projects.

2.3.1. Access to personal information: a donor driven inquiry process

115 In the European context it is indisputable that everyone has the right to make inquiries about personal data that have been collected about him or her. Due to legal provisions, investigators are obliged to disclose such data on request. In detail, data subjects have the right to be provided on request with information (1) about personal data stored about him or her, (2) about the origin of these data, and (3) about institutions or persons who have access to these data. Such claims can be made against any data processing body involved. Therefore, suitable mechanisms for granting access to personal stored data are required.

116 However, the legal duty to inform data subjects about stored personal data on request does not imply that they actually do understand what the data mean. Data are not the same as information, because information additionally includes contextual information, which provides raw data with meaning: "Data is said to denote signs, patterns, characters or symbols which potentially represent some thing (a process or object) from the 'real world' and, through that representation, may communicate information about that thing. The 'information' as such denotes the semantic content of the data communicated to a person."[199]

117 Especially in the context of biomedical research, the question arises whether researchers have to provide donors not only with raw data, but also with contextual information, since patients or tissue donors are usually not able to interpret genetic, molecular, or clinical data. Although such a duty is not codified in existing legal guidelines, it can very well be justified by the ethical principle of respect for the tissue donor because of the voluntariness, which guides the tissue donation. Thus, it may be postulated, at least for the clinical context, that investigators or research sponsors respectively, are morally obliged to support patients in interpreting raw data if they are asked. Such moral obligation could also be justified by the doctor-patient-relationship and by the principle of doing no harm. Since misinterpretation and misunderstanding might produce psychological distress, it may be an ethical

[199] Bygrave 2003, 2

obligation to give context information and to explain the importance and relevance of disclosed data to tissue donors to prevent harm.

2.3.2. Feedback of research results: an investigator driven disclosure process

Clearly different from a donor-driven inquiry process is a process that can be called an individual feedback process. In this case, the process of donor information is initiated by the researchers. Here the question arises whether the decision to offer such a process is up to the researchers, or whether a legal or ethical obligation for such an offer exists. 118

According to a recently published analysis of eleven related legal and ethical documents from Europe, the US, and the international context, seven of these documents propose criteria concerning individual feedback.[200] Four of them refer explicitly to genetic research. The other four documents, which only partially overlap with the ones just mentioned, point out the right to know for study participants. Three documents finally recommend that donors should have the right to choose whether or not they want to know. In sum, Renegar et al conclude that, "there appears no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations in the US or the EU that research results have to be, in all circumstances, returned to study participants. However some guidelines advocate a proactive return of data in certain instances."[201] 119

Hence, according to currently available documents, researchers seem not to be legally obliged to offer individual feedback processes. In light of the possible importance and implications of this question for donors and researchers, it is debatable, however, whether and under what circumstances an *ethical* obligation exists to offer such a process. 120

It might be difficult to argue that a *general ethical obligation* exists to actively feedback research data to tissue donors. Nobody expects, for instance, the active feedback of traffic control video monitoring – these data are in most cases meaningless for the individual that might appear in one of those videos. A similar argument applies in the research context, when the implications of research data are not (yet) fully understood. 121

But when a research process yields clear findings being of actual or potential relevance for a person – e.g. his or her present or future health status – it is well possible to find valid arguments for a *specific ethical obligation* to feed back research results, especially when a tissue donor or patient explicitly stated his/her interest in participating in such a feedback process in advance. The ethical principle to be applied here is the principle of avoiding harm: If a research process either intentionally or accidentally yields information that helps to avoid sickness or adverse drugs reactions, then the research subject must be enabled to use this information. Nevertheless, providing research results to participants is not yet common practice. A survey of 197 investigators shows for instance, that most of them (69 %) support the practice of returning research findings to participants, but that only a minority (31 %) actually do so.[202] 122

[200] Renegar et al 2006
[201] Renegar et al 2006, 29
[202] Rigby and Fernandez 2005

2.3.2.1. Informing about general research results

123 To fully understand the ethical challenges within the donor driven inquiry process, it is necessary to differentiate between the disclosure of general research results, representing synthesized data and conclusions drawn from a group of research participants, and the disclosure of research results being immediately or potentially important for a single individual.

124 **2.3.2.1.1. Ethical foundations.** In ethical discourse, it is widely accepted that research participants should have access to general research results.[203] Furthermore, empirical studies have confirmed that participants are interested in and want to receive general research findings.[204] Therefore, general research results of clinical studies or tissue-based research should always be made publicly available. The right of research participants, and especially of tissue donors, to be informed about such results is based on various ethical arguments. Zlotnik et al, for instance, underline the fundamental role of tissue donors for research. "The material means research subjects provide are more intimate and certainly no less crucial than financial resources (…). The request for an account of the outcome of research is correspondingly stronger – not weaker – for those who provide these most personal material means for research."[205] Similarly, the American Society of Clinical Oncology (ASCO) underlines in its policy statement concerning genetic testing for cancer susceptibility, the special interest of tissue donors in the research results. "Respect for the persons who are the sources of biologic materials for DNA research and their families necessitates recognition that these individuals have an interest in the studies that are performed on their tissues, even when the acquisition of the tissue takes place outside of the research."[206]

125 In addition, investigators' obligation to disclose general research results to tissue donors is actively derived from the fiduciary character of the relationship between researcher and donor. "The donor's involvement into research is limited to give the researcher control over a tissue sample. The research subject generally possesses neither the expertise nor the opportunity to monitor and supervise the researcher and his or her use of that tissue sample."[207] Therefore, the disclosure of general research results has been pointed out as crucial to implement the principle of donor's autonomy. To accept donor's interest in research results "transcends the subject as a tissue or DNA donor and acknowledges the subject as an autonomous individual who may have ongoing interests in medical information that may be gleaned from his/her tissue donation in present as well as future research efforts."[208] Shalowitz and Miller resume that investigators' responsibilities to make aggregate research results available to participants is based on respect for participants' self-determination and recognition of their integral role in research.[209]

---

[203] See Knoppers et al 2006; Pelias 2004; Fernandez 2003 a; Shalowitz and Miller 2005; Partridge and Winer 2002

[204] Miller et al 2008 a; Fernandez et al 2007; Dixon-Woods et al 2006; Patridge et al 2003, 2005; Bunin et al 1996; Snowden et al 1998; Schulz et al 2003

[205] Zlotnik et al 2005, 5

[206] ASCO 2003, 2405

[207] Banks 2000, 578; see also Zlotnik et al 2005

[208] Pelias 2004, 4

[209] Shalowitz and Miller 2005, 738

By making research results available, investigators give account for their research activities. According to this perspective, the authors underline that the given information on study results builds up trust between researchers and donors. Shalowitz and Miller conclude that the disclosure of research results might improve the credibility of biomedical research in general. They emphasize that the provision of research results "will make the process of research more transparent and may increase participants' willingness to enrol, thereby facilitating future studies."[210] Similarly, Fernandez et al see "many tangible benefits to offering disclosure of research results to participants, both for individual participants and for the research as a whole."[211] 126

Consequently, there are some strong arguments for investigators' obligation to inform actively about general research results, or make them at least publicly available. According to the Helsinki Declaration, researchers as well as publishers are ethically obligated to publish research results. As outlined explicitly, the research results have to be publicly available regardless of their character. "In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available."[212] Above all, the publication of negative research results as falsifications of hypotheses, for instance, is ethically required to avoid unnecessary risks and harm. It has repeatedly been underlined that unpublished data can lead to additional, redundant trials being performed, and useless or even harmful procedures remaining in use.[213] However, negative research results are usually not published by researchers or sponsors, who finance the study. But in the last years several European institutions are engaged in establishing a study registry in order to overcome this problem.[214] 127

2.3.2.1.2. Practical challenges of feedback processes regarding general research results. Generally, research results are made publicly available in scientific publications. However, Knoppers et al reviewing international guidelines and regulations concerning the feedback of research results, clearly conclude that the traditional way of publishing research results in a scientific journal "is no longer ethically sufficient. The ethical principles of respect for the person, beneficence and justice obligate the researcher to offer results in a manner that is clear and understandable to the research participants."[215] The authors suggest that the communication with research participants may be a telephone call, personal letter, news bulletin, newspaper article, website or a similar form.[216] 128

Sufficient and adequate information about the character of results *before* tissue removal is regarded as an indispensable prerequisite for patients' decision concerning tissue donation. Merz et al argue that investigators "should anticipate what information will likely be generated in the research and what will be done with that information."[217] Similarly, Clayton et al underline that patients should 129

[210] Ibid, 740
[211] Fernandez et al 2003 a, 2908
[212] WMA 2008, paragraph 27
[213] Knoppers et al 2006, 1173; see also Fernandez et al 2003a
[214] Compare for instance, http://clinicaltrials.gov (accessed May 5, 2009)
[215] Knoppers et al 2006, 1173
[216] Knoppers et al (2006, 1173) refer to the draft of the European Federation of the International Epidemiology Association (2004) that recommends: "It is advisable to publish the main results in a form that reaches the participants of the study and other interested members of the community where the study took place."
[217] Merz et al 1997, 255

be informed about what kind of information they can expect being provided by the investigators.[218]

130 The majority of authors state that no further information is required as far as general research results are concerned. However, tissue donors should be informed about possibilities of being provided with information regarding general research results. Depending on the way that general research results are disseminated, it could be necessary to ask tissue donors for consent, especially if information is available by the website or leaflet respectively.

131 Another important issue is the time chosen for disclosure of general research results. In this context Zlotnik et al highlight scientists' interest in publishing research results for the scientific community.[219] Scientific publication procedures normally discourage communication of research results prior to formal publication. Conflicts may emerge between scientists' interests to fulfil editor guidelines of scientific journals or claims of research sponsors on the one hand, and the donors' right to be provided with information about general research results as an act of accountability on the other.[220] Knoppers et al resume that existing guidelines concerning feedback processes do not address the timeframe of communication.[221] If the issue is mentioned at all, it occurs in a generalised form. The Council of Europe guidelines regarding biomedical research, for instance, state that "conclusions of the research shall be made available to participants in reasonable time" after a study has been finished.[222] However, the term "reasonable" is not defined. As a possible compromise between conflicting interests, Fernandez et al suggest disclosing results at the time of abstract publication; "doing so also would help to avoid the perception that research participants are the last to be informed of the results."[223]

132 In summarizing empirical surveys on communicating research results, Shalowitz and Miller point out that a majority of investigators surveyed generally support communicating study research results to participants.[224] However, researchers identified cost and time involved in preparing lay summaries, as well as difficulty in contacting participants as major barriers to communicating aggregate results.

2.3.2.2. Information about individually relevant research results

133 If biomedical research yields results that are of indirect or direct diagnostic or therapeutic relevance for the tissue donor, more questions regarding the investigator driven disclosure process arise. In this situation it may be up to the researcher to initiate an individual feedback process. This process, by which donors are actively approached, will be discussed in more detail. The question is whether and how such a process should be implemented in the context of ICT-supported clinico-genomic trials.

---

[218] Clayton et al 1995, 1792

[219] Zlotnik et al 2005, 11

[220] The authors (2005, 11) refer in particular to the Ingelfinger Rule of the New England Journal of Medicine (1974) and the International Committee of Medical Journal Editors guidelines (2001).

[221] Knoppers et al 2006, 1174

[222] Council of Europe 2005, Article 28, "Availability of results", (1) and (2)

[223] Fernandez et al 2003 a, 2907

[224] Shalowitz and Miller 2008; see also Fernandez et al 2003 c; Partridge et al 2004; Rigby and Fernandez 2005

2.3.2.2.1. Ethical foundations. Basically, guidelines concerning the individual feedback process do not exist.[225] If at all, the issue has been mentioned in generalised form. For example, the UNESCO Declaration on Human Genetic Data does not differentiate between general and individually important research results as a basis to decide about the feedback of research results.[226] The guidelines of the Council for International Organisations of Medical Sciences (CIOMS) distinguish more precisely between "findings of the research in general" and "any finding" related to a "particular health status", at least as far as the wording is concerned.[227] The most detailed regulations regarding the feedback of biomedical research results have been made in the additional protocol to the Convention on Human Rights and Biomedicine, adopted in 2005 by the Council of Europe. The protocol distinguishes not only between "access to information relevant to the participant arising from the research and to its overall results",[228] but it also explicitly states a duty to offer "information of relevance to the current or future health or quality of life of research participants".[229] 134

Beyond these precautious formulations in guidelines, the right to be informed about research results of individual relevance is strengthened by ethical arguments. Generally, patients have a right to be informed of any known facts that concern their current health status. The Council of Europe states explicitly, for instance, that "[e]veryone is entitled to know any information collected about his or her health".[230] This right to know is based on the ethical principles of autonomy and self-determination. Individuals should be able to get all available information that is or may become important for personal decision-making regarding their health.[231] Hence, at least the physician, who carries on special responsibility towards his/her patients, has a moral obligation to provide them with all relevant information collected about her or him. 135

In the context of the physician-patient-relationship, another important ethical principle supports the necessity of feeding back individually relevant research results: the principle of doing no harm (nonmaleficience). Following this principle, clinicians are obliged to inform patients or tissue donors respectively, about individual research results if disclosure can prevent harm.[232] The ethical foundations of the duty to re-contact have been elaborated in the context of clinical care,[233] 136

[225] Fernandez 2003 a; Renegar et al 2006; Knoppers et al 2006

[226] See UNESCO 2003, Article 10, "The right to decide whether or not to be informed about research results"

[227] CIOMS 2002, Guideline 5, Article 7, "Obtaining informed consent: Essential information for prospective research subjects"

[228] Council of Europe 2005, Article 13, V

[229] Council of Europe 2005, Article 2, "Duty of care"

[230] Council of Europe 1997, 4, Article10.2

[231] Other authors do not argue with the principle of autonomy but with the principle of respect for participants to justify the right to be informed about individually relevant research results (Partidge and Winer 2002; Fernandez et al 2003 c; Shalowitz and Miller 2005). However, respect for participants does not justify an obligation for researchers to disclose individual research results, as Ossorio (2006, 24) outlines: Obligations based on respect for participants might be fulfilled by actions other than returning research results, such as conducting formal ceremonies; providing comprehensible information about general study findings; arranging access to better health care; or planning studies that address special concerns of participants to meet their interests (see also Miller et al 2008a).

[232] For further discussion of this principle see, for instance, Banks 2000

[233] See for example, Hunter et al 2001; Knoppers 2001

but the principles apply to researchers as well, who have a duty to maximize benefits and minimize harm.[234] Pelias points out that the meaning of preventing harm has changed in the context of modern biomedical research: "As the principle of personal autonomy has become entrenched in clinical medicine and biomedical research, the admonition to do no harm has acquired new meaning. What originally was the idea of doing nothing to cause a patient's condition to worsen has evolved to the idea of causing harm by failing to inform a patient or subject fully about treatment options or research expectations."[235] As Pelias argues, the extension of the principle of personal autonomy in regard to the researcher-patient-relationship has had further consequences: The relationship between researchers and their research subjects continued to follow the principles of beneficence.[236] Hence, the duty to feedback individual research results is not only founded on the principles of nonmaleficience and autonomy, but also on the principle of beneficence. *Ethically*, physicians as well as researchers are obliged to provide patients or research subjects respectively, with individually important information if this may benefit them.[237]

137 **2.3.2.2.2. What to feed back?** The underlying principle of beneficence does not answer the question of what qualifies information as being beneficial for research subjects and, therefore, what kind of results should be returned in an individual feedback process.

138 Crucial to this general discussion, is the actual or potential clinical relevance of such results. Conservative positions argue that only research results of proven clinical validity should be fed back to patients, because results with incomplete evidence may unsettle the patient.[238] One could also argue, however, that such weak evidence could be a starting point for more thorough investigations and therefore might be relevant for patients as well.[239] Other authors propose to feed back research results only if they have clinical relevance, *and* if effective therapies or strategies of prevention are available.[240] But withholding individual research results because of this constraint has been criticized as paternalistic.[241] Referring to the importance of the principle of autonomy, paternalism is valued as an "essentially discarded concept", that is an antiquated remnant of a medicine where patients were rather objects than subjects.[242]

139 Another position arguing for limiting the obligation of disclosure to clinically relevant results stressed that research fundamentally differs from medical treatment. Merz et al, for instance, emphasise that medical research in general "is performed

[234] Wade and Kalfoglou 2006, 26
[235] Pelias 2004, 4
[236] Ibid, 2
[237] See also Luttenberger et al 2006
[238] Smith 2000; Clayton and Ross 2006
[239] Manolio 2006
[240] Recommendations of the US-American National Bioethics Advisory Commission (NBAC 1999, 9, recommendation 14), for instance, are explicitly based on the "presumption that the disclosure of research results to subjects represents an exceptional circumstance." It should only occur when "the findings are scientifically valid and confirmed, the findings have significant implications for the subject's health concerns, *and* a course of action to ameliorate or treat these concerns is readily available".
[241] Banks 2000; Fernandez and Weijer 2006; Markman 2006
[242] Markman 2006, 1422

primarily to develop generalizable knowledge".[243] Referring to genetic research, Renegar et al underline that it is usually undertaken to benefit society, not individuals.[244] Consequently, individual benefits, rights, or demands have to step behind the societal benefit of generalized knowledge. In the context of tissue-based research, Kapp for example, defines as "the chief role" of tissue donors "to serve as sources of needed data. This is a different situation than ordinarily occurs in clinical medicine, in which diagnostic or therapeutic interventions are suggested or carried out solely to benefit the current patient."[245]

But the current patient or research subject respectively, always differs from the future one. There are some reasons based on experiences with medical research to prioritise the current patient compared to the future one. As Banks points out, "notwithstanding our obvious individual and social interests in medical research, however, there has been a remarkable reallocation of weight from the phantasmal future patient to present research subjects over the past several decades. In part, this reallocation of weight has been a consequence of revelations concerning military experiments conducted by the Nazis, the U.S. human radiation experiments, and North American medical studies such as Tuskegee".[246] In this context, Banks states that informed consent has turned into a mechanism by which researchers explicitly limit their responsibilities to their research subjects. Risks and benefits are usually disclosed and explained. However, the author underlines that after consent is obtained, "the ethical weight shifts back to the traditional darling of medical research – the phantasmal future patient".[247] 140

Following this argument, the claim to feed back individual research results only if they are clinically relevant, can hardly be based on the difference between research and treatment. But one exception does exist: Individual study findings in basic research seem to be not possible. As Knoppers et al underline, this is a contradiction in the wording. "Seemingly, returning individual basic research results is impossible and nonsensical as the very purpose of this type of research is not the production of individual but generalizable knowledge. Thus, in this context, the concept of individual research results is a scientific misnomer."[248] However, the authors do not discuss how to distinguish basic from applied research, an issue of growing importance in the context of pharmaco-genomic and -genetic research.[249] 141

Beside the rather normative provisions to deny the disclosure of individually important research results unless they are clinically valid and reliable pragmatic, arguments regarding the clinical quality and relevance of such results have been put forward. Merz et al call attention to the fact that, "not all scientists agree on the 142

[243] Merz et al 1997, 255. As Meltzer (2006, 29) highlights, this distinction between research and clinical care does not mean that participants in clinical trails gain no benefits from participation. Participants may, for example, receive better care or gain access to otherwise unaffordable medication.

[244] Renegar et al 2006, 35; for a discussion of particularities concerning genetic research results, see paragraph 2.3.2.2.3/Characteristics of genetic research results in the context of cancer trials

[245] Kapp 2006, 335

[246] Banks 2000, 548

[247] Ibid, 552

[248] Knoppers et al 2006, 1172

[249] Banks (2000, 578) indirectly gives a definition describing the only situation in which the non-disclosure of individual research results might be justified: "There may be circumstances in which either the research is so preliminary or the research process is so novel or potentially inaccurate that the results of the research may be of dubious significance except as basic science."

magnitude of the risks or on the suggested limits on uses of research data".[250] For them it makes no sense to disclose research results as long as their clinical relevance and their importance for the patient are under discussion, because interpretation of data may change in the course of the validation process. Furthermore, Renegar et al point out that information quality is related to the circumstances of its production. The clinical relevance of information is influenced by the conditions under which such information is generated and interpreted. "[T]he standards to which laboratories are held will vary depending upon applicable laws and regulations. These operating standards will affect the credibility of the results and thus the risks and benefits of returning research results. It is important to emphasize that the clinical quality assurance measures in place at a laboratory do not imply clinical relevance."[251]

143 Although these rather pragmatic objections have been made to support the position that clinical relevance is one important prerequisite for the disclosure of individually important study findings towards patients, they can serve equally as an argument for an obligation to feed back individual research results irrespective of their character. Given that operating standards and clinical quality assurance measures can differ, they automatically affect the credibility of the results and the risks and benefits of feedback. If various interpretations of results and their importance exist, it can be argued for the same reasons that the only practicable way to appropriate feedback would be to feed back any result that might be of individual relevance. Even results that are not finally validated can be beneficial for the patient, because they may be the starting point for more thorough medical examination of the individual.

144 In this context one could argue that it should solely be up to the research participant to decide whether he or she wants to be informed about findings concerning his or her individual physical constitution. To delegate the decision about feedback to research participants seems to be a realistic response to the unsolved dispute concerning the quality of information to be disclosed. As Banks somehow pragmatically concludes: "Deciding not to disclose would require a much more cautious assessment of the meaning and validity of research results and a much more careful assessment of the consequences of those results to research subjects than medical researchers are used to providing."[252] Similarly, Renegar et al emphasise that, by obligating the investigators to decide about disclosure, "the nature of the data (significance, newness) to be generated will need prior consideration".[253]

145 However, objections against the offer to disclose individual research results irrespective of their character usually refer to the aforementioned principle of doing no harm in the clinical context. But it is important to take into consideration that this principle has a dimension of liability, which is presumably important for feeding back research results irrespective of their clinical relevance.

---

[250] Merz et al 1997, 256; Moreover, for differences in interpreting the clinical importance of research findings see Renegar et al 2006.

[251] Renegar et al 2006, 32 f

[252] Banks 2000, 567

[253] Renegar et al 2006, 27; the authors refer to the legal situation in the US, where IC regulations obligate researchers to provide participants with "significant new findings", if they "may relate to the subject's willingness to continue participation."

Reymond et al, for instance, highlight in their paper concerning the feedback of research results in gene expression studies, that study findings might have direct influence on therapeutic or treatment decisions. If treatment fails, because it relies on false research results, these treatment decisions might result in liability proceedings in the future. Reymond et al conclude that, "the investigators should be aware that claims against them might be expressed by the patient – in the future but on a retrospective basis".[254] Notwithstanding, fears of costly liability proceedings do not justify violations of research participants' autonomy. Furthermore, Clayton et al emphasise that there is no "look-back liability".[255] If implications of research results stay unclear, or if effective interventions are not available, there will be no liability. Liability might rather occur, if results have not been disclosed. On the one hand, it might turn out that the witheld information will be relevant for decisions concerning therapy as well as personal planning. On the other hand, potential liability factors from the perspective of the researchers and study sponsors may arise. Renegar et al call attention to the absence of experience. They conclude, "whether the risk of liability proves to be a significant disincentive or whether this risk can be sufficiently managed are questions that will likely be answered only with more experience in providing research results to participants and observing how they are subsequently used".[256] **146**

In regard to the researcher-patient-relationship, Shalowitz and Miller highlight another important aspect. According to their critique, investigators become "gate-keepers of research information relating to participants instead of offering participants the opportunity to determine what research information about them they wish to know".[257] The argument entails an aspect crucial to the discussion about the quality of research results: Disclosure of individual research results has to be *offered* as an *option*. Advocates of limited feedback, as well as of unlimited feedback regarding individually important findings, underline that research participants should be provided with the *option* to be informed about individual research results.[258] In consequence the research subjects themselves decide whether or not they want to receive research results that may be of potential relevance for them. This requirement is based on the general principles of self-determination and autonomy that – as discussed above – currently govern biomedical research. Shalowitz and Miller add to this argumentation, that "the heart of the controversy surrounding disclosure of individual research results concerns the most appropriate manner of expressing respect for participants: limiting disclosure to those results that have established clinical utility vs. recognising a presumption that results should be made available to participants".[259] However, as we will see, investigators are not relieved from any responsibility concerning the quality and content of information given in an individual feedback process. **147**

[254] Reymond et al 2003, 353

[255] Clayton et al 1995

[256] Renegar et al 2006, 30

[257] Shalowitz and Miller 2005, 738; in the discussion of their paper, Shalowitz and Miller (2006, 37) emphasise the role of the tissue donor: "[I]nvestigators should not treat participants merely as patients by disclosing only clinically relevant information, because to do so would ignore their involvement as contributors to research."

[258] Regarding the first mentioned position, see Buchanan et al 2002, regarding the second mentioned position, see the Council of Europe 2005

[259] Shalowitz and Miller 2006, 37

148 Since the different positions discussed in this section are based on different emphases of patients' autonomy, the discussion is ongoing. The disclosure of study findings is, however, not an issue in today's clinical research practice.[260] At the same time, patients increasingly demand to get access to processed data. According to currently existing empirical studies, patients' interest in individual feedback is generally high.[261] An empirical survey of 500 US-study participants documents, for example, that the respondents want to know about individual study findings even if they are of no direct relevance for the study participants.[262]

149 **2.3.2.2.3. Characteristics of genetic research results in the context of cancer trials.** In the discourse on feedback of individually relevant research results, quite a few authors reflect on the particular character of genetic information. Analysing ethical guidelines in the UK, Europe and on an international level (UNESCO, WHO, CIOMS etc.); Knoppers et al generally conclude that an ethical duty to return individual genetic research results exists, which is "subject to the existence of proof of validity, significance and benefit".[263] This is especially applicable if data comprise not only preliminary research results, but relevant medical information such as validated genetic disease predispositions: "If others know about genetic predispositions, there are no economic or even legal grounds (for example patent protection, intellectual property right, personal rights of third parties) to exclude data subjects from that knowledge".[264] Miller et al point out that even aggregate genetic results may have highly individual implications. It is possible, for example, that participants interpret research findings linking visible phenotypic characteristics (e.g. sex, specific dysmorphology) to distinctive genetic features (e.g. the prevalence of specific mutations) as individually relevant.[265]

150 However, Renegar et al underline that genetic research results is a vast category of different kinds of information, ranging from validated and non validated, highly and poorly predictive, probabilistic and deterministic:[266] According to this definition, genetic research data are "by their very nature not individually identifiable, understandable or significant".[267] They are almost always characterised by a lack of independent replication and of established common interpretation among researchers and clinicians. Referring to a Canadian interview-study, Miller et al highlight implications of the disclosure of individual genetic research results for the relationship of research and clinical care.[268] Even though interviewed researchers felt duty bound to communicate the test results they perceived as clinically relevant, they were concerned about limitations inherent in the use of research results for the provision of clinical care. In research, the test quality of individual results generally is less important, and the accuracy and reliability of individual results produced in

[260] Fernandez et al 2003b

[261] Richards et al 2003; Hoeyer et al 2004; Ormond et al 2004; Dinnet et al 2006; Wendler and Pentz 2007; Moutel et al 2005

[262] Wendler and Emanuel 2002

[263] Knoppers et al 2006, 1170

[264] Weichert 2002, translated by Kollek

[265] Miller et al 2008 a; from this follows, according to the authors, that the distinction between aggregate and individual results becomes obsolete. They rather suggest differentiating between different types of information (population-salient versus individual-salient).

[266] Renegar et al 2006, 31

[267] Knoppers et al 2006, 1170

[268] Miller et al 2008b

the research lab might therefore be reduced. However, interviewed participants did not generally anticipate such limits. They generally expected to learn their research results. Indeed, some only took part in the research in order to get such information. Persons considering genetic testing often express a desire for 'certainty' about risk, prognosis, and impact of surveillance and treatments and frequently classify test results into a dichotomy of 'affected' or 'not affected'. As a consequence, disclosing genetic research results could generally mislead participants, in so far that they might overestimate the significance of the experimental test results or over generalize them.[269] As Renegar et al point out, even results that are widely recognised among geneticists do not necessarily lead to clear clinical interpretations or practical implementation for patients. They conclude that these characteristics entail a careful risk/benefit assessment for returning results to research subjects.[270]

151 This conclusion particularly applies to genetic research results of a predictive character. Results may generally range significantly in the precise degree to which they identify a characteristic. Taking into account the complexity of many genetic disorders, for instance, many genetic testing results may not be 100 % predictive, but rather partially predictive[271] – they are probabilistic in character. Discussing ethical issues concerning DNA-banking in the context of HIV-research, de Montgolfier et al stress that information about genetic predisposition has to be formulated in an exceedingly careful manner. They draw on the psychological challenge to give appropriate information in a counselling process, "calling into question the patient's pugnacity towards the disease, his or her compliance with preventive measures, and plans to procreate".[272]

152 In this context the American Society of Clinical Oncology (ASCO) states that tests for genetic variants that indicate a low or moderate risk for cancer susceptibility belong to clinical research, not treatment: "Genetic testing for these variants, including pharmacogenetic and pharmacogenomic testing, currently is in the realm of clinical research rather than standard clinical."[273] However, it remains doubtful to strictly differentiate, for example, between cancer studies analyzing gene association and gene expression, since gene expression studies might reveal data about genetic traits and predispositions as well. ASCO therefore underlines that, "it is important to recognize that the distinction between studies assessing somatic alterations in abnormal tissue and those evaluating germline genetic variations is somewhat artifactual".[274]

153 Apart from implications of predictive genetic information, another characteristic attribute of genetic research results is in the discussion. It is possible that a result that has no clear clinical benefit at the time of the research will turn out to be very

[269] Ibid; Ormond 2006, 31

[270] Renegar et al 2006, 31; a similar position was advocated for the first time by the WHO (2003, 14, recommendation 8) in its statement on genetic databases in 2003: Although genetic research data will usually remain of abstract significance, sometimes it might be valuable in the clinical setting. According to the WHO, some conditions should be met before disclosure: "(a) The data have been instrumental in identifying a clear clinical benefit to identifiable individuals; (b) the disclosure of the data to the relevant individuals will avert or minimise significant harm to those individuals; (c) there is no indication that the individuals in question would prefer not to know."

[271] Klitzmann 2006, 35

[272] De Montgolfier et al 2002, 668

[273] ASCO 2003, 2399

[274] Ibid, 2405

important to the participant at a later time.[275] This possibility is underlined as the very nature of genetic research results. In conclusion, the high uncertainties in the interpretation of genetic data define the preliminary character of decisions about their individual relevance categorically. As Renegar et al put it, the feedback of genetic research results "can involve both risks and benefits for the participants, and these can be expected to change over time".[276]

154 Concerning gene expression studies on cancer, Reymond et al raise the question of whether the feedback of prognostic information is ethically justifiable, or even demanded. The authors call particular attention to the usually uncertain character of gene expression information in cancer trials. "It is usually difficult or even impossible for the investigators to recognise in an early phase the future significance of novel research results."[277] Beyond the problem of liability mentioned above, the authors highlight that information given at an early stage can provoke fear and anger due to its preliminary character. To protect the patient *and* the researcher, the authors recommend that any prospective gene expression study should define clearly that prospective study results would have no influence on diagnosis or therapy of the individual study participant.[278]

155 But as Markman illustrates, clinical research on cancer might yield, nevertheless, results of prognostic significance. In this context, the fear of harming patients by providing them with such uncertain results can increase paternalistic attitudes of physicians and lead to insufficient appraisal of patients' autonomy. Since patients could be harmed by being excluded from individual information, such a paternalistic approach does not satisfy the ethical requirement of nonmaleficience. Rather, it should be analyzed, whether patient's participation would be more satisfying in the decision-making about which data should be fed back. Since empirical data is limited, attitudes of cancer patients towards feedback processes of data should be further examined.[279]

156 Currently, only surveys regarding patients' general perspective on prognostic information about cancer are available. They have shown that even test results about disease predisposition – e.g. genetic testing of BRCA1 or BRCA2 mutations – are strongly requested by study participants.[280] Although focusing on general clinical practice without explicitly relating to research settings, the recent Japanese survey of Miyata et al is interesting. The authors analyse answers of 246 participants regarding their attitudes towards diagnostic and prognostic information.[281] Con-

[275] Knoppers et al 2006, 1174; see also Renegar et al 2006; Reymond et al 2003; Banks 2000

[276] Renegar et al 2006, 30; additionally, Renegar et al (2006, 32 f) stress the influence of conditions under which information is generated and interpreted. They especially refer to operating standards in laboratories and their relevance for the credibility of the results and thus the risks and benefits of returning research results.

[277] Reymond et al 2003, 353

[278] Ibid

[279] Referring to the US, Markman (2006, 1421 f) highlights that, "limited existing data in the oncology literature appear to support the conclusion that the majority of cancer patients who become research participants would like to be given information about the trial when it is completed". Similarly, Fernandez et al (2006, 141) point out that, "subjects are increasingly vocal in expressing a right to see the information they helped to generate".

[280] Bottorff et al 2002; Jacobsen et al 1997; Ludman et al 1999; O'Neill et al 2007; Struewing et al 1995

[281] Miyata et al (2004, 5) outline that, "characteristics of the respondents may not be wholly representative of the general population". The survey was undertaken in an urban area of Japan;

cerning prognosis, the participants of the survey had to choose between the following options: non-disclosure, disclosure of general nature but not in detail, postponed full-disclosure, and immediate full-disclosure.[282] Miyata et al gather from their data that providing general information on prognosis can satisfy the majority of patients. They conclude that, "any disclosure policy should also try to acknowledge and meet patients' wishes of being informed together with their families and of being given information at a later time".[283]

2.3.2.2.4. To whom to feed back? Not only cancer studies, but also tissue-based research in general, may reveal data on germ line mutations that are of predictive nature for future diseases. For this reason, rights and interests of other family members concerning the disclosure of information have ethically to be considered as well. 157

As far as research involving human DNA is concerned, genetic information "is not only an individual, but also a family affair".[284] The familial dimension of genetic information has even provoked questions regarding privacy. It has been argued that genetic information cannot – by its very nature – be private. From this point of view, it is therefore not necessary to apply the usual professional codes of respect for confidentiality to genetic research results. In contrast to this, "a case can also be made for genetic information being regarded as the most private information of all", as Clarke et al argue.[285] 158

Hence, it is not surprising that the discussion on rights and interests of family members concerning feedback processes is controversial. In the core of the dissent is the intrinsic character of autonomy. Crucial to personal autonomy is – inter alia – a right *not* to know. From this follows that patients or research subjects respectively, have the right to decide whether or not they want to be provided with information concerning their current or future health status. If a subject refuses to be informed with predictive genetic information, his/her right of autonomy might conflict with the interests of genetic family members who want to know. 159

According to the dominant view in literature, individual rights generally outweigh those of relatives. But concerning the family's interests, a momentous exemption has been made. It is widely accepted that only the person who undergoes a procedure that yields personal genetic information of predictive character, has to decide how to deal with the generated information and whether or not to communicate it to relatives potentially at risk. Nevertheless, under certain circumstances third parties might be granted a right to access personal information, even in absence of research subjects' consent, as stated in various ethical guidelines and statements. "Where there is a high risk of having or transmitting a serious disorder and prevention or treatment is available, immediate relatives should have access to stored DNA for the purpose of learning their own status", states the Ethics Committee of the Human Genome Organization (HUGO).[286] Similarly, the WHO recommends allowing disclosure of the data as far as it "will avert or minimise 160

cultural differences, for example, may be supposed, so that answers of people in Europe would potentially differ from those collected in the survey.

[282] Miyata et al 2004, 2

[283] Ibid, 5

[284] Andorno 2004, 437

[285] Clarke et al 2005, 561; see also Andorno 2004

[286] HUGO Ethics Committee 1998, 2

significant harm".[287] Here, the scope is even broader, since the text refers to "relevant individuals" and "third parties", and, therefore, not only to close family members.[288]

161 For physicians or health care providers in general, such exemptions may lead – at least hypothetically – to a conflict between their responsibility to avoid harm on the one hand, and their ethically founded duty to respect individual rights of self-determination and confidentiality on the other hand. The problem is that it is not clear what the term 'significant harm' really means.[289] Parker and Lucassen point out that significant or serious harm is always open to interpretation. The authors conclude that, "the question of what constitutes 'serious' harm is likely to be an ethical question of continuing practical importance in clinical practice".[290]

162 Another starting point for the ethical debate concerning the balance between individual autonomy and informational interests of relatives is the right to know. It is reasonable to assume that family members have a right to know if genetic information reveals serious risks for themselves. This would open to them the option to change their life plans, or eventually prevent or treat diseases.[291] This matter of fact can motivate relatives to ask for access to personal genetic information. However, it can also be argued that, because of the right to know, relatives have the right to not be confronted with any information they probably do not want to know.[292]

163 According to the ongoing ethical debate, it can be stated that physicians are not obliged to provide family members with personal genetic information of their patient, regardless of whether or not the affected patient has given consent.[293] It has been argued that such a breach of confidentiality "may also compromise the autonomy of the patient's relatives, who may desire not to know genetic risks within family".[294]

164 De Montgolfier et al discuss the problem of confidentiality connected to predictive genetic information by referring to the very special case of HIV-infected patients. On the one hand, there are various reasons for patients to deny consent to disclose individual genetic research results towards relatives: Relationships to family members may be disturbed or patients may feel guilty or ashamed. On the other hand, the identification of, for example, "a predictive pharmaco-genetic factor may have consequences for other members of the family, taking the same drugs, or other

---

[287] WHO 2003, 14, Rec 8 (b)

[288] WHO 2003, 13, Article 4.3; smilarly, the US-Common Rule notes that other persons' and common interests justify a breach of individuals' right to confidentiality as an exception. Referring to these wordings, Andorno briefly discusses the relation between the individuals' right not to know and public health interests. For a discussion on ethical guidelines, see Andorno 2004, 437; see also Lehmann et al 2000

[289] According to Andorno (2004), for instance, the risk of serious harm implies the availability of preventive or therapeutic measures.

[290] Parker and Lucassen 2003, 71

[291] Andorno 2004

[292] Data Protection Working Party 2004, 8

[293] Lehmann et al 2000; Clayton 1998

[294] ASCO 2003, 2403; in its Declaration on Human Genetic Data, the UNESCO (2003, 43, Article 10) even recommends "the right not to be informed should be extended to identify relatives who may be affected by the results". However, it has consistently been asked how patients' relatives can exercise this right, "if they probably even ignore that a family member has been tested" (Andorno 2004, 438).

drugs, prescribed for a completely different disease but acting on the same metabolic pathways".[295] The authors conclude that the decision to share information should be left to the patient after he/she has been correctly informed by the physician about the interest of sharing information with relatives.[296] Similarly, the American Society of Clinical Oncology (ASCO) presumes that, "the cancer care provider's obligations (if any) to at-risk relatives are best fulfilled by communication of familial risk to the person undergoing testing, emphasizing the importance of sharing this information with family members so that they may also benefit".[297]

However, the ASCO's recommendation grounds on the current state of genetic 165
research on cancer. Since the disease probability, medical benefits associated with cancer, and genetic testing are still being defined, relatives are not supposed to be harmed seriously by non-disclosure.[298] Contrarily, it seems more likely to increase emotional and psychological distress of healthy family members by providing them with genetic information concerning cancer predisposition. As already mentioned, only some genetic variants in cancer signify a moderate or high risk. Therefore, information about genetic predisposition in cancer is – in most cases – only moderately predictive and measures of prevention are rare or do simply not exist. Thus, it remains questionable, "whether the added information balances the risk of increased familial anxiety that may result".[299]

The few existing empirical data on this issue suggests that patients do not accept 166
disclosure of their data to relatives without consent. Similarly, studies of physicians' beliefs about the confidentiality of genetic information have shown that only a minority (>35 %) of physicians would disclose genetic information to at-risk family members against a patient's wish.[300] Patients do want to authorize the dissemination of their personal medical information by themselves and feel, at the same time, morally obliged to inform family members concerned, especially when the disease is preventable.[301] Although barely available, empirical data also suggest that the issue of familial anxiety is very important for attitudes towards the disclosure of genetic information within the family. Clarke et al, for example, recorded in their empirical study, experiences of genetic counsellors and clinical geneticists with nondisclosure in families.[302] Most frequently, individuals explained their decision to withhold predictive genetic information with the desire to avoid causing anxiety.[303] The authors conclude, in cancer families "affected individuals may be reluctant to raise anxieties in their healthy relatives in the absence of a clear practical benefit".[304]

[295] De Montgolfier et al 2002, 670
[296] Ibid
[297] ASCO 2003, 2403
[298] Ibid
[299] Burke and Diekema (2006, 36) refer to the concern unique to genetic research involving children: As a consequence of knowing their child carries a genetic trait associated with a certain condition, parents may treat their children differently, for example, by 'medicalising' their child's life and becoming overprotective.
[300] Geller et al 1993; Wertz et al 1990
[301] Knoppers et al 2006; Plantinga et al 2003; Lehmann et al 2000; Benkendorf et al 1997; Durfy et al 1999
[302] Clarke et al 2005; the survey was carried out in 14 regional genetic services, 12 in the UK and two in Australia. Interestingly, the 65 cases of non-disclosure represented less then one percent of all genetic clinical consultations during the ten-month study period.
[303] Clarke et al 2005, 559
[304] Ibid, 560

167 **2.3.2.2.5. Practical challenges of feedback processes regarding individual research results.** Whereas the provision of general study results, due to its impersonal character, may be just a matter of adequate announcement, the feedback of individually relevant research results depends on the donor's informed consent. In bioethical discourse, there is a broad agreement that it is the donor and not the researcher who decides whether or not he or she wants to receive individually relevant research results. If the issue is mentioned in ethical guidelines, the wording is unambiguous: Potential donors have to be informed about their rights within the consent process. "When human genetic data, human proteomic data or biological samples are collected for medical and scientific research purposes, the information provided at the time of consent should indicate that the person concerned has the right to decide whether or not to be informed of the results."[305]

168 Basically, a prior consent concerning individual research results is necessary to implement not only the right to know, but also the right *not* to know.[306] As the Council of Europe emphasises in its guidelines concerning biomedical research, the communication of individually relevant information yielded by a research project must take into account that confidentiality has to be protected and that any wish of a participant not to receive such information has to be respected as well.[307] Similarly, Knoppers et al point out that the implementation of the right not to know depends on the informed consent process.[308] Therefore, the question regarding feedback of individual research results needs to be discussed before the research even begins. At that time, the participant can exercise a choice concerning possible future communication of research results. Especially in the context of genetic research, consent has to be obtained at the very beginning to permit donors "to exercise a right not to know about genetic risks or predisposition to disease".[309]

169 Referring to the ethical principle of respect for patients' autonomy, several authors argue that donors should decide not only if they want to receive research results. "The prudent approach is to allow the research subject to elect what kind of information he or she wishes to receive, if at all."[310] As far as genetic research is concerned, Sass similarly argues that, "health literate individuals will have to make autonomous choices about how they want to deal with the wealth of new genetic information".[311] Regarding the feedback of individual genetic research results, he suggests to supersede the current consent doctrine by a contract model to give patients individual options to choose (a) for mandating disclosure of individual

[305] UNESCO 2003, 43, Article 10, "The right to decide whether or not to be informed about research results"

[306] Andorno 2004; Reymond et al 2003; Fernandez 2003 a; De Montgolfier et al 2002; after a controversial discussion in the 1990 s, nowadays it is widely accepted in the context of genetic research and diagnosis, that the right not to know is regarded as an expression of autonomy. Neglecting this issue may otherwise impose an ethical duty on participants to receive research results (Ravitsky and Wilfond 2006; Pullman and Hodgkinson 2006).

[307] Council of Europe 2005, Article 27, "Duty of care"; in article 10 of the European Convention on Human Rights and Biomedicine (Council of Europe 1997, 4, Art.10.2), the right to be informed about "any information collected about his or her health" is accompanied by the clear statement that, "wishes of individuals not to be so informed shall be observed".

[308] Knoppers et al 2006, 1173

[309] Merz et al 1997, 254

[310] Banks 2000, 580

[311] Sass 1998, 292

predictive, preventive, or therapeutic knowledge, (b) for refusal of all or some information, and (c) for postponing such a decision based on then existing individual circumstances or clinical results.[312]

In any case – whether participants generally consent to feedback or whether they consent to different levels of information – a number of scholars postulate that the consent given before the removal of tissue is only a preliminary one. For this reason, it has been proposed that feedback of individually important research results should be organized as a tiered decision-making process. The first decision is supposed to be before the study begins. After being informed about the objectives and procedures of the study, participants or tissue donors respectively, are asked if they want to get feedback of individually important research results at all. The second step of the decision-making process is supposed to be at the moment when research results are available, which may be of relevance for specific individuals or groups of participants. At this point, donors who agreed on an individual feed back process should be informed and asked, whether they want to receive concrete results that may be relevant for them. As Renegar et al highlight, such a "two-step-process for documenting the subject's decision to receive (or not to receive) results takes into account participants may change their minds during the course of the study".[313] Ormond stresses, for instance, that participants are more likely to desire genetic test results hypothetically than actually.[314] 170

A tiered model of consent to feedback of genetic research findings meets not only the uncertainties in the interpretation of genetic research results. Another strong argument for a step-by-step-model arises from patients' perceptions and understandings of informed consent procedures. There is empirical evidence that research participants usually do not remember the content of information given in the consent process, or even do not recognise at all that they gave consent.[315] Wendler et al point out that the rapid oblivion of given information is a serious problem: "If subjects continue to forget the risks of disclosure (…) the provision of results could increase the risks of genetic research by increasing the information that subjects may disclose."[316] Therefore, if a second consent must be obtained at the time concrete genetic research results of individual importance have become available, an additional occasion to provide patients with information and counselling will arise. Besides, questions concerning the feedback of research results of importance for relatives should explicitly be addressed at that stage of the consent process as well. 171

Generally, information about the feedback process given before tissue removal has to take into account various aspects. First of all, information about study results has to occur in an understandable and comprehensive manner. Shalowitz and Miller point out, for example, that comprehensible results are important for participants to exercise their right to self-determination: At least if results "are to be meaningful and useful to participants' personal decision-making, they must be 172

[312] Ibid, 295

[313] Renegar et al 2006, 35

[314] Ormond 2006, 31

[315] For a detailed discussion of research participants' loss of information during the consent process and opportunities offered by ongoing communication and tiered consent models to response adequately to this challenge, see paragraph 2.2.2.2.2/The character of information given in the consent process.

[316] Wendler et al 2002, 261

disclosed in a manner that is as understandable as possible." Furthermore, information should be as specific as possible, especially when patients are invited to choose between different types of feedback regarding individual research results.[317] As Reymond et al state, referring to feedback processes within gene expression studies in the context of cancer trials, it has to be clearly addressed that results may be uncertain, that they might lack significance, or that they may even be falsified in the ongoing research process.[318] Authors also call attention to the fact that it is usually very difficult to evaluate the clinical value of genetic information.[319] They additionally mention that information about genetic predisposition can cause fear and that it has to be ensured that participants do not feel pressured to obtain results once, for example, a causal gene has been identified.[320] Altogether, the authors insist on *informed* consent to feed back genetic research results.

173 Referring to the ethical principle of doing no harm, Eriksson and Helgesson reflect on another important aspect of adequate information.[321] Since the consent to feedback can raise unrealistic expectations, patients have to be informed about the possibility that research results may *not* have any individual benefit or importance. Raising expectations and not fulfilling them is seen as psychological harm.[322] Indeed, empirical data have shown that research subjects often expect a certain benefit in participating and that they perceive clinical trials in the context of curing and therapy. Analysing interviews with participants of clinical drug trials, Corrigan, for instance, emphasises that all interviewed participants thought that the new drug on study "was likely to be an improvement on existing alternative drug treatment".[323] Similarly, a survey among 287 participants of cancer clinical trials in the US shows, for instance, "major deficiencies" in how the purpose of the trial are understood: Although many of the respondents declared that they were satisfied with the consent process and understood given information, just a few were aware "of non-standard treatment, the potential for incremental risk or discomfort, the unproven nature of treatment, and the uncertainty of benefits to self".[324] Thus, it seems very likely that participants expect benefit for themselves by participating in research.

174 As Kodish et al exemplify by the field of paediatric oncology, clinical investigators are exceptionally challenged, because they have to find a balance between their role as physicians and those as researchers.[325] The authors conducted interviews with clinicians or investigators respectively, in the context of clinical trials in children's cancer research. The big majority of them did not approach the interviewees neutrally, but had a clear intention in mind to get consent for participation in the trial.[326] Kodish et al, therefore, insist on the distinction between "therapeutic research" and "research with the prospect of direct benefit", because "the terms

[317] Options to be chosen could be: Feedback of results only, if they refer to prognostic information; feedback of results only, if they are predictive; feedback of results only, if prevention strategies already exist, etc.

[318] Reymond et al 2003 or Pelias 2004

[319] See for example, the 'result-evaluation approach' presented by Ravitsky and Wilfond 2006

[320] Ormond 2006, 31

[321] Eriksson and Helgesson 2005

[322] Ibid, 1072

[323] Corrigan 2003, 788

[324] Joffe et al 2001, 1775

[325] Kodish et al 1998

[326] Ibid, 2470, 2476

investigators use have a significant impact on their own approach to research recruitment, and on the informed consent process itself".[327] As Joffe at al conclude, "research ethics rest on the realisation that the goals of advancing science or treatment, however noble, could conflict with the interests of present patients".[328] Thus, to avoid that research is equated with medical treatment or understood as part of it, tissue donors should be provided with sufficient as well as with unbiased as possible information about the character of expected results.

175 Indeed, it is repeatedly underlined that informed consent procedures may overstrain patients. Hardly readable information, questions merely listed in consent forms, and the complex issue in general might challenge the ability of patients to comprehend, in particular if they have recently been confronted with the diagnosis of a severe illness such as cancer. In the context of genetic research, the complexity of information is a general problem, because genetic information is often not comprehensible by laypersons. In a recent qualitative study about attitudes of breast cancer patients towards tissue-based research participants expressed concerns that individual results might be too difficult to understand since they can only be expressed as risk estimates.[329] As Shalowitz and Miller conclude, it might be necessary to use "established counselling methods to communicate complicated or uncertain results".[330] In the counselling process, Ormond stresses that participants should, on the one hand, learn about the potential limits of the research results and, on the other hand, be encouraged to consider their own personal values in determining the risks and benefits of such information.[331]

176 Existing ethical guidelines refer to the issue only indirectly. The Council of Europe, for instance, recommends that "information of relevance to the current or future health *or* quality of life" should be communicated "within the framework of health care or counselling".[332] The American Society of Clinical Oncology (ASCO) mentions pre- and post-test counselling only in the specific context of genetic testing on cancer to discuss possible risks and benefits of cancer, early detection and prevention modalities.[333] Since genetic knowledge might simultaneously cause far-reaching social or psychological consequences, individual feedback processes should always be supplemented by medical consultation and genetic counselling.[334]

177 However, some intrinsic limits of genetic counselling have to be taken into account. As Van den Boer-van den Berg and Maat-Kievit state, "informing is not as value free as it sometimes seems to be, certainly not for the one who receives the information".[335] Referring to genetic counselling in the case of Huntington's disease, they make some general remarks concerning the counselling situation. "If a genetic counsellor thinks he/she ought to inform a couple of all findings, even if the findings are uninformative or difficult to interpret, he/she creates an environment in which decision 'to do' something with the test results seems wiser than 'to do nothing'."[336]

[327] Ibid, 2468
[328] Joffe et al 2001, 1776
[329] Kaphingst 2006, 396
[330] Shalowitz and Miller 2005, 739
[331] Ormond 2006, 31
[332] Council of Europe 2005, Article 27, "Duty of care"
[333] ASCO 2003, 2398
[334] Luttenberger et al 2006
[335] Van den Boer-van den Berg and Maat-Kievit 2001
[336] Ibid, 41

178 Merz et al approach this problem by arguing for counselling provided *before* generating and processing information. The "potential for use of research information in the clinical management of patients" requires the supply of "adequate counselling before developing information about the patients."[337] This argument is relevant in the context of genetic research. Here, the right to know, as well as the right *not* to know, require adequate counselling about the character of possible future research results. As Williams concludes, professional counselling before participation in genetic research could sometimes be necessary to ensure that the ramifications of participation in genetic research are properly disclosed and comprehended by the research participant.[338]

179 In the realm of informed consent concerning feedback of individually important research results, it is necessary to highlight some issues concerning data protection and personal rights. First of all, potential tissue donors have to be informed that the re-identifiability of their personal data is mandatory for individual feedback processes.[339] Therefore, an important prerequisite for such a feedback process is that genetic data are not anonymized, but pseudonymized. This means that generated data can be linked back to a specific person by specified procedures. In order to protect rights and interests of donors, the feedback process itself must be designed in a way that in the course of such a process, no unauthorized person gets access to information about the genetic constitution of a specific individual.

180 Interestingly, authors have not paid much attention to the question regarding *who* has to disclose research results towards patients. Referring to the ethical requirement to disclose individually relevant research results, Knoppers et al point out that, "only a few guidelines at the international level specify with whom this duty lies."[340] In most cases the patient-physician-relationship is supposed to be an adequate social basis for the disclosure of sensitive information.[341] It is also emphasised that physicians are better qualified than researchers, e.g. bench scientists, to translate research results to the participant.[342] In conclusion, physicians of donors' choice should be involved in the transfer of information to the patient.[343]

181 To avoid that unauthorised persons access stored personal data, de Montgolfier et al organize their DNA-bank in a way that "only the physician responsible for the patient has the key to make the connection between a result and a patient".[344] Luttenberger et al, who describe the process of pseudonymization in the case of a German biobank,[345] propose that the donor and his/her physician should get access to individual genetic data together only before the donor's physician has proved to be entitled to trigger the individual feedback process. Therefore, according to this

[337] Merz et al 1997, 254

[338] Williams 2001, 451

[339] The information that identifiers will not be removed totally has to be given as well, in regard to a donor's right to withdraw consent to the use of a tissue sample. See paragraph 2.2.2.4/The right to withdraw consent

[340] Knoppers et al 2006, 1175

[341] Andorno 2004

[342] Dressler and Juengst 2006, 19

[343] Knoppers et al 2006; Banks 2000

[344] De Montgolfier et al 2002, 669; the paper discusses issues of confidentiality, feedback and informed consent referring to a DNA-bank of HIV-patients in France.

[345] The case study is done in the context of Schering AG's GENOMatch Biobank (Luttenberger et al 2006).

model, neither party alone can see these data. Additionally, before individual data are forwarded to the physician of the requesting donor, the identity of the genetic data has been validated without connecting them to the personal data of the donor.

Another important issue that has to be addressed is financial supply to organize the feedback process. As de Montgolfier et al point out, the return of research results "also has financial aspects, which have not received much attention to date" and propose that, "a specific budget could be estimated at the beginning of a research project".[346] Fernandez et al call explicitly for adjusting the budget and duration of funding according to the required efforts of disclosure.[347] Another position argues that counselling, for instance, is not justifiable from an economic point of view. "Some object that the costs and burdens of disclosing study results to participants, including contacting participants and maintaining trained counsellors on staff, will tax already strained research budgets and make future studies more difficult."[348] Even patients occasionally express concerns regarding the research budget. In the aforementioned survey, examining the attitudes of breast cancer patients towards tissue-based biomedical research, some participants put on record that the feedback of individual research results could constitute a "logistical burden" for research projects.[349] Costs for counselling can, for instance, be very high, since genetic counselling can take months of intensive meetings and may involve other family members.[350] Hence, costs and therefore breadth of genetic counselling and disclosure have to be taken into consideration. Counselling may, for instance, be provided only when research results are available, or may be extended by additional counselling before the consent form is signed. Furthermore, the statement of costs should include costs arising from the dissemination of general research results, as for instance, printing costs for leaflets or salaries for web-based services. 182

Principally, it has to be taken into account that counselling and disclosure always require special expertise, because researchers are normally not trained in communication to the general public. They "need to be alert for the moment when dissemination requirements go beyond their own expertise", states Zlotnik et al and ask for the engagement of educational and communication experts who can responsibly popularise and contextualise results.[351] 183

2.4. Summary of consolidated ethical requirements

The research project ACGT aims to provide the cancer research community with an ICT infrastructure on a European level, able to integrate clinical, biomedical, and genomic information on cancer. In order to reach this goal, several preconditions have to be fulfilled beyond technical requirements. Firstly, patients affected by 184

[346] De Montgolfier et al 2002, 669

[347] To evaluate the requirements for disclosure, Fernandez et al (2004, 1418) propose the use of a hierarchy of studies, whereby studies are divided according to their therapeutic versus nontherapeutic intent and on a continuum from relatively low risk of participation to high risk; see also Shalowitz and Miller 2008

[348] Shalowitz and Miller 2005, 739 f; see also Banks 2000

[349] Kaphingst et al 2006, 396

[350] Klitzmann 2006, 35

[351] Zlotnik et al 2005, 11

cancer are needed to volunteer to take part in clinico-genomic trials. Secondly, genomic data of patients are needed in addition to socio-demographic and clinical data. Therefore, samples of tumour and blood have to be collected and analyzed from the involved patients.

185 The current ethical debate concerned with tissue-based research shows that new questions regarding the widely acknowledged doctrine of informed consent and the disclosure of research results arise. In the context of clinico-genomic research on cancer and its integration into an ICT-supported structure, these questions have to be addressed and analyzed in order to protect patients' right of autonomy and self-determination – the most basic principles to be respected in the context of medical research involving patients.

2.4.1. Ethical requirements

186 Summarizing the ethical discussions presented in this paper, it is obvious that ICT-supported clinico-genomic research has to take into account several ethical requirements. According to this demanding assignment, the major challenges are to design (1) the informed consent process, (2) the donor driven inquiry process, and (3) the investigator driven feedback process of individually important study findings.

2.4.1.1. Summary: The informed consent process

187 The doctrine of informed consent is one of the most well known elements of medical ethics and bioethics today. In ethical terms, the requirement for informed consent is based on the principles of respect for persons and respect for human dignity. Recognized as a condition *sine qua non* for any preventive, diagnostic or therapeutic medical intervention, the doctrine represents an essential ethical and legal requirement to protect patients' rights to integrity and self-determination.

188 In current clinical research, the doctrine of informed consent is widely accepted and practised. But with respect to tissue-based or biobank research, the discussion has changed remarkably. Doubts have been raised concerning the applicability of the doctrine in its current form. Some authors think that the established informed consent procedure is not sufficient to meet the challenges that arise from tissue-based research, especially the uncertainty concerning future research projects, as well as future outcomes. Questioning its applicability for tissue-based research in general, others want to see the consent procedure designed as a contract between researcher and donor. Finally, informed consent has been criticized as a mere ritual. Clinicians and researchers often consider the informed consent process as paperwork to be done, mainly for legal reasons. According to this reading, current informed consent procedures do not serve as an instrument to ensure patients' autonomy, but to avoid litigation and to solve questions of liability. However, despite such doubts, most scholars still maintain the informed consent as an instrument to implement the principle of autonomy. While this position is widely accepted, the debate on form and scope of consent in tissue-based research is highly controversial.

189 The discussion on different models of consent (see paragraph 2.2.2.1/Models of consent) has shown that one of the major challenges is the question regarding the possible future uses of donated tissue samples. The practice of obtaining consent for

unspecific future use of samples and data generated from clinical trials has been criticized as not being adequate for genetic research. But a convincing model of consent corresponding with patients' rights and, at the same time, enabling investigators to use tissue samples in the future for purposes not known at the time consent was sought and given, still has to be found. The *specified consent*, restricted to concrete research questions and projects, fails to meet the interests of tissue-based research; the *blanket consent*, allowing unlimited future research, fails to meet the general standards regarding the quality and content of information required by the current informed consent doctrine. Furthermore, blanket consent can hardly be regarded as legally sufficient for genetic and/or genomic research. *Tiered consent*, arranging different levels of authorisation in the consent procedure has been proposed as being able to provide an appropriate solution because it offers to donors the possibility to authorize a broader, or more restricted range of research to be done with their samples and data, and time frame they may be used for research. However, this model subdivides study subjects into different groups, which have to be treated differently. That is why it is difficult to handle in practice. Therefore, a model of consent referring to a *purpose of intermediate scope* (e.g. clinico-genomic research on cancer) in the *context of a specific structure or project* (e.g. ACGT) may be within the limits of ethical as well as legal considerations. This model also includes the necessity to ask for re-consent if the scope of consent (clinico-genomic research on cancer/ACGT project) will change.

Additionally, the informed consent process itself is questioned in whether it **190** should be understood as a one-time action or as an ongoing process. A number of well-founded arguments have been introduced into the debate to take consent as a process unfinished at the moment a tissue donor signs the consent form. Although some circumstances differ remarkable from tissue-based research with adults, research involving children illustrates that ongoing communication is not only necessary, at least as far as genetic research is concerned, but possible as well. It may be assumed that the interest in ongoing communication about research is related to the severity of the disease the patient is suffering from. Because of the lack of empirical evidence, it remains a point of discussion whether consent as a process generally strains patients. To provide patients continuously with information concerning the research process, or to keep communication going respectively, might be seen as an expression of respect as well. Thereby, ongoing communication might facilitate obtaining consent for research. Furthermore, re-consent is crucial in the feedback process.

Objections against consent as an ongoing process are mainly based on unfavour- **191** able experiences with re-consent made in the US-health care system. Data on patients' attitudes towards such a model from different countries is limited. Therefore, further investigation is needed in different cultural settings. The same is true for patients' apparent lack of interest in the question of consent. There is an urgent need to build an empirical basis for scholarly discussions, as well as for practical solutions concerning patients' attitudes towards different models of consent in tissue-based research in Europe.

As already mentioned, the communication and decision-making process con- **192** cerning research participation might distress patients with serious conditions in a way that they are unable to make an autonomous decision, or even to understand the information provided in the consent process. This matter of fact poses

particular challenges in the way information will be given to enable informed and conscious consents. In this context, the right to withdraw consent is in the focus of the discussion. Although it is desirable to clear up, or rather avoid misconceptions, it remains extremely questionable whether an obligation to present the reasons for the personal decision to withdraw given consent is an appropriate way to reach these goals. Additionally, respect for research subjects' autonomy and self-determination does not permit the leaving of individual decisions concerning research participation up to the judgement of second or third parties. As a consequence, donors must have the option to withdraw their consent without reasoning. Misconceptions about consent and withdrawal procedures must be avoided by appropriate information and communication.

2.4.1.2. Conclusions: How to design the informed consent process

193 Taking the fundamental concerns into account, clinico-genomic research supported by an ICT infrastructure should design the informed consent procedure by enhancing donors' autonomy as the main objective. With regard to the shortcomings of the specified, the blanket and the tiered consent models, the intermediate scope model seems to be the most appropriate solution to meet the complex challenges of donors' autonomy.

194 The intermediate scope model can be developed and tailored to the specific requirements of ICT-supported clinico-genomic research projects like ACGT. This would mean obtaining the general consent to participation together with the initial consent to feedback of research results, not later than data will be transferred to the infrastructure, and to ask again for re-consent when concrete study findings of potential individual relevance are available. Thereby, this consent procedure promotes an ongoing communication between clinician and patient over time.

195 Because of the projected Europe-wide cooperation within clinico-genomic research projects, it is furthermore indispensable to ask for permission for sharing data, information, and (potentially) tissue samples. To be clear and reliable about the scope of consent, the consent should be restricted to the ACGT-project only. Therefore, the timeframe and the group of researchers using data or samples respectively will be limited to the existence of the research project ACGT as well. Fundamentally, the informed consent process, including the patient information, has to be consistent with each clinical trial within ACGT.

196 The discussion on the character of information (see paragraph 2.2.2.2.2/The character of information) has shown that the patient can only make independent decisions with adequate information provided in the consent process. Referring to the principle of autonomy and respect for participants, authors regularly stress the importance of comprehensive and understandable information. However, in practice, this claim is faced by a number of obstacles. There is empirical evidence that patients usually lose sight rapidly of the information given in the consent process. Understanding informed consent as an ongoing process might reduce the loss of information as well as the lack of understanding.

197 The information and decision-making process concerning research participation might distress patients with serious conditions in a way that they are unable to make an autonomous decision, or even to understand the information. This matter of fact poses particular challenges on the way information will be provided to enable

informed and conscious consents. Regarding the presentation of information, the following aspects are important for possible donors to make their own decisions, whether or not they are willing to participate in clinico-genomic research:

Be informed clearly: The objectives, intention and range of research, as well as the specific characteristics of the research structure, have to be addressed and explained in a comprehensive and understandable way. Potential donors should be able to understand the kind of data that will be processed as well as the extent of projected data interchange. 198

Be aware of legal rights: Furthermore, potential donors should be aware of their legal rights concerning the withdrawal of consent at any time, as well as disclosure of stored data and information. In this context, it is indicated to explicitly refer to the general right to information based on the EU-directive of data protection. However, it is still open to discussion whether or not the right to access stored personal data also comprises the right to be informed about its relevance and importance. Thus, it is up to the research facility whether or not further information and explanation concerning stored personal data will be provided. From an ethical point of view, however, a mere disclosure of data without any explanation can hardly be assumed to be sufficient. 199

Be informed about consequences: As far as the decision about the feedback of individual research results is concerned, it is important that potential donors understand the possible consequences of the disclosure. As discussed in this paper (see in particular paragraph 2.3.2.2.5/To whom to feed back?), the decision to feed back individual research results must be made by the tissue donor, not the researcher or health care provider. Hence, information about possible consequences should be provided in a way that enables potential donors to decide whether or not they want to be informed about individually important research results. The question whether or not donors' relatives will be informed about study findings that may be of potential relevance for themselves has to be left to the donors' discretion. 200

Be aware of counselling: To meet the manifold information duties, it is advisable to offer adequate explanation and, if necessary, counselling within clinical trials before consent is obtained and during the whole research processes. Especially in the highly exploratory field of clinico-genomics, an extended need for explanation and counselling can be assumed. Hence, expertise for explanation and should be provided in the context of the clinical trials. 201

To facilitate potential donors' decision-making process regarding the participation in a research project such as ACGT, the patient information should consider at least the following aspects: 202

- Information about the main intentions of the project and the range of possible uses of samples and data
- Information about measures taken to protect donors' personal rights and to guarantee confidentiality
- Information concerning the right to withdraw consent at any time
- Information about donors' legal rights in regard to the disclosure of stored data and information
- Information concerning the feedback process of individual research results
- Contact information for donors to address inquiries
- Information about the timeframe of storage and consent

203 Beside the quality of information and its comprehensibility, it is indispensable to ensure that donors consent voluntarily and freely, which means without being constrained nor defrauded. Moreover, consent should be given explicitly. A pragmatic implementation of this demand is a written and signed consent form.

204 Obtaining informed consent is particularly challenging for research involving children. Depending on age, minors are either de facto or de jure not competent of giving consent. Therefore, consent must be obtained from the parents or legally authorized representatives respectively. But it is widely accepted, that children's assent is also necessary according to the minors' capacity. Therefore, minors as well as their parents have to be provided with information about the nature and course of the trial, the possible risks and benefits, and implications of participation. According to the minors' capacity of understanding, the information has to be formulated in a child-oriented manner. Nevertheless, the ethical debate (see paragraph 2.2.2.2.3/ Particularities of consent to research involving children) has shown that no consensus exists on how to appraise a child's capacity appropriately. The age recommended as level of attained maturity ranges from seven to 15 years. Nevertheless, psychologists after the Piaget-era assume that no clear defined stages of development exist. The child's development is rather seen as an ongoing process. Therefore, it finally remains to the discretion of the practitioner to assess the child's capacity to give assent.

205 Accordingly, it is recommended to give paediatric participants the option to re-consent when they become mature. In order that grown up participants can make their independent decisions, researchers have to provide them with sufficient information about storing procedures and confidentiality protections, including potential risks of storing and processing data in the future. Therefore, an ongoing communication with parents *and* children seems to be required to avoid coercion and involuntariness of minors.

206 Last but not least: Not only the donors, but also the users of the ICT infrastructure have to be informed about rules for informed consent and other ethical requirements before gaining access. Concerning, for example, the future of ACGT as a research structure involving several hospitals in Europe, users have to know what kind of limits the given informed consent puts on the use of samples and data. Furthermore, to achieve consistent ethical standards within an ICT structure, it is vital that investigators commit themselves as well. To participate in ACGT, for instance, hospitals and research institutions should declare in a written form that they will meet the requested standards of consent and information. Given the importance of ethical and legal aspects for the legitimacy of biomedical research, it is reasonable to demand a statement regarding practical details of how potentially participating institutions want to implement ethical standards required in the prospective research project.

2.4.1.3. Summary: Donor driven inquiry processes and investigator driven individual feedback processes

207 Since clinico-genomic research projects like ACGT are projected as research structures involving hospitals and research institutions all over Europe, information that flows within such projects will reach a high degree of complexity. The design of data and information disclosure must not only take a variety of medical, ethical and legal aspects into account, but has also to include organisational and technical issues.

Disclosure of general study findings is comparatively easy to organise. In bioethical discourse (see paragraph 2.3.2.1/Informing about general research results), it is widely agreed that general research results must be accessible for research subjects. Public availability of study results not only makes the process of research more transparent; it also expresses respect for the research subject and his or her contribution to research. Especially in tissue-based research, donors usually have no other opportunity to be informed of what have been done with their sample. By making study findings available, investigators brief donors on their activities using tissue-samples and data. Thus, the tissue donors who participated in research projects should actively be offered summaries of research results. 208

However, there is no doubt in ethical discourse (see paragraph 2.3.2.1.2/Practical challenges of feedback processes regarding general research results) that the traditional way of making study findings publicly available – e.g. publication in a scientific journal – does not meet the demands posed by the complexity of current biomedical research objectives. Scientific discourse on the meaning of genetic information, for instance, is usually not easy to comprehend for laypersons. For this reason, scientific outcomes should be published as popularised summaries. Proposals in the literature of how to disseminate general research results include personal letters, news bulletins or leaflets, printed or electronic newsletters, or other web based services. 209

Higher requirements have to be made on data administration and data protection arising from the legal duty to disclose stored personal data on donor's request. As discussed in this paper (see paragraph 2.3.1/Access to personal information), anybody has the right to access personal data stored about him or her. The right to access such data, which is based on ethical principles as well as on legal provisions, is a passive one. Translated into the ICT-structure and into one of the trials involved in the research project, the implementation of this right requires an organisational structure that is suitable to reply to the donor's requests for information about personal data stored about him or her. 210

The investigator-initiated feedback of individually relevant research results can be called the greatest challenge for data administration and data protection within an ICT-supported infrastructure. First of all, it requires that data are not be anonymized, but pseudonymized. It is the only way to enable feedback processes of individually important research results, and to allow individual donors to withdraw consent concerning the usage of their tissue sample and data. The process of feeding back individually relevant data also requires technical mechanisms, which allow to access data of those donors who want an individual feedback. Moreover, precautionary measures have to be generated to avoid access of unauthorised persons to personal data. 211

In addition to organisational and technical questions, several important ethical aspects of the issue need to be considered. The first one is the type of data to feed back. Some researchers argue that only results of clinical relevance should be fed back. However, as discussed extensively (see paragraph 2.3.2.2.2/What to feed back?), the relevance of research results is not easy to define. Genetic research results are usually characterised by a lack of established common interpretation and independent validation. As a result, interpretation of preliminary study results may change as data become more reliable. Hence, statements about their individual relevance are always preliminary in character. Since such information could some- 212

times be helpful, but sometimes also harmful, patients could be harmed by being excluded from individual information as well as by being provided with it. Clinical relevance thus cannot serve as a sole criterion to regulate the feedback of individual research results. Therefore, it is recommended to give patients the option to decide about feedback of personal data, especially in such a highly exploratory field as clinico-genomic research on cancer.

213 Furthermore, in new research areas such as gene expression studies, or clinico-genomic research in general, it is difficult to draw the distinct line between fundamental and clinical research. In recent years, several approaches have been made to cope with the increasing lack of clarity regarding the traditional demarcations of clinical, fundamental, applied, or translational research. But attempts to reclaim traditional demarcations usually fail. The Consortium on Pharmacogenetics, for instance, suggests making the distinction between pharmacogenetic drug trials and hypothesis testing studies (see paragraph 2.3.2.2.2/What to feed back?). Whereas drug trials might produce results that are directly interesting and beneficial for the participant, hypothesis-testing studies usually have no direct medical relevance for patients. However, this distinction may not always apply; in the context of the research project ACGT, individually relevant results are expected in the course of genomic research (see paragraph 2.3.2.2.3/Characteristics of genetic research results).

214 Another question is how to balance the individual's right of self-determination and the interests and rights of relatives. As far as genetic information on cancer susceptibility is concerned, individuals' rights clearly supersede interests of family members. Since genetic research on cancer usually yields only moderate predictive results, it seems more likely to increase emotional and psychological distress by healthy family members providing them with research findings, than by not disclosing them.

215 The specific challenges concerning feedback of individual research results within the ICT infrastructure of ACGT can be summarised as follows:

216 *Individual cancer prognoses based on gene expression signatures are still uncertain*. These uncertainties may even grow, since different models to connect genomic data with clinical outcomes might give rise to different interpretations of available data. Uncertain prognoses because of genomic study findings may provoke fear and anger, possibly even for no reason. However, since gene expression information might have a direct influence on therapeutic or treatment decisions, individual feedback processes should be provided in the context of such research.

217 *Tissue-based cancer research might reveal data of a predictive nature, which may also be relevant for family members*. Since such data on possible germ line variants usually have a low predictive value, they are of little help for healthy family members and may even create emotional and psychological distress. However, in case of familial variants of cancer, where an increased risk within the family is already known, confidentiality has carefully to be protected towards the patient or tissue donor, as well as towards his or her relatives. In these cases it should be up to the donor to inform family members of the possible relevance of his or her results for them. In principle, the issue of disclosing genetic information to family members has particularly to be discussed within the context of each research project, because new aspects will probably arise in research, as well as in clinical practice.

Research involving children has to protect their right not to know. As far as children are involved in clinico-genomic pilot trials, their right to know, as well as *not* to know has to be protected. At latest when children attain full age, they are entitled to be provided with information about personal study findings. At the same time, they are allowed to exercise their right *not* to know. For the latter reason, research results should not be entered into medical records of children. Furthermore, with regard to children's informational rights, the issue should be discussed whether individual study findings will remain re-identifiable without time limit, and, if at all, when such time limit should be set. In this context, it has to be stressed that it is recommended to give paediatric participants the option to re-consent when they become mature. Within the re-consent procedure, they have to be provided with sufficient information about storing procedures and confidentiality protections, including potential risks of storing and processing data in the future. 218

2.4.1.4. Conclusion: How to organize donor driven inquiry processes and investigator driven individual feedback processes

Since clinico-genomic research may yield individually relevant results, an ICT-infrastructure for clinico-genomic research must – from the ethical point of view – be able to actively offer such findings to patients. 219

Before patients consent to tissue donation for research, information about the general character of genetic research results has to be provided. This also includes information concerning the feedback of research results, the possible relevance of such results for the individual and his or her relatives, as well as the possibility that research results may *not* have any individual benefit or importance. Furthermore, potential donors have to be informed that re-identifiability of genetic data is necessary to give individual feedback at all. 220

The clinical relevance of personal research results is not easy to evaluate. Therefore research teams or operators within the ICT-structure respectively, should carefully assess the relevance of the results they expect and inform donors' physicians, at least briefly, about their conclusions in regard to the quality of the findings for the individual donor. 221

Donors who have initially consented to participate in feedback processes should then be contacted by the doctor and asked whether or not he/she wants to receive results that could be important for him/her. Since the donor's consent implements the principles of autonomy and self-determination, which also comprise his/her right to know or *not* to know, he or she should have the option to consent again to disclosure when study findings are available. 222

To avoid unauthorized persons accessing stored personal data, it is proposed that the donor and his/her physician of choice gain access to individual genetic data together only before the donor's physician has proved to be entitled to trigger the individual feedback process. Furthermore, a careful arrangement of feedback processes includes financial and logistical supply. 223

To ensure that donors understand the information provided, individual feedback processes should also be accompanied by counselling. From this follows that physicians of donors' choice should always be involved in the transfer of information to the patient. 224

Given the complexity of ethical aspects to be considered in regard to disclosure and feedback, the task of communicating information generated within the research 225

structure to tissue donors should not be underestimated. In this context, it might be prudent to establish within ICT-structures a multilingual, internet-based information service for donors. The information service could be responsible for publication and dissemination of general study findings and other news concerning research activities within the network. It could also be designed as an initial contact point for donors who look for more or specialized information that passes them on to other persons or places offering adequate expertise. Especially when more clinics and trials become involved in the research project, it is advisable to integrate such a service into the ICT-architecture.

226 Moreover, establishing such a web-based service would initiate further, ongoing examination of ethical requirements, data protection measures and feedback processes within ACGT. The design of such processes could continually be revised and new challenges for patients' rights arising from future research activities could be approached more easily. Finally, beyond the obvious practical benefits of such a service, its establishment is an expression of respect for tissue donors' autonomy and altruism.

227 Generally, the ethical standards of an ICT-infrastructure for clinico-genomic research need to be continuously observed to ensure long-term adherence to existing ethical standards and to identify new questions and challenges, which have not yet been anticipated. Therefore, a continuous monitoring of existing tools and instruments for data protection, as well as of the whole structure of information, flows in regard to patients' rights and interests is a basic prerequisite for patients' trust into a research structure.

228 However, to take patients concerns seriously, a better understanding of their perspectives is indispensable. Without patients who volunteer in clinical trials, future clinico-genomic research is not possible. Some authors have expressed concerns that patients might be overstrained by the demands of such a project or not interested in research at all. Since these perceptions are usually derived from a small empirical basis of data mostly collected in the context of the US-health care system, it is necessary to assess views and attitudes of patients in Europe towards the feedback of research results, as well as towards focus, scope and character of consent processes.

2.5. Outlook: Ethical challenges in the european context

229 There are some ethical challenges related to the implementation of an ICT-supported research infrastructure involving several clinics in different European countries. We address here in a generalised manner, some of the issues we consider important in the European context and, therefore, to be discussed and related to the architecture of the research projects in time.

2.5.1.1. Revision of data protection and information flows

230 The extent of data interchange as well as the variety of access possibilities projected in a cross-national ICT-structure requires the establishment of data protection tools and systems developed conscientiously and carefully. From the perspective of patients' rights, the structure of data and information flows is challenged by conflicting requirements: On the one hand, confidentiality has to be

protected, on the other hand, stored information has to be accessible on request or even actively be disclosed.

Since until now, only a few Grid structures have been built up for health research purposes, analysis of data protection tools and of systems regarding patients' rights is rare. In order to ensure long-term data protection and confidentiality, it therefore seems advisable to continuously revise existing tools and instruments, as well as the structure of data interchange and information flows. Benkner et al, for example, refer to this argument. In their paper related to the European GEMSS-project, they state that the security of the structure "must be periodically reviewed".[352] Since ICT-structures are generally projected to be continuously enlarged, it would be farseeing not only to discuss the issue of regular revision process itself, but also to exchange views and experiences concerning its practical implementation. 231

Furthermore, Benkner et al propose to make patients "aware of the processing that will occur, and be able to review and correct the information held about them".[353] Hence, even if such an active participation of patients seems to be improbable in the review process, they must have the possibility to review and correct individual data and information. Hence, appropriate instruments must be implemented within the ICT-structure to ensure the access to stored data and information on the review of security measures. EU-law guarantees a right to information about stored data. However, it remains an open question whether patients need to be actively informed about their right to access information stored about them. It would be advisable to address the issue explicitly in the consent form. 232

2.5.1.2. Community interests

To ensure that patients' rights will be guaranteed in the long-term within Europe-wide ICT-supported infrastructures for biomedical research, it is useful to be clear about possible implications that the administration of health care in Europe might have in the future concerning these rights. At least, it is advisable to take structural tendencies of European health care policies into consideration. 233

Especially in countries with a state-run health care system, the law tends to prioritize community interests, with possible adverse effects on privacy rights. In her analysis of recent regulations concerning research and consent in the UK, Case even sees a fundamental change regarding patients' rights to confidentiality, self-determination and autonomy.[354] Referring to the British law, she notes a distinction between physical and informational autonomy, which made it possible to dispense from consent in research concerning information and data. Somewhat fatalist, she concludes with the assumption "that privacy will regularly be subordinated to community interests".[355] 234

However, societal interests have been discussed repeatedly in debates about tissue or blood donation for research purposes in recent years. Following the argument of the British Medical Council, for example, "in benefiting from the National Health Service, patients should be encouraged to give something back for the public good".[356] 235

[352] Benkner et al 2005, 179. GEMSS stands for Grid-Enabled Medical Simulation Services (EU IST-project 2002–2005, www.gemss.de)

[353] Ibid

[354] Case 2003, 215

[355] Ibid, 234

[356] MRC 2004, 4

Similarly, the Swedish authors Eriksson and Helgesson point out that biobank research is a "public endeavour to promote the common good".[357] They even state a moral obligation to donate biological samples and to allow it to be used in future medical research: "If you expect to receive the best possible treatment, you ought to contribute to the processes by which such treatment is established. If you do not, you are a *free rider*".[358]

236 A minority in the discussion argues that community interests are supposed to be superior to personal rights, by connecting the issue to the broader context of economical changes within European health care systems. To the same extent, the necessity to cut expenditures grows, values as solidarity and society interests gain significance in public discussion. That is why the current concept of patient's autonomy and self-determination might be called into question by public health issues in the future.

237 Beyond these general considerations regarding changes of ethical priorities, patients' rights of privacy, confidentiality and self-determination might be jeopardised in practice when it comes to the question of disease registries. Some years ago, for example, the British General Medical Council (GMC) prohibited almost conclusively the disclosure of patient details to cancer registries without expressed consent. In the discussion on the draft guidelines medical profession, however, members asserted it would be impracticable to obtain express consent, because the consent procedure would overstrain cancer patients. The fear was "that cancer registries in the UK would collapse if informed consent were to be made a precondition to the communication of patient details".[359]

238 Many EU member states have, for example, carried out cancer registries. The issue of registration is an important challenge for patients' informational autonomy. Therefore, it should be discussed within ICT-structures how to deal with conceivable requests for data transfers into national disease registries. For instance, the installation of registries regarding gene expression in cancer may be envisaged in the future.

---

[357] Eriksson and Helgesson 2005, 1075; for clinical research, Evans (2004, 198) draws a similar conclusion: "By analogy with the paying of income tax, patients should not be allowed to 'veto' their social responsibility to take part in clinical research".

[358] Ibid

[359] Case 2003, 225

3. Legal requirements

3.1. Introduction

Chapter 3 analyses the legal requirements for establishing an integrated Clinico-Genomic ICT environment employing data extracted from human tissues. 239

An in-depth analysis of the European Data Protection Directive 95/46 EC, which introduces rules applicable to every processing of personal data on a European level is the starting point of this chapter. The Directive sets out the rights of the data subject and control mechanisms, regulates the transfer of personal data into third countries and establishes general rules on the lawfulness of the processing of personal data. 240

Under ■0 the results of the abstract analysis are applied to a genetic research project. 241

Within genetic research projects, the data of patients will be collected and/or stored in databases (in most cases connected via a GRID infrastructure), so that researchers participating in the project can access the patients' data for research purposes. For the success of the project and to ensure the patients' acceptance, it is crucial that the data flow is conducted lawfully. 242

With regard to data protection, the characteristics of genetic data are the determining factor. Due to the fact that they provide information not only about the data subject itself but also about his or her relatives and possible diseases etc, genetic data is highly sensitive data, which can only be processed under special requirements. Within the analysis of necessary requirements importance is laid on the question of whether anonymous or pseudonymous data should be processed within a research project. In addition, the dangers of possible de-anonymisation will be discussed and the legal question of whether or not additional knowledge is attributable to the data controller. Furthermore, the legal issues which arise from the inclusion of a trusted third party into the processing of data will be presented. 243

3.2. Theoretical analysis

3.2.1. European Data Protection Directive 95/46/EC

3.2.1.1. Genesis

The first pieces of legislation in the field of data protection were not enacted until the early 1970s. The first important international instruments on data protection were the OECD *Guidelines Governing the Protection of Privacy and Transborder Flows of Personal Data*[360], adopted by the OECD Council on 23. 9. 1980 and the CoE *Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data*[361], adopted by the CoE Committee of Ministers on 28. 1. 1981. 244

[360] http://ec.europa.eu/justice_home/fsj/privacy/instruments/oecdguideline_en.htm (accessed 05 February 2010)

[361] http://conventions.coe.int/Treaty/en/Treaties/Html/108.htm (accessed 5. 2. 2010)

However as these instruments were not binding for the Member States, a large range of heterogenic regulations were adopted in the different European countries and the internal market was increasingly affected.

245 Therefore the EC *Directive on the Protection of Individuals with Regard to the Processing of Personal Data and on the Free Movement of Such Data* was adopted by the European Parliament and the Council on 24. 10. 1995. It is by far the most influential, comprehensive and complex international policy instrument, enacted to enshrine two of the oldest ambitions of the European integration project, namely the achievement of an Internal Market (in this case the free movement of personal information) and the protection of fundamental rights and freedoms of individuals (in this case to create an equivalent standard of data protection). Member States of the EU were given until 24. 10. 1998 to bring their respective legal systems into conformity with the provisions of the Directive. At present however, a large range of legal and quasi-legal instruments on data protection can be found in the Member States.

246 In the Directive both objectives are equally important. In legal terms however, the existence of the Directive rests on Internal Market grounds. Legislation at the EU level was justified because differences in the way that Member States approached this issue impeded the free flow of personal data between the Member States. The legal base for this was Article 100 a (now Article 95) of the Treaty. However, the proclamation of the *Charter of Fundamental Rights of the European Union* by the European Parliament, the Council and the Commission in December 2000 and in particular Article 8 thereof has given added emphasis to the fundamental rights dimension of the Directive.

247 Article 8 incorporates the right to privacy as an essential freedom and states that personal data must be processed fairly for specified purposes and on the basis of the consent of the data subject concerned or some other legitimate basis laid down by law. Moreover Article 8 constitutes everyone's right of access to data which has been collected concerning him or her, and the right to have it rectified.

3.2.1.2. Scope of the Directive

248 If research with genetic data has to be fulfilled in compliance with the rules of the Data Protection Directive 95/46/EC the Directive has to be applicable.

249 **3.2.1.2.1. Personal data.** Article 3 (1) of Directive 95/46/EC points out that the Directive is applicable only to the processing of "personal data".

250 "Personal data" is defined in Article 2 lit. a) as being data covering any information relating to an identified or identifiable natural person called the "data subject". Furthermore an "identifiable person" is one who can be identified directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity.

251 Therefore one can adhere to two cumulative conditions for data or information to be "personal": first, the data must relate to or concern a person and; secondly, the data must facilitate the identification of such person. Often the first condition will be embraced by the second as information will normally relate to or concern a person if it facilitates that person's identification. Therefore the main criterion

appearing in these definitions is that of identifiability i. e., the potential of information to enable identification of an individual.[362]

However, data that does not refer to a natural person is not subject to the processing-restrictions of the Directive. Accordingly data concerning objects as well as data no longer referring to a natural person (anonymous data) is not covered by Directive 95/46/EC. 252

3.2.1.2.1.1. Anonymous data. Directive 95/46/EC is not applicable to the processing of personal data that was rendered anonymous. Therefore it is of high importance to distinguish whether the research project in question processes personal or anonymous data. 253

Whereas the first draft of Directive 95/46/EC included in Article 2 lit. b) a definition of anonymisation, the Directive in its final version failed to do so. 254

The first draft of Directive 95/46/EC defined anonymous data as personal data modified "in such a way that the information they contain can no longer be associated with a specific individual or an individual capable of being determined except at the price of an excessive effort in terms of staff, expenditure and time"[363]. The "excessive effort" was cancelled in the final version. The only reference to anonymous data in the applicable Directive can be found in Recital (26) of Directive 95/46/EC. Recital (26) states that Directive 95/46/EC shall not apply to data rendered anonymous in such a way that the data subject is no longer identifiable. The economic and social committee initially welcomed this change because it was thought that excluding the "excessive effort" would limit the scope of anonymous data and the term "excessive effort" would be obsolete in the context of the rapid development in the information technology sector.[364] 255

In conclusion, Directive 95/46/EC considers data as anonymous only if the data subject is no longer identifiable. This means the link that refers to the data subject is irrecoverably erased. German legislation seized the suggestion of the proposal and, unlike the European legislation, implemented the "excessive effort" in its definition of anonymous data (§ 3 (6) of the Federal Data Protection Act (BDSG)). 256

Meanwhile the European perception regarding "anonymous data" seems to change. In 2003, the European Commission published its "*First report on the implementation of the Data Protection Directive*".[365] Referring to a document of the European Privacy Officers Forum (EPOF) from 2002,[366] the Commission pointed out that the interpretation of certain provisions of Directive 95/46/EC had to be reasonable and flexible. In this context the EPOF stated that the definition of anonymisation should be pragmatic and should emphasise that the capability of identification must be subject to a reasonableness standard. EPOF declared that the German definition would satisfy both requirements. Moreover, in spring 2007 the Article 29 Data Protection Working Party published an opinion on the concept of 257

[362] Bygrave, Data Protection Law, p. 41 f.

[363] Proposal for a council directive concerning the protection of individuals in relation to the processing of personal data COM (90) 314

[364] Opinion of the economic and social committee on the proposal for a council decision in the field of information security, Official Journal C 159, 17/06/1991, p. 38

[365] http://eur-lex.europa.eu/LexUriServ/site/en/com/2003/com2003_0265en01.pdf (accessed 5. February 2010)

[366] http://ec.europa.eu/justice_home/fsj/privacy/docs/lawreport/paper/epof_en.pdf (accessed 5. February 2010)

personal data[367] stating that a mere hypothetical possibility to single out the individual is not enough to consider the person as "identifiable."[368]

258 These statements give reason to assume that in the meantime the European Commission approves a definition of "anonymous data" that includes an "excessive effort". Therefore information concerning personal or material circumstances that can only be attributed to an identified or identifiable individual with a *disproportionate amount of time, expense and labour,* is *de facto* anonymous data.

259 *3.2.1.2.1.2. Pseudonymous data.* In contrast to some national data protection regulations, Directive 95/46/EC does not explicitly recognise the concept of "pseudonymous data". The German Federal Data Protection Act for example defines in section 3 paragraph (6a) pseudonymising as "replacing a person's name and other identifying characteristics with a label, in order to preclude identification of the data subject or to render such identification substantially difficult". Especially in a medical research project, the use of pseudonymous data can be very beneficial for the patient because it is possible to re-identify the patient and to let him benefit from newly developed treatments. However, in the European regulatory framework the concept of "pseudonymous data" does not exist.

260 **3.2.1.2.2. Territorial application.** The territorial scope of Directive 95/46/EC is clearly defined: The Directive is applicable whenever personal data is processed within the European Union.

261 However, despite the supranational principles set up by the Directive, there is no common European wide regulation because the Directive grants the Member States a certain discretion about how to transform the principles into national law.[369]

262 Further, the Directive was incorporated on 25. 6. 1999 into the 1992 *Agreement on the European Economic Area* (EEA) in such a way that States which are not Members of the EU but are party to the EEA Agreement (i. e. Norway, Iceland and Liechtenstein) are legally bound to bring their respective laws into conformity with the Directive, which is what they have subsequently done.

3.2.1.3. Fair and lawful data processing

263 **3.2.1.3.1. General.** Exceptions from the general prohibition on processing personal data are listed in Article 7 of the Directive 95/46/EC. Summarizing the exemptions, it can be said that the processing of personal data is permitted if the data subject has given his or her consent or if the processing occurs in his or her interest or in the public interest. However, the processing of personal data is limited by the fundamental rights and freedoms of the data subject. This is also reflected in the basic principle of *purpose specification*. For the processing the purposes of personal data must be adequate, relevant and not excessive in relation to the purposes for which they are collected and/or further processed. Personal data must not be further processed in a way that is incompatible with those purposes.

264 *3.2.1.3.1.1. Requirement of a legal basis.* Under the Directive, the processing of personal data generally is prohibited. However the processing may be lawful if certain preconditions are fulfilled.

[367] http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/2007/wp136_en.pdf (accessed 5. February 2010)

[368] Opinion 4/2007 on the concept of personal data, pp. 15 ff

[369] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, Rn 24

Article 7 (a)–(f) contains a catalogue of cases in which Member States may permit the processing of personal data. According to Article 7 and Recital (30) personal data may only be legitimately processed if the processing is carried out with the unambiguous and explicit consent of the data subject. Moreover data processing may also be legitimate in a number of circumstances where consent may be implied, for example, if processing is needed to perform a contract between the data controller and the data subject or the data processing is necessary in order to protect the vital interests of the data subject. 265

Furthermore, data processing may be lawful without the explicit consent of the data subject concerned on grounds of public interest, such as where processing is necessary for compliance with a legal obligation to which the controller is subject, or is necessary for the performance of a task carried out in the public interest or exercise of official authority pursuant to Article 7 (e). 266

Finally, processing may be undertaken under Article 7 (f) if it is necessary for the purposes of the legitimate interests pursued by the controller or by the third party or parties to whom the data are disclosed, except where such interests are overridden by fundamental rights and freedoms of the data subject. However, if data is processed pursuant to Article 7 (e) or (f) the data subject may, according to Article 14, object to the processing of data pertaining to him.[370] 267

In addition the Directive states in Article 8 that the processing of certain types of data which are regarded as especially sensitive for the data subject, shall be subject to even more stringent controls than other personal data[371]. 268

3.2.1.3.1.2. Technical and organisational measures. A security policy can be enforced in two ways: Through technical measures (e.g. using firewalls and access control in applications) and through organisational measures (e.g. assigning responsibility for the security of data in a clear way). 269

Because of the increased specialization of healthcare providers and the increased complexity of care and research procedures, the size of the team of care or research providers dealing with one patient is constantly growing. Teams of ten to fifty are common. Consequently many people have increasing (potential) access to the personal clinical information of a large number of patients and organisations rely less on trust. Therefore enforcement of rules becomes essential. The increased use of IT means that technical measures to enforce the security policy are unavoidable. 270

Accordingly, Article 17 requires that Member States provide that the controller must implement appropriate technical and organisational measures to protect personal data against accidental or unlawful destruction or accidental loss, alteration, unauthorized disclosure or access, in particular where the processing involves the transmission of data over a network, and against all other unlawful forms of processing. 271

In addition, the Recommendation *on the Protection of Medical Data*[372] of the Committee of Ministers to Member States, R(97)5, provides some further guidance for healthcare providers. Recommendations are not legally binding on Member States, but are incentives for certain behaviour. 272

[370] See below 3.2.1.5.6.

[371] See ■0 sensitive data

[372] http://www1.umn.edu/humanrts/instree/coerecr97-5.html (accessed 5. February 2010)

273 The text of the recommendation contains the following excerpt:

"9.1 Appropriate technical and organisational measures shall be taken to protect personal data – processed in accordance with this recommendation – against accidental or illegal destruction, accidental loss, as well as against unauthorised access, alteration, communication or any other form of processing. Such measures shall ensure an appropriate level of security taking account, on the one hand, of the technical state of the art and, on the other hand, of the sensitive nature of medical data and the evaluation of potential risks. These measures shall be reviewed periodically".

274 Such appropriate organisational measures to ensure the confidentiality, integrity and accuracy of processed data may include:

- to prevent unauthorised persons from gaining access to data processing systems with which personal data is processed or used (access control),
- to prevent data processing systems from being used without authorization (authorization control),
- to ensure that persons entitled to use a data processing system have access only to the data to which they have a right of access, and that personal data cannot be read, copied, modified or removed without authorization in the course of processing or use and after storage (access control),
- to ensure that personal data cannot be read, copied, modified or removed without authorization during electronic transmission or transport and that it is possible to check and establish to which bodies the transfer of personal data by means of data transmission facilities is envisaged (transmission control),
- to ensure that it is possible to check and establish whether and by whom personal data has been input into data processing systems, modified or removed (input control),
- to ensure that in the case of the commissioned processing of personal data, the data is processed strictly in accordance with the instructions of the principal (job control),
- to ensure that personal data is protected from accidental destruction or loss (availability control),
- to ensure that data collected for different purposes can be processed separately.

275 Additionally, in the field of data processing regarding genetic research it might be useful, if not essential, to integrate a Trusted Third Party.

276 A Trusted Third Party in this context is a security authority that performs security related functions and cryptography methods. In particular it can ensure, acting independently, that only pseudonymised genetic data is processed and transmitted within the research consortium via the network.[373]

277 **3.2.1.3.2. Sensitive data.** Directive 95/46/EC distinguishes between certain types of data. Some data contains information that affects the privacy of a person more than other data. Therefore this special kind of data has to be protected more strictly because of its sensitive quality.

278 *3.2.1.3.2.1. Definition.* Directive 95/46/EC defines sensitive data as a special category of data in Article 8 (1). This special category of data contains personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and the processing of data concerning health or

[373] See detailed below under ■0

sex life. References to other sorts of data that Member States regarded as sensitive had to be dropped from the lists in data protection laws in the EU as the list of data categories in Article 8 of the Directive was intended to be exhaustive[374]. Whether certain data should be regarded as sensitive has to be decided in each particular case. However, the special categories listed have in common that they bear an extremely high risk of discrimination and therefore have to be protected more strictly.

Genetic data belongs to health data. Therefore, genetic data is seen as sensitive data accordingly to the list of special categories of data in Article 8 (1). 279

3.2.1.3.2.2. Prohibition of data processing. The processing of this special category shall be prohibited by the Member States according to Article 8 (1). 280

Prima facie there is no difference between the processing of sensitive data and other kind of personal data as the processing of personal data shall also be prohibited by the Member States according to Article 6 (1) and Article 7, unless the processing is permitted by law or by the data subject itself[375]. 281

However certain personal data contains information affecting the privacy of a data subject more than other data. Therefore the Member States have agreed on the better and stronger protection of this more sensitive data.[376] 282

Hence the Directive introduces very strict exemptions in Article 8 paragraphs 2, 3 and 5. Only if these conditions are fulfilled can the processing of sensitive personal data be lawful. As these conditions are stricter than the conditions for a lawful processing of other personal data stated in Article 7, sensitive personal data is better protected than other data which does not reveal racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and the processing of data concerning health or sex life. 283

The Member States are also authorized to impose other exceptions than those stated in Article 8 paragraphs 2, 3 and 5 if the Member States obey the conditions introduces in Article 8 paragraph 4. 284

Therefore, the processing of sensitive personal data is not prohibited per se. 285

However, the decision whether or not the processing of sensitive personal data may be lawful is complicated. 286

3.2.1.3.2.3. Exceptions. The Directive states several exceptions to the prohibition on processing sensitive data in Article 8 paragraph 2. Once the conditions of these exceptions are fulfilled the processing of sensitive data is no longer prohibited. In these cases the protection of the privacy of a data subject is less important than the purpose pursued by these exceptions. 287

The exceptions stated in Article 8 paragraph 2 are (in simplified form): 288

- explicit consent by the data subject
- processing is necessary for purposes in the field of employment law
- processing is necessary to protect the vital interests of the data subjects
- processing is carried out by a foundation, an association or another non-profit-seeking body
- processing of data made public by the data subject
- processing of data necessary for the assertion of claims

[374] Bygrave, Data Protection Law, p. 69
[375] See above ■0
[376] OJ C/1992/311/p. 30

289 Exceptions concerning the processing of data for the purposes of preventive medicine, medical diagnosis, the provision of care or treatment are dealt with in Article 8 (3).

290 Article 8 (4) gives Member States a broad scope to lay down exemptions in addition to those laid down in Article 8 paragraph 2 either by national law or by the decision of the supervisory authority. Member States are authorized to deviate from the prohibition on processing sensitive data for reasons of substantial public interest such as public health, social protection, scientific research or government statistics. Also in these cases Member States must provide specific and suitable safeguards to protect the fundamental rights and the privacy of individuals.

291 This exception as well as the one stated in Article 8 paragraph 3 might be corresponding to the data processing within genetic research projects. This will be analysed carefully below under ■0.

292 Finally, Article 8 paragraph 5 states another exemption from the prohibition of processing sensitive data for data concerning criminal offences and similar issues. Those derogations provided for in paragraph 5 as well as paragraph 4 from the data processing-prohibition stated in paragraph 1 have to be notified to the Commission.

3.2.1.4. Duties of the data controller

293 According to Article 2 lit. d) the data controller shall mean the natural or legal person, public authority, agency or any other body which alone or jointly with others determines the purposes and means of the processing of personal data. Where the purposes and means of processing are determined by national or Community laws or regulations, the data controller or the specific criteria for his nomination may be designated by national or Community law.

294 According to Article 6 paragraph 2, the data controller has the duty to ensure that personal data is processed fairly and lawfully. Consequently the controller has to ensure that personal data is only collected for specified, explicit and legitimate purposes and not further processed in a way incompatible with these purposes. Moreover the data controller has to warrant that data is not excessively processed in relation to the purposes for which it is collected and/or further processed. Furthermore every reasonable step must be taken by the data controller to ensure that data which is inaccurate or incomplete, having regard to the purposes for which it was collected or for which it is further processed, are erased or rectified.

295 Likewise the data controller has to make sure that the data is kept in a form which permits identification of data subjects for no longer than it is necessary for the purposes for which the data was collected or for which it was further processed.

296 Pursuant to Article 17, the data controller must implement appropriate technical and organisational measures to protect personal data against accidental or unlawful destruction or accidental loss, alteration, unauthorized disclosure or access, in particular where the processing involves the transmission of data over a network, and against all other unlawful forms of processing.

297 Since it is the data controller who is liable for the legality of data processing and the fulfillment of the obligations towards the national data protection authority and the data subjects, it is essential that the data controller is always identifiable.

298 Accordingly, Article 10 and 11 state that the data controller must provide a data subject with the identity of the controller and of his representative.

Furthermore, Article 12 states that the data controller has to provide every data subject with information about the processing of his or her data. 299

Article 23 states that any person who has suffered damage as a result of an unlawful processing operation or of any act incompatible with the national provisions adopted pursuant to the Directive is entitled to receive compensation from the data controller for the damage suffered if the data controller fails to fulfill his duties in accordance with the Directive and thus fails to respect the rights of data subjects. However, the data controller may be exempted from this liability, in whole or in part, if he proves that he is not responsible for the event giving rise to the damage. 300

3.2.1.5. Rights of the data subject

The processing of personal data affects the privacy of the data subject. Therefore, the data subject has to be granted special rights in order to enable him or her to protect his or her privacy. These rights are introduced in Articles 10–12 and 14 of the Directive, whereas Article 13 states the exemptions and restrictions of the data subjects' rights introduced in Article 10–12. 301

3.2.1.5.1. Information duties regarding data collection from the data subject. The Data Protection Directive distinguishes between two types of data collection: Article 10 deals with data collected from the data subject himself; Article 11 deals with information duties when data has not been obtained from the data subject. 302

According to Recital (38) the principles of fair data processing require that the data subject must be in a position to learn of the existence of a processing operation. Additionally, where data is collected from him or her, the data subject must be given accurate and full information bearing in mind the circumstances of the collection. The data subject should be able to assess the situation and make his or her decision on reasonable grounds. 303

Data collection is defined as the collection of information with a certain aim. It can be the immediate taking notice of information, storage on a data carrier or the reception of a data carrier with the possibility of using the information. Not falling within the scope of the definition is the situation in which the data controller gets the information without asking for it. Data is not collected from the data subject if he or she does not know about the data collection or if he or she cannot avoid the data collection.[377] 304

As data collection depends on a decision of the data subject, he or she has to be informed about whether or not the collection is compulsory. This aims at protecting the data subject from disclosing information under the wrong assumption that the disclosure is compulsory or that a refusal could have disadvantageous consequences. Therefore, the principles of fair data processing require information whenever it is doubtful whether the said person assesses the situation correctly.[378] 305

The Data Protection Directive does not set up requirements concerning form and procedure of the information duties. It only requires the said person to receive the information from the data controller or his representative at the instigation of the data controller. The data controller can make use of his own staff or third parties. Oral information is possible, but for practical reasons, written information, usually on the data collection forms, is most common, as it enables the data controller to 306

[377] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 180/181
[378] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 180/184

produce written evidence that the information process was correct. The data subject must be informed when data is collected, even if the storage of the data concerned takes place later.

307 As the Data Protection Directive aims to make sure that the person concerned is informed, the duty to inform the said person does not apply if the person is already aware of the information. It does not depend on how and in which form the person got the information, as long as he or she received it close to the time of decision making so that the information received will be a part of the decision making process.[379]

308 Article 10 lit. a) states that the data subject has to be informed about the identity of the data controller and of his representative. This includes the name and address under which correspondence can be delivered. The information must be precise enough for the data subject to make use of his right to information and correction without difficulties, either in writing or personally. If a third party is involved in the data processing, their name and address have to be published as well.

309 Moreover, the data subject has to be informed about the purposes of the processing for which the data is intended. Such processing can only be for the fulfilment of one of the legitimate purposes enumerated in Article 6 Data Protection Directive. The data subject must be informed about all intended purposes. This information enables the data subject to assess whether the data collected meets the intended purposes and can be collected lawfully.

310 Furthermore, the data subject has to be given further information to guarantee fair processing in so far as it is necessary, having regard to the specific circumstances in which the data is collected.

311 Information is necessary as the said person needs it to assess correctly possible consequences of his or her taking part in the data collection process and to make an informed decision. Further information is generally required if data processing results in acquiring knowledge about other categories of data, e.g. by interpretation of psychological tests or analysis of blood or tissue samples.[380]

312 The recipient of the data collected is of special importance if the data is collected especially for his or her purposes, e.g. credit information services. In general, information about the category to which the recipient of the data belongs is sufficient.[381]

313 **3.2.1.5.2. Information duties regarding data which has not been obtained from the data subject.** In contrast to Article 10, Article 11 of the Data Protection Directive applies if data is not collected from the data subject him- or herself. Nevertheless, the data subject has to be informed and the information requirements set up by Article 11 are nearly identical to those set up by Article 10.

314 The most important difference is the point of time when the information duties apply: Article 10 requires that the information duties are fulfilled at the time when the data is collected from the data subject.[382] In contrast to this, Article 11 states "*the data controller or his representative must at the time of undertaking the recording of personal data or if a disclosure to a third party is envisaged, no later*

[379] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 181/182
[380] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 183/184
[381] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 183/18
[382] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, p. 180

than the time when the data are first disclosed provide the data subject with […] information". Whenever it is planned to pass the data obtained on to a third party, the information duties only have to be met when the data is actually passed on. If the data obtained is stored without being passed on to a third party, the data subject has to be informed at the time of undertaking the recording. In both cases, the data subject must be informed as soon as possible of the operation in question.[383]

The scope of the word "obtain" comprises the collection of data as it is defined for Article 10. It applies to all cases of "collection" apart from those where data is collected from the data subject himself. The most important cases of application under Article 11 are those where data is requested from another person or institution, the calling up of data which is held ready by another person or the collection of data without the said person being able to make a decision about or to influence the collection, e.g. visual or audible recording or any other form of registration of characteristics, activities or behaviour of the person concerned.[384] 315

As the data subject does not take part in the data collection, he or she has to be informed about the categories of data to be processed. Likewise the data controller has the duty to inform the data subject whether or not the data collection is compulsory.[385] 316

Article 11 paragraph 2 states that the information duties of paragraph 1 do not apply to cases in which the provision of such information proves impossible or would involve a disproportionate effort or if recording or disclosure is expressly laid down by law. 317

"Disproportionate effort" does not mean the absolute effort, but the effort in relation to the data subject's interest to be informed. The informational interest of the third person is valued more highly if the data processing enhances the risk of misuse of the data. The data subject must be given the possibility to protect him or herself by making use of his or her rights. If the data concerned will only be used for statistical purposes or if there are effective safeguards against data processing with a link to the person concerned, a lesser effort can be seen as disproportionate. The Data Protection Directive explicitly mentions the examples of statistical purposes or purposes of historical or scientific research. 318

In principle, the data controller has to inform the data subject, but the Data Protection Directive does not impose the duty on the data controller if it is impossible. Neither has he or she the right to collect data especially for the purpose of informing the data subject as new risks for the data subject would result from the additional data collection. 319

Furthermore there is no duty to inform the data subject if recording or disclosure is expressively laid down by law because in this case, the data subject knows or can easily get to know the content of the regulation.[386] 320

3.2.1.5.3 Right of access. Article 12 Data Protection Directive is the central provision guaranteeing the data subject's legal safeguards. The heading "right of access" gives a limited idea of the contents of Article 12, because Article 12 does not 321

[383] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, p. 18
[384] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 186/187
[385] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, p. 187
[386] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 187/188

only contain a right of access. Moreover, it comprises the right to rectification, erasure or blocking of data. The rights guaranteed by Article 12 arise from the data subject's personal rights.[387]

322 Recital (41) emphasizes the importance of the right of access: "Whereas any person must be able to exercise the right of access to data relating to him which are being processed, in order to verify in particular the accuracy of the data and the lawfulness of the processing; whereas, for the same reasons, every data subject must also have the right to know the logic involved in the automatic processing of data concerning him, at least in the case of the automated decisions referred to in Article 15 (1); […]." The right of access is limited by trade secrets, intellectual property and in particular the copyright protecting software. However, these considerations must not result in the data subject being refused all information. There must be a consideration in each individual case as to which information can satisfy both the right to intellectual property and the data subject's interest in the protection of his or her personal data.[388]

323 Article 12 lit a), sub-paragraph 1 states the data subject's right and the data controller's duty to inform the data subject if data with a link to the person concerned exists or not. All further information only has to be passed on to the data subject if his or her personal data is processed.[389]

324 Sub-paragraph 2 states the data controller's duty to inform the data subject in an intelligible form about the data undergoing processing and of their source. "Data" means any information about the person concerned. "Intelligible" means that it depends on the intelligibility of the information from a typical data subject's point of view. Moreover, the data subject has to be provided with any available information regarding the source of the data processed because the Data Protection Directive requires not only information concerning the category of the source, but concrete information also.[390]

325 Sub-paragraph 3 states the data controller's duty to pass on information concerning the knowledge of the logic involved in any automatic processing of data concerning the data subject at least in the case of the automated decisions referred to in Article 15 (1). Here the Data Protection Directive has a broader scope than Convention 108 of the Council of Europe[391] and average European data protection legislation. The Data Protection Directive goes further than storage and single data processing operations (transfer, rectification, erasure), placing the general term "processing" in the centre of the protection.[392]

326 **3.2.1.5.4. Right to rectification, erasure or blocking.** Article 12 lit. b) grants the right to rectification, erasure or blocking of data and the processing of data which does not comply with the provisions of the Data Protection Directive, in particular because of the incomplete or inaccurate nature of the data.

327 "Rectification" aims at securing the objective correctness of the data concerned.

328 "Erasure" means that the data controller does not have personal data any longer. This can be achieved by destruction of the data medium, deletion of the informa-

[387] Ehmann, Eugen/Helfrich, Marcus, EG-Datenschutzrichtlinie, 1999, pp. 173/174
[388] Ehmann, Eugen/Helfrich, Marcus, EG-Datenschutzrichtlinie, 1999, pp. 175/176
[389] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, p. 193
[390] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, p. 194
[391] http://conventions.coe.int/Treaty/en/Treaties/Html/108.htm (accessed 5. February 2010)
[392] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 194/195

tion or removal of the link between the data and the person concerned which makes the identification of the person concerned impossible. As a result, the data controller no longer has possession of personal data.

"Blocking" means that the data controller does not entirely give up the data at his disposal, but that he defines which parts of the data won't be used at all or not to a significant extent.[393] 329

Furthermore, Article 12 lit. c) states that the data controller has to give notice to third parties to whom the data has been disclosed of any rectification, erasure or blocking carried out in compliance with (b), unless this proves to be an impossible effort or involves a disproportionate effort. 330

3.2.1.5.5. Exemptions and restrictions. Article 13 lists the cases in which Member States may adopt legislative measures to restrict the scope of the obligations and rights provided by Article 6 (1) (principles relating to data quality); 10, 11(1) (information to be given to the data subject); 12 (right to access, rectification, erasure or blocking) and 21 (publication of processing operations). 331

The Data Protection Directive allows exemptions and restrictions but it does not impose an obligation on the Member States. The Directive does not allow exemptions and restrictions in further cases than in those listed in Article 13. 332

Article 13 paragraph 1 lists the following cases: national security, defense, public security, criminal prosecution, economic or financial interests of a Member State, monitoring, inspection or regulatory functions connected, the protection of the data subject or the rights and freedoms of others.[394] 333

Article 13 paragraph 2 opens a further possibility to restrict the rights of the persons concerned: scientific research and statistics. Based on scientific methods, the aim of scientific research is to investigate phenomena and to acquire new knowledge as well as to correct and to integrate previous knowledge. It is based on gathering observable, empirical and measurable evidence subject to the principles of reasoning. The aim of scientific research and of statistics is not to generate information concerning an individual. 334

But there are some differences to paragraph 1: 335

First, paragraph 2 only refers to the rights safeguarded by Article 12, but not to the collection of data. Secondly, an exemption is only lawful if there are "adequate legal safeguards, in particular that the data is not used for taking measures or decisions regarding any particular individual". Furthermore, the Directive requires that the data concerned is "processed solely for purposes of scientific research" and is kept in personal form only for a period which does not exceed the period necessary for the sole purpose of creating statistics. "Adequate legal safeguards" could be the restriction to certain fields of scientific research, the exclusion of sensitive data, anonymization or regulations concerning the civil and criminal liability of the data processor and his employees.[395] 336

3.2.1.5.6. Right to object. The right to object to the use of personal data concerns the use of personal data from the time of its collection up to the time of its destruction. It also includes its disclosure to third parties for this purpose. The right to object enables a data subject to ensure that his or her data is not processed as 337

[393] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 197/198
[394] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 201–209
[395] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 210/211

soon as he or she claims legitimate interests or overriding rights and freedoms which overweigh the interests of the controller in processing his or her data.

338 Accordingly, Article 14 states the right of the data subject to object at any time on compelling legitimate grounds relating to his or her particular situation to the processing of data relating to him or her. In case of a justified objection, the processing instigated by the data controller may no longer involve this data.

339 Article 14 lit b. states the right "to object to the processing of personal data relating to him which the data controller anticipates being processed for the purposes of direct marketing, or to be informed before personal data is disclosed for the first time to third parties or used on their behalf for the purposes of direct marketing, and to be expressly offered the right to object free of charge to such disclosures or uses".

340 In order to make the data subject aware of the existence of the right to object, the Member States shall take all necessary measures.

3.2.1.6. Transfer of personal data to third countries

341 The transfer of personal data to third countries is set out in Articles 25 and 26 of Directive 95/46/EC. Articles 25 and 26 contain rules providing for restrictions to be put on the flow of personal data to countries without sufficient levels of data protection. The main aim of these rules is to hinder data controllers from avoiding the requirements of the Data Protection Directive by shifting their data-processing operations to countries with more lenient requirements. Whilst Article 25 specifies the principles of data transfer to third countries, the derogations are listed in Article 26 Directive 95/46/EC.

342 Third countries within the meaning of the Directive are countries which do not belong to the European Union (EU) or European Economic Area (EEA); accordingly Directive 95/46/EC is not applicable in these countries[396].

343 Article 25 (1) stipulates that data transfer "may take place only if […] the third country in question ensures an adequate level of protection". And Article 25 (2) points out that the adequacy of protection "shall be assessed in the light of all circumstances surrounding a data transfer or set of data transfer operations […]". Such circumstances surrounding a data transfer can include the "nature of the data, the purpose and duration of the proposed processing operation or operations, the country of origin and country of final destination, the rules of law, both general and sectoral, in force in the third country in question and the professional rules and security measures which are complied with in that country" (Article 25 (2)).

344 Moreover, the Article 29 Data Protection Working Party[397] has adopted a discussion document on the "*Transfers of Personal Data to Third Countries* –

[396] See above ■0

[397] The Article 29 Data Protection Working Party was established by Article 29 of the Directive 95/46/EC. According to Article 30 of that Directive it shall (inter alia) examine any question covering the application of the national measures adopted under the Directive 95/46/EC in order to contribute to the uniform application of such measures, give the Commission an opinion on the level of protection in the Community and in third countries,, advise the Commission on any proposed amendment of this Directive, on any additional or specific measures to safeguard the rights and freedoms of natural persons with regard to the processing of personal data and on any other proposed Community measures affecting such rights and freedoms and give an opinion on codes of conduct drawn up at Community level.

Possible ways forward in assessing adequacy" in 1997[398] and a working document concerning "*Transfers of personal data to third countries: Applying Articles 25 and 26 of the EU data protection directive*" in 1998[399] giving more detailed criteria for the consideration.

The assessment whether the respective third country ensures an adequate level of data protection lies firstly in the responsibility of the data controller who wishes to export the data and secondly of the national data protection authorities in the EU Member States.[400] Article 25 (6) enables the Commission to make determinations of adequacy which are binding on the Member States. 345

These decisions of the Commission involve a proposal from the Commission, 346

an opinion of the group of the national data protection commissioners (Article 29 Data Protection Working Party), an opinion of the Article 31 Management committee delivered by a qualified majority of Member States, a thirty-day right of scrutiny for the European Parliament to check if the Commission has used its executing powers correctly. The European Parliament may, if it considers it as appropriate, issue a recommendation and the adoption of the decision by the College of Commissioners. 347

The effect of such a decision is that personal data can flow from the EU Member States and three EEA member countries (Norway, Liechtenstein, and Iceland) to that third country without any further safeguard being necessary. The Commission has so far recognized Switzerland, Canada, Argentina, Guernsey, Isle of Man and the US Department of Commerce's Safe Harbour Privacy Principles as providing adequate data protection.[401] 348

If the third country in question does not ensure an adequate level of protection in accordance with Article 26 (1) a transfer or a set of transfers of personal data to those third countries may take place on condition that: 349

(a) the data subject has given his consent unambiguously to the proposed transfer; or
(b) the transfer is necessary for the performance of a contract between the data subject and the controller or the implementation of precontractual measures taken in response to the data subject's request; or
(c) the transfer is necessary for the conclusion or performance of a contract concluded in the interest of the data subject between the controller and a third party; or
(d) the transfer is necessary or legally required on important public interest grounds, or for the establishment, exercise or defense of legal claims; or
(e) the transfer is necessary in order to protect the vital interests of the data subject; or
(f) the transfer is made from a register which according to laws or regulations is intended to provide information to the public and which is open to consulta-

[398] Art 29 Data Protection Working Party, 26. 6. 1997, Document XV D/5020/97 EN, available at: http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/1997/wp4_en.pdf (accessed 5. February 2010)

[399] Art 29 Data Protection Working Party, Document XV D/5025/98 EN, available at: http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/1998/wp12_en.pdf (accessed 5. February 2010)

[400] Bygrave, Data Protection Law, p. 81

[401] http://ec.europa.eu/justice_home/fsj/privacy/thridcountries/index_en.htm (accessed 5. February 2010)

tion either by the public in general or by any person who can demonstrate legitimate interest, to the extent that the conditions laid down in law for consultation are fulfilled in the particular case.

350 A further derogation may take place if a Member State authorises the proposed transfer accompanied by "*adequate safeguards*" instigated by the data controller for protecting the privacy and other fundamental rights of the data subject (see Article 26 (2)). The Member State has to notify to the Commission and the other Member States of the authorizations it grants pursuant to Article 26 (2). Such safeguards may result from *appropriate contractual clauses*. The Commission stipulated standard contractual clauses that may be used to govern the transfer of personal data to third countries that do not offer an adequate level of protection.[402]

3.3 Data protection within a trans-european research project – using the example of ACGT

3.3.1. Data flows

351 Within genetic research projects like ACGT, genetic data has to be exchanged to achieve the projects goals. Genetic data of a patient shall be collected and stored in different databases so that researchers participating in the project can do research using the patient's data. It is obvious that the dataflow is a crucial part of the success of genetic research projects. Only if this dataflow can be designed in a lawful and fair way, will it be accepted by the participating patients. Therefore, the lawfulness of the dataflow is a crucial factor for the success of genetic research projects, if not the most crucial factor.

352 To ensure compliance of the project itself with all relevant legal and ethical issues, it is of high importance to identify, qualify (from a legal point of view) and structure the data flows within the research project. At first, data are produced during the patients' therapy. Clinical trials are characterised by a multitude of data flows between different institutions.

353 To illustrate the data flows in current clinical practice, one can examine the Nephroblastoma trial run by the University of Saarland, which is one of the trials within the genetic research project ACGT, can be used as an example of clinico-genomic trials.

[402] See Model Contracts: http://ec.europa.eu/justice_home/fsj/privacy/modelcontracts/index_en.htm (accessed 5. February 2010)

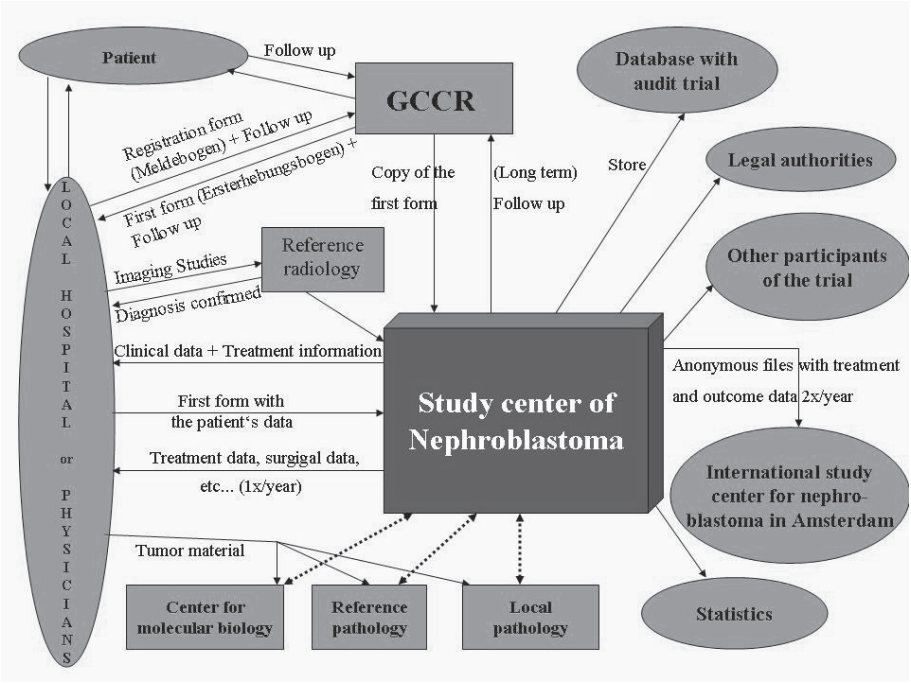

Figure 1: Data flows within the Nephroblastom trial as part of the genetic research project ACGT (GCCR = German Childhood Cancer Registry)

The figure shows the complexity of the data flows that occur in a medical research trial. A lot of data processing, in particular data transmission, is needed to carry out the research. 354

The easiest way to run such a trial from a legal perspective would be to use only anonymous data. The processing of anonymous data doesn't need a legal basis or an informed consent of the data subject as anonymous data is not personal data. Anonymous data can therefore not affect patients' privacy and would not fall under the scope of the Data Protection Directive.[403] 355

However the analysis of data flows shows that most of the data cannot be processed anonymously. As the identification of each patient has to be guaranteed in order to give the best possible therapy, most of the data needed for such a clinico-genomic trial has to be processed in a pseudonymous way. Rendering data pseudonymous means replacing a person's name and other identifying characteristics with a label, in order to preclude identification of the data subject or to render such identification substantially difficultly for the data user. 356

The data flows shown in *figure 1* can be divided firstly into data flows that need to be personalised and thus must be pseudonymized before publication, with the effect that data protection legislation is applicable for such data processing and secondly into data flows that can be anonymous, therefore data protection legislation would not be applicable to the processing. 357

[403] See the more detailed explanation above under ■0.

358 Most of the involved parties only process pseudonymous data without having the link to the individual. Therefore one could argue that this kind of pseudonymous data has to be treated as anonymous data by a data controller, who does not have the link to the individual and therefore does not know the particular data subject. The consequence would be that a data controller who does not have the link to a data subject would not need a basis of authorisation for the processing of that data, as this data processing would not fall under the scope of the Data Protection Directive.

359 That is why we analyse the meaning of the term "anonymous data" in the European context with the primary goal of classifying some pseudonymous data, where re-identification is almost impossible, as anonymous data, so that a basis of authorisation is no longer needed.

360 A further step will be to identify one or many data controllers within figure 1 above. The data controller is responsible for the lawfulness and fairness of the data processing. He can delegate the processing. In the case that other bodies (third parties) are commissioned to collect, process or use personal data, the responsibility for compliance with the data protection provisions rests with the data controller. For the data transfer between the data controller and the data processor no basis of authorisation is needed. In other words the less data controllers there are within a genetic research project, the easier it gets to process data within the project.

361 On the other hand, it gets more difficult for the data controllers to ensure compliance with the legal framework of data protection as they would be responsible for more actions and more data processing units. Therefore it is of vital importance to provide guidelines for the data controller and a reliable framework for the exchange of data within the project. That is why the data flow of such projects has to be designed in a way that a data controller can comply with all the provisions in an easy way. If this framework gets too complex, no researchers (who are no data protection experts) would use the network. So the data flow design of the project has to keep this in mind and provide a data exchange ensuring that a researcher complies with all the data protection legislation if he uses the network's platform according to the instructions.

362 Having this in mind, a new model for the data flow within ACGT was elaborated, which can easily be adapted to other genetic research networks. This model will be examined in detail in the following section especially its conditions, the exact implementation and the parties involved.

3.3.2. Legitimate processing of genetic data (Directive 95/46 EC)

363 Genetic data is a very sensitive type of data and may even be the most sensitive data that exists about a human being. Therefore the legitimate processing of genetic data has to comply with strict regulation. However, the processing of genetic data is quite a new phenomenon. As a consequence not all the questions regarding the legitimate processing of personal data have yet been answered. New problems arise, dealing especially with the questions under what conditions the processing of genetic data is lawful and who is allowed to process this kind of data. These questions will be examined and answered in the following section.

3.3.2.1. Genetic data

364 Genetic data contains a huge amount of information about the person it refers to. It provides information about his or her descent, ethnic origin, and, with a certain

probability, about future diseases, chances of healing and much more. Each individual's genetic data is unique and can even contain information about yet unborn relatives. Therefore, each person can be reliably identified by their genetic data.

Due to the amount of information they carry concerning an individual's state of health, origins and descent, genetic data has to be classified as highly sensitive. Because of this, genetic data has to be protected from a legal point of view as well as from an ethical point of view in a highly strict way as the unlawful processing of genetic data would put the privacy of the data subject at high risk. 365

3.3.2.1.1. Special characteristics of genetic data with regard to data protection. The characteristic features of genetic data are its uniqueness and the highly sensitive quality of the information it contains. Consequently, European data protection legislation ranks data concerning health, such as genetic data[404], as data requiring special protection. Therefore, the processing of these kinds of data is subject to restrictions. 366

The regulation of the processing of personal data is based upon two main ideas. The first idea is that the economical, social, cultural and individual activities, with no public or private distinction, require in various extents the processing of information relative to natural persons. The second idea is intimately bound to the first one and is that natural persons must be protected against any infringement to their fundamental rights and freedoms that might arise from the processing of information relative to them. In other words, the processing of personal data is frequently needed for multiple good reasons. However at the same time, the processing of personal data induces the danger to expose natural persons to grave risks of discriminations or infringements to their fundamental rights and freedoms. With respect to this and with this aim in view, the processing of personal data must comply with several rules expressing the balance between all the interests in presence. In this context Directive 95/46/EC aims to ensure the protection of fundamental rights and freedoms of natural persons (data subjects) and in particular their right to privacy with respect to the processing of personal data (Article 1 paragraph 1). This protection requires regulating the processing of personal data in order to prevent any infringement of the fundamental rights and freedoms of the data subject. 367

To be effective and coherent, this regulation has to be built on the analysis of the risks capable to affect the fundamental rights and freedoms of the data subject. It is only possible to determine the conditions under which personal data can be processed in full respect of the fundamental rights and freedoms of data subjects when these risks are identified. 368

This risk assessment is particularly important since the recent evolutions of Information and Communication Technologies have multiplied the possibilities of processing personal data and therefore increased the risk of infringement to the fundamental rights and freedoms of the data subject. 369

The use of new technology should naturally induce the assessment of the new risks attached to its implementation, especially in healthcare regarding the protection of medical data. 370

[404] See Working Document of the Article 29 Data Protection Working Party: Working Document on Genetic Data, p. 5 (available at: http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/2004/wp91_en.pdf; accessed 5. February 2010)

371 The general principle is that the risk of infringement to the rights and freedoms of the data subject does not depend on the informational content but on the purpose of the processing of the personal data. In other words, the potential or actual danger for the fundamental rights and freedoms of the data subject has to be assessed regarding the purpose of the processing of the personal data.

372 But the principle is slightly – though not entirely – different for sensitive data[405]. It is commonly admitted that the sole content of this data already exposes the data subject to the risk of infringement of his or her fundamental rights and freedoms, whatever could be the purpose of the data processing. To put it another way, any use of sensitive data is susceptible to creating grave risks of discrimination for the data subject. Therefore sensitive data requires a special protection taking into account the content and the purpose of its processing.

373 With this end in view, the Directive has decided that "*data which is capable by its nature of infringing fundamental freedoms or privacy should not be processed* (…)"[406]. The ban on processing medical data is the special protection provided by the Directive to ensure the respect of the fundamental rights and freedoms of the data subject regarding the processing of his or her medical data.

374 Hence the ban on processing medical data should not be seen as opposing the free movement of personal data. The ban on processing medical data is more a limit than an exception to the free movement of personal data. In fact the free movement of personal data can only be conceived in the full respect of the fundamental rights and freedoms of the data subject and this respect includes the ban on processing medical data.

375 Nevertheless, the Directive grants permission to process medical data in seven hypotheses. In these hypotheses the legitimacy of the processing of medical data (the balance between the interests in presence[407]) is formally presumed (cf. *infra* the necessity to really assess its legitimacy). This comes from the fact that, in principle, the situations described in these hypotheses should justify the processing of medical data, without prejudice for the other conditions ensuring the lawfulness of the data processing.

376 These exceptions to the ban on processing medical data must be strictly interpreted. The processing of medical data is strictly forbidden beyond these exceptions.

377 The first hypothesis granting permission to process medical data is that with the consent of the data subject (Article 8 paragraph 2 lit. a). The data subject's consent is frequently presented as the natural base for the legitimacy of the processing of medical data. Therefore, probably the most relevant exception for research purposes within genetic research projects is the "[e]xplicit consent by the data subject to the processing of this data" (Article 8 paragraph 2 lit. a).

378 However in the case of a scientific project, it must be considered that to consent in advance to each individual operation performed upon the data is almost impossible as normally in the course of a project new research methods are developed which may demand other operations performed upon the data than those to which the patient has previously consented. The cooperation with other scientists may also

[405] Usually, sensitive data are personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership and personal data concerning health or sex life (Article 8 of Directive 95/46/EC)

[406] Directive 95/46/EC, Recital 33

[407] Cf. *infra* for the identification of these interests

require the extension of the consent. On the other hand it may be doubted whether a consent which is worded too extensively is still valid.

In general such consent must be given in writing or in a comparable form. Article 8 paragraph 2 of the Directive does not state this explicitly however according to Article 7 lit. a), a data subject has to give his or her consent unambiguously even if only non-sensitive personal data is processed. Therefore Article 7 does not state the need for written consent explicitly but as the consent has to be given in an unambiguous way, a written consent is regularly needed according to Article 7 lit. a). 379

A fortiori, although it is not stated explicitly in Article 8 paragraph 2, the consent to a processing of sensitive personal data also has to be given in writing, as the processing of sensitive personal data effects the privacy of a data subject more than the processing of non-sensitive personal data. Therefore, the level of protection of sensitive personal data has to be at least as high as the level of protection of non-sensitive personal data (see 0 for more detail). 380

Another exception allowing for the processing of sensitive data is where "processing is necessary to protect the vital interests of the data subject or of another person where the data subject is physically or legally incapable of giving his consent"[408]. 381

The notion of "vital interest" means expressly and exclusively the situation of an imminent danger to the life of a natural person. This covers the protection of the vital interests of the data subject but also of any other natural person. However, in this last situation the Directive adds that the data subject must be physically or legally incapable of consenting to the processing of his or her medical data. It can not be deduced from this disposition that the data subject physically or legally capable of consenting, could, without any consequence, refuse to authorize the processing of his or her medical data when the vital interests of another person are at stake. The qualification of this behaviour should be qualified under the applicable law. However for research networks such as ACGT, this exception is not applicable as the participating patients are not legally or physically incapable of consenting to the processing of their medical data. 382

Article 8 paragraph 3 of the Directive states another possibly important exception for scientific research projects like ACGT. It states that the processing of sensitive personal data is permitted if the processing of the data is required for the purposes of preventive medicine, medical diagnosis, the provision of care or treatment or the management of health-care services, and where this data is processed by a health professional subject under national law or rules established by national competent bodies to the obligation of professional secrecy or by another person also subject to an equivalent obligation of secrecy. 383

Scientific research projects often aim to improve the treatment of (future) patients, as does ACGT. If the processing of sensitive data is required for the provision of treatment, this processing is permitted if it is done by a health professional or another person subject to the obligation of secrecy provided for in the Directive. 384

This exception only allows the processing of sensitive data if it is required for the concrete treatment of a concrete patient (data subject). Therefore scientific research projects aiming to improve the treatment of several patients in the future do not fall under that exception. 385

[408] Directive 95/46/EC, Article 8.2, c)

386 According to Article 8 paragraph 4, Member States may lay down additional exemptions by national law or by decision of the supervisory authority for reasons of substantial public interest, subject to the provision of suitable safeguards.

387 Thus the Directive does not state exemptions from the prohibition on processing of sensitive data, but empowers the Member States to introduce national exemptions for reasons of substantial public interest and subject to the provision of suitable safeguards.

388 The disadvantage of that regulation for European scientific research projects is that it is the free choice of the Member States to introduce such exemptions in their national law. Furthermore, the conditions for a processing of sensitive data because of a particular public interest can differ between the Member States, as the Directive empowers the Member States to introduce such regulation and does not harmonize it in detail. Therefore, it is very difficult for European projects to comply with all the national regulation regarding the processing of sensitive personal data for reasons of substantial public interest.

389 Examples of a substantial public interest are introduced by Recital (34) of the Directive:

"(34) Whereas Member States must also be authorized, when justified by grounds of important public interest, to derogate from the prohibition on processing sensitive categories of data where important reasons of public interest so justify in areas such as public health and social protection – especially in order to ensure the quality and cost-effectiveness of the procedures used for settling claims for benefits and services in the health insurance system – scientific research and government statistics; whereas it is incumbent on them, however, to provide specific and suitable safeguards so as to protect the fundamental rights and the privacy of individuals."

390 Scientific research is mentioned explicitly in Recital (34) as a possible example of an important public interest. Member States can therefore introduce regulation permitting the processing of sensitive personal data for scientific research purposes under the condition to provide specific and suitable safeguards so as to protect the fundamental rights and the privacy of individuals. As mentioned above, these exemptions introduced by the different Member States shall be notified to the Commission (Article 8 paragraph 6). The exemptions can be introduced either as national law or by decision of the supervisory authority. No Member State is forced to introduce such an exemption and the exact definition of this exemption is left up to the Member States. For a trans-European scientific research project like ACGT, this exemption is not very helpful either, as it cannot be guaranteed that each

391 Member State has introduced such an exemption. Besides, even if this exemption was introduced in each Member State the different national laws would not be fully harmonized. It would not be practicable to examine all the national exemptions of the Member States for scientific research and create the model of the data flow within the network according to common rules stated in each national law as the lowest common factor.

392 The legitimacy of the processing of sensitive data – the balance of the interests at present – has to be assessed now.

393 First the present interests have to be identified. Are they only the interests of the data controller and of the data subject or should we also consider the interests of third parties concerned and the interests of society as a whole? In our view, these

last two categories of interests should be taken into account when evaluating the legitimacy of the processing of sensitive data.

The explicit and valid consent of the data subject presumes, until proven to the contrary, the existence of an acceptable balance between the present interests in the processing of his or her medical data. However in this case, it is quite difficult to assume that the data subject has adequately taken into account interests other than their own. 394

In any case, the processing of medical data will not be legitimate if the balance between the present interests is not respected, even with the regular consent of the data subject. 395

The legitimacy of the processing of sensitive data is usefully strengthened by the additional consent of the data subject nevertheless. That is the reason why we must firmly approve and recommend the ethical practice of aiming to obtain the consent of the data subject when processing medical data. This practice is frequent in the conduct of clinical trials and in telematic networks in healthcare. 396

Finally, it has to be stressed that no other legal basis can legitimate the processing of sensitive data. That excludes the use of the hypotheses of formal legitimacy enumerated in Article 7 of the Directive for non-sensitive personal data. For example, the data controller may not legitimate the processing of sensitive data by the balance of the present interests without respecting the hypotheses enumerated in Article 8. 397

In conclusion it may be said that the protection of sensitive data implies the need to fix the rules applicable to the processing of sensitive data and hence to determine their conditions. 398

With regard to their highly sensitive nature, medical data requires a special protection taking into account its content and the purpose of its processing. Therefore Directive 95/46/EC has decided to prohibit the processing of medical data. However the Directive provides that this ban does not apply in several cases. In these cases the legitimacy of the processing of medical data is formally assumed without prejudice to the other conditions ensuring the lawfulness of the data processing. These exceptions to the ban on processing medical data have to be interpreted strictly. 399

Furthermore, the Data Protection Directive would still be applicable if such an exemption would be used to legitimate the processing of genetic data. It would be much more practicable for a scientific researcher involved in a trans-European project such as ACGT, if the data he or she uses would not fall under the scope of the Directive at all. As mentioned above, only "personal data" falls under the scope of the Data Protection Directive. From the legal point of view, it would be best for a scientific researcher, if he or she could use non-personal data for his or her research. On the other hand, the identification of the data subject is needed from the medical point of view, as the patient may benefit from the scientific research with his or her data. 400

In the following section it will be examined whether genetic data can be anonymised in a legal sense at all and if so under what conditions. Besides, it must always be taken into account that the data subject shall benefit from the research for example that carried out in trans-European research projects like ACGT and must therefore be identifiable. 401

402 **3.3.2.1.2. Anonymisation of genetic data.** As described above, the data flow model for genetic research projects has to take into account both the legal situation and the medical requirements. This means that the model must ensure the legitimate processing while the medical requirements, i. e. the re-identification of the data subject providing him or her new developed treatments, must not be forgotten. The challenge is to develop such a model that combines these two approaches in a practicable and lawful way.

403 The solution used most often in scientific research projects not using unique data like biometric or genetic data is to pseudonymise the data used for the research. Most of the time it is of no importance for researchers to know the exact person to which the data he or she examines refers. Hence the data subject's name and other identifying characteristics are replaced with a label in order to preclude identification of the data subject or to render such identification substantially difficult. The person can only be re-identified by using the appropriate key. This pseudonymous data may be regarded as anonymous data for the researcher who doesn't have the link to the data subject. Hence, the Data Protection Directive would no longer be applicable to this data processing.

404 Article 6 paragraph 1 lit. e) Directive 95/46/EC states that in principle, i. e., as soon as the research purpose allows it, genetic data has to be rendered anonymous in such a way that the data subject is no longer identifiable (see Recital 26). As soon as his or her data is rendered anonymous, the data subject requires no further protection because re-identification is impossible due to the lack of reference to the aforesaid person. As the processing of anonymous data offers the best protection for such a person, anonymisation of personal data has to be given priority over possibly relevant exemptions from the general prohibition on processing sensitive data (Article 8 Directive 95/46/EC). Consequently, when genetic data has to be processed, it must be carefully considered whether it is possible to process it in anonymised form. If this is the case, it is not necessary to obtain the person's consent, because the processing of anonymous data does not fall within the scope of the Data Protection Directive. As a result, anonymous data can be processed without restrictions. At least from a data protection point of view, due to the lack of reference to a person, anonymous data can be collected, stored and published without restrictions.

405 The important question at this stage is whether pseudonymous genetic data can also be regarded as anonymous data for the data controller or whether genetic data always have to be qualified as personal data because of the uniqueness of such data?

406 Take the example of a study on HIV. In the course of the study, a gene sequence which is sufficiently large for identifying a person is published on the internet without personal details. If there is already genetic information about the concerned person stored for a different purpose e.g. because of a saliva-test or as a compulsory requirement for the signing of a life insurance contract with a high amount insured, the identification of the person concerned and his or her HIV disease would be possible for all persons who have access to these data bases by a matching-procedure.

407 Although this scenario is only a worst-case scenario, it shows that the unique quality of genetic data causes the problem that despite comprehensive anonymisation, a re-identification of the person involved is possible if relevant additional knowledge exists.

408 If this is the case, the question arises whether it is possible at all to render genetic data anonymous in order to comply with data protection legislation or if genetic

data generally has to be classified as personal data. This is the big difference between "normal" data and "unique" data such as biometric and genetic data. Whenever there is a personalized reference data set available, the concerned data subject can always be identified by a matching procedure. This is generally not the case if "normal" data is processed.

The crucial question is how to define the term "anonymous". The Directive itself doesn't contain an explicit definition of this term, as the definition of this term was deleted from the original draft of the Directive during the consultations. 409

Only Recital (26) of the Directive contains a definition of this term: 410

Whereas the principles of protection must apply to any information concerning an identified or identifiable person; whereas, to determine whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the controller or by any other person to identify the said person; whereas the principles of protection shall not apply to data rendered anonymous in such a way that the data subject is no longer identifiable; whereas codes of conduct within the meaning of Article 27 may be a useful instrument for providing guidance as to the ways in which data may be rendered anonymous and retained in a form in which identification of the data subject is no longer possible. 411

According to the wording of Recital (26), data can only be classified as anonymous, if the anonymisation is irreversible and thus re-identification of the data subject is impossible for everybody. As stated above, the re-identification of a data subject is always possible (at least with a certain effort) if a reference data set of the data subject's genetic data is available. Therefore, genetic data can never be classified as anonymous data according to Recital (26) as genetic data can never be anonymised in such a way that re-identification of the concerned data subject will never and under no circumstance be possible. 412

Nevertheless as mentioned above under ■0, on the basis of European legislation, the anonymisation of genetic data seems to be possible, accepted and not objected to. For example, the Article 29 Data Protection Working Party accepts the anonymisation of genetic data – which, according to the wording of the Data Protection Directive cannot be rendered anonymous – as a means to limit the dangers of genetic research.[409] 413

On the contrary: In the first place, the European Economic and Social Committee (EESC) supported the deletion of the term "disproportionate effort" from the draft. They argued that the current definition of anonymous data in the Data Protection Directive restricted the scope of the definition. Furthermore, they said that the term "disproportionate effort" is misleading in the face of rapid development of electronic data processing (EDP).[410] 414

However there is a new view: In the First Report on the implementation of the Data Protection Directive 95/46/EC,[411] the Commission states, that the interpretation of the Directive must be sensible and flexible and draws attention to an article 415

[409] See Working Document of the Article 29 Data Protection Working Party: Working Document on Genetic Data, p. 11 (available at: http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/2004/wp91_en.pdf; accessed 5. February 2010)

[410] Official Journal C 159, 17/06/1991, p. 38 (40)

[411] First report on the implementation of the Data Protection Directive (95/46/EC) of 2003; available at: http://eur-lex.europa.eu/LexUriServ/site/en/com/2003/com2003_0265en01.pdf (accessed 5. February 2010)

of the European Privacy Officers Forum (EPOF),[412] which emphasizes the practical orientation and exemplary function of the German definition of "anonymisation". Moreover, in spring 2007 the Article 29 Data Protection Working Party published an opinion on the concept of personal data[413] stating that the extent to which certain identifiers are sufficient to achieve identification is something dependent on the context of the particular situation. A mere hypothetical possibility to single out the individual should not be enough to consider the person as "identifiable". The criterion of "all the means likely reasonably to be used either by the controller or by any other person" should in particular take into account all the factors at stake. Where identification of the data subject is not included in the purpose of the processing, the technical measures to prevent identification have a very important role to play according to the Article 29 Data Protection Working Party. Putting in place the appropriate state-of-the-art technical and organisational measures to protect the data against identification may make the difference as to whether or not the persons are identifiable, taking account of all the means likely reasonably to be used by the controller or by any other person to identify the individuals. Therefore, the Article 29 Data Protection Working Party holds the view, that the term "anonymous data" in Data protection Law covers not only data where the data subject is no longer identifiable in any circumstance, but also data where the risk of re-identification is negligible.

416 The German transposition of the Data Protection Directive contains a broader definition, which is similar to the definition of the first suggestion of the Commission with regard to the Data Protection Directive.[414] Section 3 paragraph 6 BDSG (Federal Data Protection Act) defines anonymisation as the modification of personal data, so that the information concerning personal or material circumstances can no longer or only with a disproportionate amount of time, expense and labour be attributed to an identified or identifiable individual. In conclusion, the BDSG accepts two groups of anonymous data: first, data which can no longer be turned into personal data; and secondly, data which is *de facto anonymous* because it can only be turned into personal data with a disproportionate amount of time, expense and labour.[415]

417 Therefore, according to that definition, genetic data can also be regarded as anonymous data under certain conditions. The conditions under which genetic data can be qualified as anonymous data for a data controller, for example a researcher within the project, shall be examined in the following section.

418 Although the wording of Recital (26) of the Data Protection Directive 95/46/EC does not immediately suggest this, it is generally assumed – in compliance with the

[412] EPOF, Comments on Review of the EU Data Protection Directive (Directive 95/46/EC) of 2002, available at: http://ec.europa.eu/justice_home/fsj/privacy/docs/lawreport/paper/epof_en.pdf (accessed 5. February 2010)

[413] http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/2007/wp136_en.pdf (accessed 5. February 2010)

[414] Article 2 lit. b of the Proposal for a Directive of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data of 18/7/1990

[415] See: Metschke/Wellbrock, Datenschutz in Wissenschaft und Forschung, Berlin 2002, pp. 20 ff., available at: www.datenschutz-berlin.de/attachments/47/Materialien28.pdf?1166527077 (accessed 5. February 2010)

Directive – that data, which can be de-anonymised only with a disproportionate amount of time, expense and labour, can be classified as anonymous.[416]

The question at this stage is how to define the term "disproportionate" and especially the person to which the amount of time, expense and labour has to be disproportionate to de-anonymise the concerned data subject. In other words: Is it possible that a piece of genetic data is anonymous for one researcher, while it is personal for another? Does the classification of disproportionate effort depend exclusively on the data controller or also on a third person? 419

Recital (26) of the European Data Protection Directive states: "Whereas, to determine whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the controller or by any other person to identify the said person." However, it is pointed out[417] that following this view, data might be regarded as anonymous data although a risk of de-anonymisation still exists. 420

Despite Recital (26), the central question of this opinion is, whether or not de-anonymisation is possible for the data controller. Following this view, the initial point is the distinction[418] between a data controller who actually has access to additional knowledge enabling him to identify the said person, and a data controller who does not have access to this knowledge meaning that the person is not identifiable for him. Therefore, it is assumed that the term "personal data" is relative.[419] 421

Given that the term "personal data" is relative, i. e. depending on the additional knowledge of each particular data controller, the question arises, how pseudonymous data – i. e. data, whose identifying characteristics were replaced by a reference code in order to eliminate the possibility of identification of the concerned person, or at least, to make it significantly more difficult – has to be treated by a data controller, who does not have access to the additional knowledge. 422

As stated above, pseudonymised data is significantly more useful in the framework of a medical research project. Only if the identification of the said person remains principally possible, can the patient benefit from the research results. If the data controller does not have access to the key which enables him or her to identify the particular patient, the data in question is anonymous for the data controller. The risk of identification for the said person remains the same. On closer examination, the key which is used for decrypting the pseudonym, is merely accessible through additional knowledge which turns anonymised or pseudonymised data into personal data, provided that the data controller has access to the additional knowledge. Therefore, safely encrypted pseudonymised data has to be classified as anonymous data if the data controller does not have access to the key. In consequence, data protection legislation is not applicable to the particular data processing of this particular data controller[420]. Therefore it depends on the additional knowledge of the data controller, whether or not certain data can be qualified as anonymous data. 423

---

[416] Redeker, Konrad/Karpenstein, Ulrich: Über Nutzen und Notwendigkeit, Gesetze zu begründen, in: NJW 2001, p. 2825 (2830)

[417] Metschke/Wellbrock: Datenschutz in Wissenschaft und Forschung, Berlin 2002, S. 21, available at: www.datenschutz-berlin.de/attachments/47/Materialien28.pdf?1166527077 (accessed 5. February 2010)

[418] See also figure 2.

[419] Ibid

[420] See for example: Gola, Peter/Schomerus, Rudolf: BDSG, Munich 2007,] § 3 marginal number 46

424 However, the crucial question remains, which additional knowledge has to be attributed to the data controller. It mainly depends on the accessibility of additional knowledge which allows the re-identification of the particular person.[421] What is beyond dispute is that the additional knowledge which the data controller posesses is attributable to him or her. If the data controller actually has access to additional knowledge e.g. a database, which includes both the genetic information of the said person and his name or other identifiers, then the genetic data of the concerned data subject has to be treated as personal data with all the consequences and all the restrictions of processing.[422] This applies even if the genetic data of the data subject is processed anonymously and a matching procedure is not planned. The possibility of linking certain data to a certain data subject is sufficient to qualify primarily anonymised data as personal data. The intention of the data controller, whether he or she wants to establish the link and de-anonymise the particular data, remains unnoticed.[423]

425 As a second step the question arises, if and to what extent additional knowledge is attributable to the data controller, which he or she does not currently have but which could be obtained by him or her or any other person. In answering this question, two different aspects have to be considered: first it has to be determined if only legally accessible additional knowledge is attributable to the data controller; and secondly it has to be answered whether additional knowledge, that is only available to a third person, is also attributable to the data controller who doesn't have access to that knowledge by him- or herself.

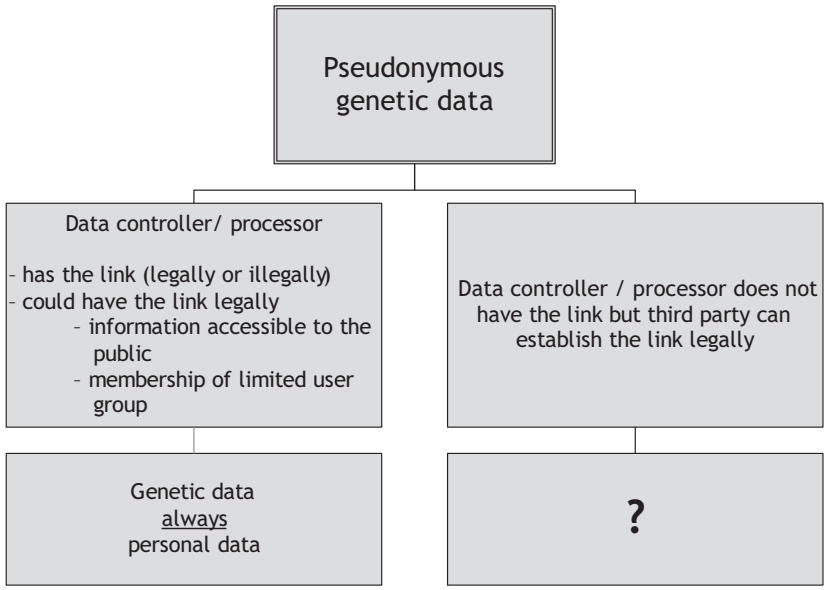

Figure 2: Quality of pseudonymous genetic data

[421] Dammann, Ulrich, in: Simitis, Spiros (Ed.): Bundesdatenschutzgesetz, Baden-Baden 2006 § 3 marginal number 29

[422] See also figure 2

[423] Gola, Peter/Schomerus, Rudolf: BDSG, Munich 2007,[]§ 3 marginal number 44

3.3.2.2. Relevance of the character of data processing for the distinction between personal data and anonymous data

Austria has already introduced a solution to this problem in its Data Protection Act. A new category of data in addition to personal data and non personal data was introduced in the course of the transposition of the Data Protection Directive: indirectly personal data (section 4 number 1 of the Austrian Federal Act Concerning the Protection of Personal Data (DSG 2000).[424] 426

Data is indirectly personal for "a controller (sub-paragraph 4), a processor (sub-paragraph 5) or recipient of a transmission (sub-paragraph 12) when the data relates to the subject in such a manner that the controller, processor or recipient of a transmission cannot establish the identity of the data subject by legal means".[425] The use of indirectly personal data is not considered an infringement of confidentiality interests requiring protection, neither if non-sensitive data is processed (section 8 paragraph 2 DSG 2000) nor if sensitive data is processed (section 9 number 2 DSG 2000). 427

If data is only indirectly personal for a recipient (e.g. pseudonymised data), transborder transmission and committing of data do not require authorisation (section 12 sub-paragraph 3 no. 2 DSG 2000). Data applications that merely include indirectly personal data are not subject to notification (section 17 sub-paragraph 2 no. 3 DSG 2000). The data subject cannot exercise the right to information (section 26 DSG 2000), rectification, erasure (section 27 DSG 2000) and to objection (section 28 DSG 2000) if only indirectly personal data is used. 428

If data is only indirectly personal for the controller (section. 4 no. 4 DSG 2000) and it will be used for scientific or statistical research purposes where the goal is not to obtain results in a form referring to specific data subjects, the controller has the right to use indirectly personal data without having to comply with further requirements (section 46 sub-paragraph 1 no. 3 DSG 2000). In this case he does not need the informed consent of the concerned data subject to process its data lawfully. 429

Whenever it is possible, data used for scientific purposes should be rendered pseudonymous or anonymous (section 46 paragraph 5 DSG 2000). This applies especially in the area of medicine, where the Austrian Medical Drugs Act imposes the duty to pseudonymise the data concerned.[426] Further safety requirements for indirectly personal data can be found in the "Medizintelematikgesetz".[427] 430

In conclusion, according to the Austrian data protection legislation, additional knowledge is only attributable to the data processor if it is accessible to him by legal 431

[424] Compare Government bill for the Data Protection Act 2003, 1613 of the annexes to the Stenographic Records of the National Council XX. GP, 37: "*Um hier im Hinblick auf das Schutzinteresse eine sinnvolle Abstufung vornehmen zu können, wurde die in der Richtlinie enthaltene Unterscheidung zwischen direkter und (nur) indirekter Identifizierbarkeit nutzbar gemacht; wenn es für den konkreten Verwender der Daten nicht möglich ist, den – z. B. in Form einer laufenden oder sprechenden Nummer – vorhandenen Personenbezug auf eine in ihrer Identität bestimmte Person zurückzuführen, dann ist der Gebrauch solcher "nur indirekt personenbezogener" Daten durch diesen Verwender unter erleichterten datenschutzrechtlichen Bedingungen erlaubt.*"

[425] § 4 No. 1, 2. clause DSG 2000 (translated by the authors)

[426] Compare: §§ 46 Abs. 3, 36 No. 8 AMG, 55 Abs. 1 MPG; Compare: Knyrim, Rainer/Momeni, Daria: Datenschutz bei klinischen Prüfungen und medizinischen Studien, in: RdM 2003 p.68

[427] Medicine Telematics Act (translated by the authors); Article 10 of the Health reform act 2005, BGBl I 2005 Nr. 179

means e.g. by using the internet, which is open to the public. The ability of third parties to re-establish the reference to the individual concerned remains unconsidered.[428]

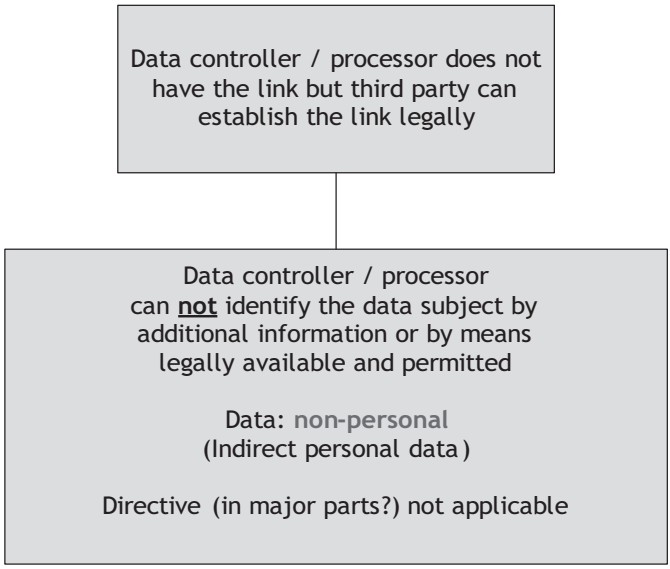

Figure 3: Indirect personal data (Austrian approach)

432 However, the Austrian regulation regarding research in genetic data in accordance with data protection requirements cannot simply be applied to other Member States of the European Union. Although the European Directive on the Protection of Personal Data (95/46/EC) has harmonized data protection legislation throughout Europe, a certain amount of freedom was given to the Member States to implement the Directive into national law.[429] Moreover, the Directive does not contain any regulation in certain areas, so that in consequence, data protection legislation in the EU Member States still differs significantly.[430]

433 The question to what extend and whose additional knowledge can be attributed to a data controller is discussed controversially.

434 First it is discussed whether knowledge that the data controller does not have and could only get by using illegal means (for example by hacking into a database, like a biobank) is attributable to him or her.

[428] See figure 3

[429] See for example: Brühann, Ulf: Die Veröffentlichung personenbezogener Daten im Internet als Datenschutzproblem, in: DuD 2004, p. 201 (201)

[430] But national transposition of the Directive 95/46/EC must not violate fundamental rights or principles like the principle of proportionality protected by Community Law, see: ECJ "Lindqvist" judgement of 6. 11. 2003, C-101/01: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:62001J0101:EN:HTML (accessed 5. February 2010), see summary 5 f. and holdings 87, 91 ff. The Member States may only take measures to ensure the protection of personal data that are consistent both with the provisions of Directive 95/46 and with its objective of maintaining a balance between freedom of movement of personal data and the protection of private life. However, nothing prevents a Member State from extending the scope of the national legislation implementing the provisions of Directive 95/46 to areas not included in the scope thereof, provided that no other provision of Community law precludes it

Some authors state that it can remain unnoticed, whether additional knowledge was or could be obtained lawfully or unlawfully. Following this view, it only depends on the actual availability of knowledge which can be used to identify the concerned data subject.[431] This would mean that although the data controller doesn't have legal access to the knowledge, this knowledge would have to be regarded as his or her knowledge. So, whenever there is a reference data set of a particular data subject available, the processed data has to be regarded as personal data for the data controller, although he doesn't have legal access to this additional knowledge. In practice this means that a data controller has to regard all the data to be processed as personal data as he cannot know whether or not a reference data set is available somewhere in the world. 435

As genetic data contains very sensitive information about the concerned person, this opinion provides a comprehensive safeguard for this person. Nevertheless, from our point of view, this opinion is not in accordance with Recital (26) of Directive 95/46/EC, which states that "account should be taken of all the means likely reasonably to be used […] to identify" the said person. The opinion presented above states that every kind of additional knowledge is attributable and not only such additional knowledge which can be reasonably used. Consequently this is not in accordance with the Data Protection Directive. Moreover, in practice, a distinction between personal and non-personal data would no longer be possible for the data controller so that the scope of application for regulations on data protection would be extended too far. For these reasons, under the rule of law, additional knowledge which is attributable to the data controller should be reasonably at his disposal, which normally means that it could be legally obtained.[432] 436

Secondly, the question arises whose knowledge can be attributed to a data controller?. In other words, can only this kind of knowledge that a data controller actually has or could legally have access to be attributed to him or her? Or can this kind of knowledge to which only a third person has access be attributed to a data controller? 437

With regard to this question, scientists in German legal literature, as presented above, predominantly hold the view that only knowledge which the data controller actually has or which is legally accessible for him- or herself can be attributed to this data controller.[433] In this respect, the German position is similar to the Austrian concept. Consequently, only such knowledge, which is accessible for him or her, e.g. 438

[431] Weichert, Thilo: Rechtsquellen und Grundbegriffe des allgemeinen Datenschutzes, in: Kilian, Wolfgang/Heussen, Benno (Eds.): Computerrechts-Handbuch, Munich 2009, No. 131 p. 14 marginal number 58

[432] See for example: Saeltzer, Gerhard: Sind die Daten personenbezogen oder nicht?, in: DuD 2004, p. 218 (220); Dammann, Ulrich, in Simitis, Spiros (Ed.): Bundesdatenschutzgesetz, Baden-Baden 2006, § 3 marginal number 37; Sieber, Ulrich: Strafrecht und Strafprozessrecht, in: Hoeren, Thomas/Sieber, Ulrich (Eds.): Handbuch Multimedia Recht, Munich 2006, No. 19 p. 206 marginal number 552. Bygrave emphasizes the criterion of probability. All probably used means should be taken into account. It has to be decided in each single case, whether the use of illegal means is probable in that case, but the criterion of probability should be construed more stringently if the means are illegal: see Bygrave 2003, p. 45.

[433] Compare for example: Dammann, Ulrich, in: Simitis, Spiros (Ed.): Bundesdatenschutzgesetz, Baden-Baden 2006, § 3 marginal numbers 37 ff. Saeltzer, Gerhard: Sind die Daten personenbezogen oder nicht?, in: DuD 2004, p. 218 (222); Roßnagel, Alexander/Scholz, Philip: Datenschutz durch Anonymität und Pseudonymität – Rechtsfolgen der Verwendung anonymer und pseudonymer Daten, in: MMR 2000, p. 721 (723).

on the Internet, can be attributed to the data controller, whereas knowledge stored in data bases, e.g. of law enforcement agencies, which are not legally accessible to the data controller, is not attributable to him or her.

439 The data controller would thus be free to deal with the data as he chooses, e.g. publish it on the Internet, as this kind of genetic data would have to be regarded as anonymous data according to that opinion. Hence, the Data Protection Directive would not be applicable in that case.

440 But this would enable, for example, law enforcement agencies or any other third party having a reference data set or another link to re-establish the reference to an individual by matching the data published on the Internet with data from their own data bank. The privacy of the data subjects, for example of the patients taking part in the genetic research project, would be affected.

441 With regard to the Data Protection Directive 95/46/EC, this opinion cannot convince. The question of whether certain additional knowledge is attributable to the data controller, and if, in consequence, a person is identifiable for the data controller, must in the first place be answered by statutory interpretation of the European Data Protection Directive (95/46/EC), corresponding with European law. Recital (26) states that in order to determine whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the data controller or by any other person to identify the said person. The interpretation of the wording of the Recital suggests that not only those means which can be legally used by the data controller can be attributed to the data controller him/herself. Furthermore, the Recital states that means which can be reasonably used by a third person to identify the said person must be attributed to the data controller as well. Without doubt, one of the means which can be reasonably used by a third person is the use of knowledge, which is legally accessible to the third person und which the third person can use with reasonable effort. The conclusion drawn from this directive-corresponding interpretation is that not only knowledge which is accessible to the data controller him or herself is attributable to the data controller, but also knowledge which is accessible only to a third person.[434]

442 A teleological interpretation of Article 2 lit a) and Recital (26) of the Directive suggests that the interpretation presented above is convincing. According to Article 1 No. 1 of the Directive, the Data Protection Directive 95/46/EC aims to protect the fundamental rights and freedoms of natural persons, and in particular their right to privacy with respect to the processing of personal data. This Directive comprises the protection of the individual against unlimited collection, storage, use and transmission of his or her personal data.

443 In the framework of a genetic research project, the data processor usually doesn't have access to the reference data set to link his data to a particular person. According to the opinion that only this kind of knowledge to which the data controller has actually or could legally have access to could be attributed to him or her, the data dealt with would be de facto anonymous data. Therefore, data transfers in genetic research projects wouldn't fall into the scope of data protection legislation. The data processor could do with this genetic data whatever he wants, for example publish it on the internet or transmit it abroad. As a result, third parties could access the data and re-establish the link to the said person if they had a

[434] See also: Bygrave 2003, p.45

reference link to the person and an interest in the connected information. Criminal prosecutors or insurance companies, which sometimes own gene banks, could, for example, have a great interest in knowing if a person, whose reference link they have got, has a certain disease. But this would be an infringement of the citizen's right and freedom to decide for him- or herself, who is at which point of time allowed to access which particular part of his or her personal data. The aim of data protection law and the Data Protection Directive 95/46/EC would be undermined.

For this reason it is necessary, in accordance with the wording of the European Data Protection Directive and the sense and aim of data protection law and the Directive, to also attribute that kind of additional knowledge to a data controller, to which only a third person has legal access. If a third party can legally access knowledge which can be used to identify the said person, the genetic data concerned is personal data for the data processor as well, although the data processor himself cannot identify the person. 444

As a consequence, the data processor would have to treat all genetic data as personal data in order to avoid responsibility, as he cannot know whether there is a reference link to a person for a certain set of genetic data he uses available to a third party. Every data processing operation of personal data requires permission, either by law or by consent of the concerned person. Therefore, each data controller within the genetic research project would need an informed consent for each data processing operation as a consequence of that opinion, since a legal basis is generally not available for this kind of data processing taking place, for example, within the research project ACGT. 445

From this follows that, on the one hand, the said person's privacy would be effectively protected. But on the other hand, this interpretation would have the effect of a strong restriction on medical research, as an informed consent would be needed for each single data processing operation. The legal validity of an extensive consent of the said person, which also comprises future data processing, including operations which are not known at the point of time when the consent is given, is debatable. The processing of genetic data would be hindered, if not impossible at all, so that, as a consequence, (future) medical genetic research would be affected adversely. 446

For these reasons, the interpretation supported above must be applied restrictively. The privacy of the concerned data subject is not in danger if, firstly, the data processor him- or herself cannot legally access the additional knowledge of a third party and, secondly, the third party cannot access the data processor's data. In these cases, when neither the data controller nor the third party can establish the link alone, the identification of the said person is not possible, at least in consideration of the present state of the art, or the identification would require an unreasonable effort. Attributing additional knowledge of third parties to a data controller also in these cases would extend the scope of data protection legislation too far and would oppose the aim of data protection in general. 447

In conclusion, the attribution of additional knowledge of third parties depends on the situation of the data processing operation in question.[435] If there is any danger that a third party can access the data processor's data (e.g. following publication or data transmission) and identify the said person, data protection legislation must 448

[435] See figure 4 below

provide effective protection of the individual's privacy. For this reason additional knowledge of a third party must be attributed to the data controller if data processing causes any danger for the person's privacy, e.g. in case of data transmission or publication. In consequence, this would mean that for every transmission or publication of de facto anonymous data a permission (either by law or consent of the said person) is required, because the data processor cannot know, for which of the genetic data sets to be processed additional knowledge (e.g. a personalized reference data set) exists.

449 Data processing operations which do not cause any danger for the individual's personal rights and privacy, e.g. adequately secured storage or use of de facto anonymous data, do not require any consent of the patient or any permission by law:

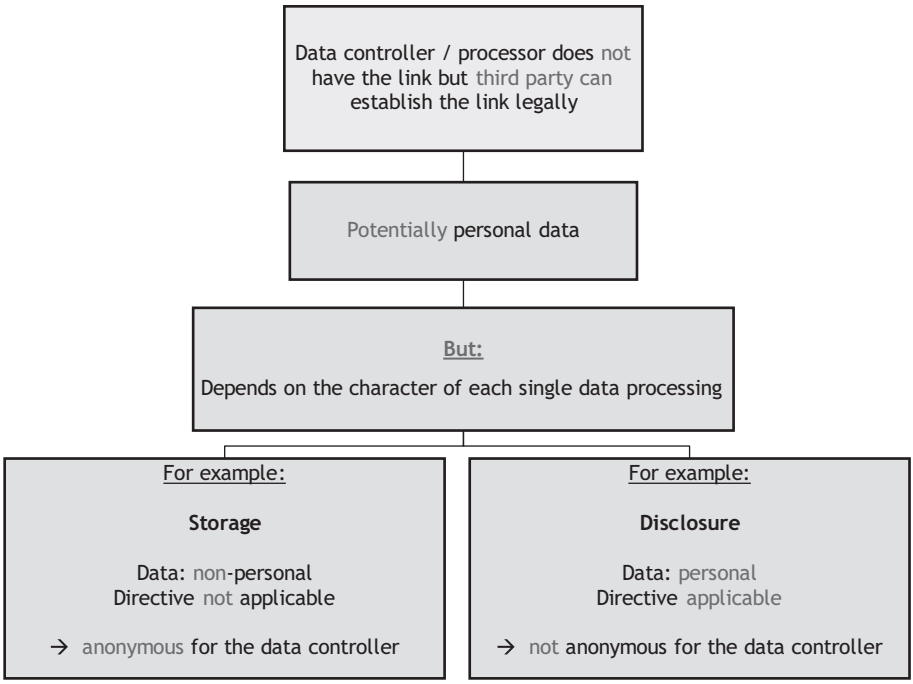

Figure 4: Character of each single data processing (ACGT approach)

450 This solution offers sufficient protection of the concerned individual's right of privacy without restricting medical research too much. The opinion supported above is also in accordance with Recital (26) of the Data Protection Directive, which states explicitly that in order to determine whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the controller or any other person to identify the said person. Reasonably, a third person only uses means to identify the said person if he can also access the data to be processed. If he cannot access the data, the third person does not reasonably use any means for identification, so that, following the directive-corresponding interpretation of Article 1 No. 1 and Recital (26) of the Data Protection Directive 95/46/EC, these means and also the third person's knowledge cannot be attributed to the data controller with the result, that this data for him is de facto anonymous data.

Therefore, Data Protection legislation **is applicable** whenever de facto anonymous data is transmitted and published. Data protection legislation **is not applicable** when de facto anonymous genetic data is stored and used if: 451

– firstly, the data controller cannot legally access additional knowledge of third parties and;
– secondly, third parties cannot access the data controller's data.

3.4. Data protection framework within genetic research networks

These results must now in a second step be transposed in a data protection framework within genetic research projects. The transposition has to guarantee compliance with current data protection legislation on the one hand and promote genetic research on the other hand. Therefore, we propose a Data Protection Framework for genetic research projects that consists of three pillars: the anonymisation of genetic data (first pillar) and as fallback scenarios informed consent (second pillar) and national exceptions to the ban of data processing (third pillar). We call this three pillar system the *Data Protection Safety Net:* 452

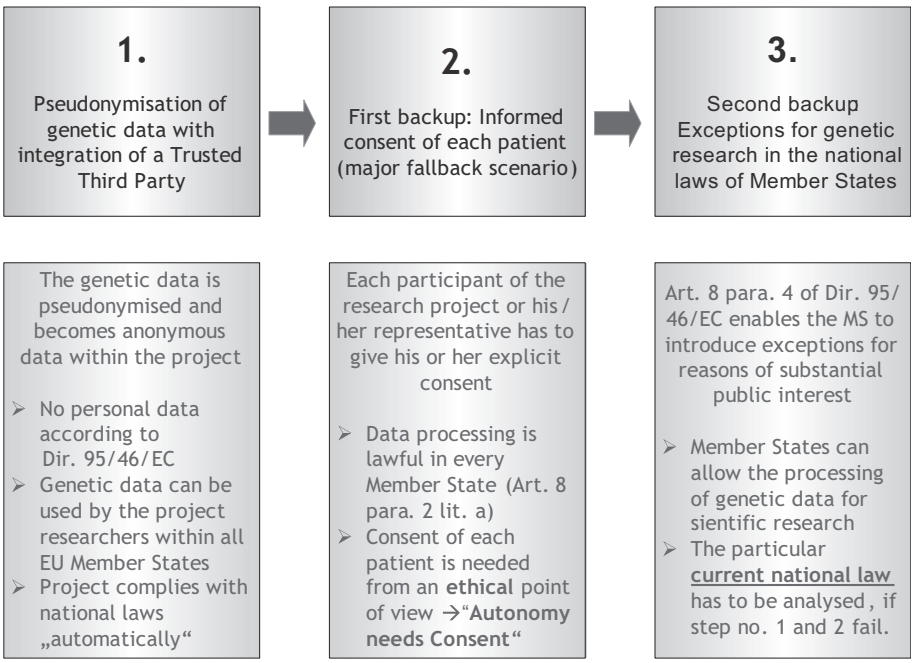

Figure 5: Data Protection Safety Net

The Data Protection architecture must therefore be set up with the prior aim to work with anonymous data wherever this is possible. Anonymisation is the best way to protect patients' privacy. 453

The architecture of data flows combined with data security measures have to guarantee the data that is used, stored and exchanged within the genetic research network is de facto anonymous. The most important data security measure consists of contracts to be signed by all partners taking part in the research project and by all 454

end users (like researchers) who get access to the research network. Thus, we create a closed user group who process only de facto anonymous data by using technical and legal means. As analysed above, the Data Protection Directive is not applicable for the processing of de facto anonymous genetic data within closed user groups.

455 Apart from this, it has to be taken into account that the proposed Data Protection architecture has to be compatible with the ICT infrastructure and policies of all participating healthcare organisations. Therefore, a Data Protection Architecture within such a network will be characterised by a multiplicity of security and network infrastructures. Thus, it will be of high importance to have minimal impact on the local IT infrastructure of every healthcare organisation for two major reasons: firstly, it is most likely that access from the outside to the hospitals' IT-infrastructure is heavily restricted, if not forbidden; secondly, and from a legal point of view even more important, only one authorised body should be responsible for data protection compliance within the GRID infrastructure. The proposed Data Protection Architecture therefore has to run independently from the local IT-infrastructures being a self-contained data protection framework in compliance with the applicable data protection legislation.

3.4.1. Anonymisation of genetic data within research networks

456 The following figure 6 illustrates the proposed solution for the de facto anonymisation of genetic data within research networks.

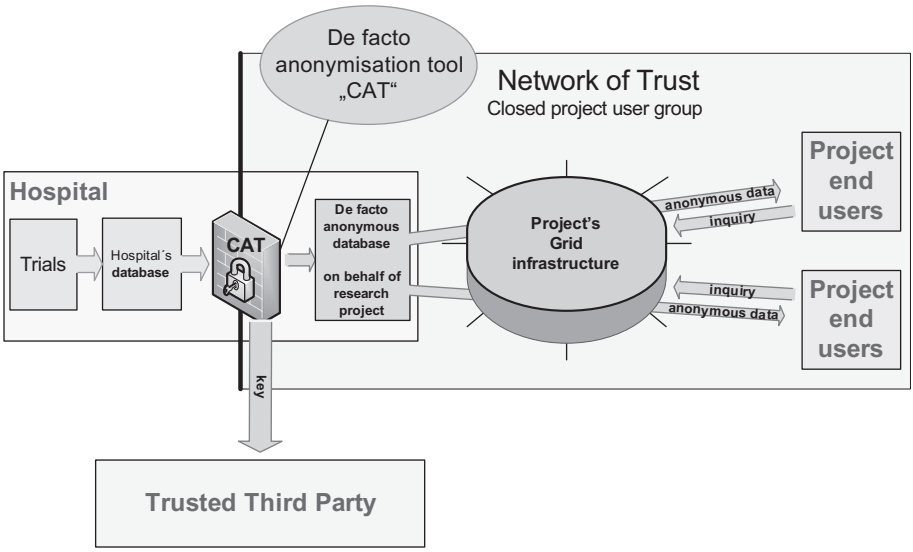

Figure 6: De facto anonymisation within research networks

457 Genetic data of the patient that is taken by the attending physician in the hospital is analysed and stored within the hospital. The hospital and its different departments are obligated to work with pseudonymised patient's data for all cases in which the physical examinations do not need the identification of the patient.

458 If a patient agrees to participate in the research project, the physician transmits his or her data to a project database located within the specific hospital, which is

physically as well as organisationally disconnected from the hospitals other databases. During the transmission to the project database the genetic data will be de facto anonymised by a pseudonymisation tool that guarantees an equivalent high standard for all genetic data transmitted from the participating hospitals to the research network. This has the effect that all genetic data processed within the network is pseudonymised on a level that is state-of-the-art. Research projects can provide such a pseudonymisation tool, but hospitals are not bound to use such a tool, the project can only commit the hospitals by binding contracts to guarantee a state-of-the-art pseudonymisation. The link of this pseudonymisation is held by a security authority named "Trusted Third Party". After this pseudonymisation the data is stored in the project database, possibly located in the hospitals or at the Trusted Third Party. From this moment the data is de facto anonymous. The de facto anonymous data and the links from the pseudonymisation must be stored in separate data bases, whereas at least the link has to be stored at the Trusted Third Party. The network's end users will only work with de facto anonymous genetic data.

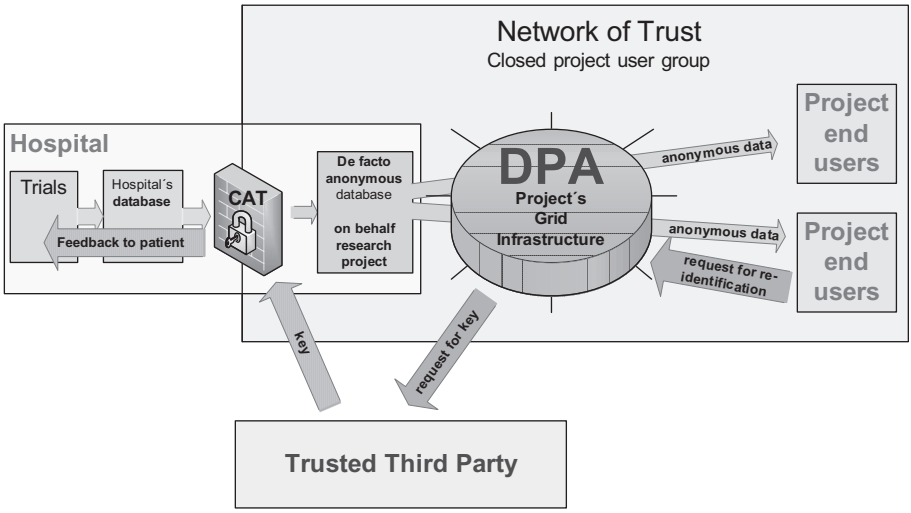

Figure 7: De-anonymisation procedure within research networks

However, if a patient needs to be identified, in case of an end user (researcher) detecting a new treatment, the cooperation of the Trusted Third Party, indicated in figure 7 above, is necessary – as only this security authority has the link for the de-anonymisation. 459

3.4.2. Necessary legal agreements, contracts and informed consents

In order to ensure compliance with current data protection legislation and especially to guarantee that data processed within the research network is and stays de facto anonymous, several contracts have to be concluded and the informed consent of the participating patients have to be obtained. 460

A patient, who is willing to participate in the research project, has to sign the informed consent regarding the processing of his or her data within the research network after having received all required information from his or her attending 461

physician. The patient information explains and defines the context and limitations under which the data can be examined, analysed and used. The informed consent is needed for ethical reasons (as explained above) and as a fallback scenario in case the anonymisation of a patient's data fails.

462 Besides, there must be contracts between the data exporters (e.g. healthcare organisations) and the research project on the one hand and between the end users and the research project on the other hand to guarantee compliance of all participants with the set up Data Protection Framework. In order to be able to conclude contracts, a legal entity has to be established that is empowered to conclude contracts on behalf of the research project. Furthermore, it will act as an internal Data Protection Authority (DPA) see under ■0.

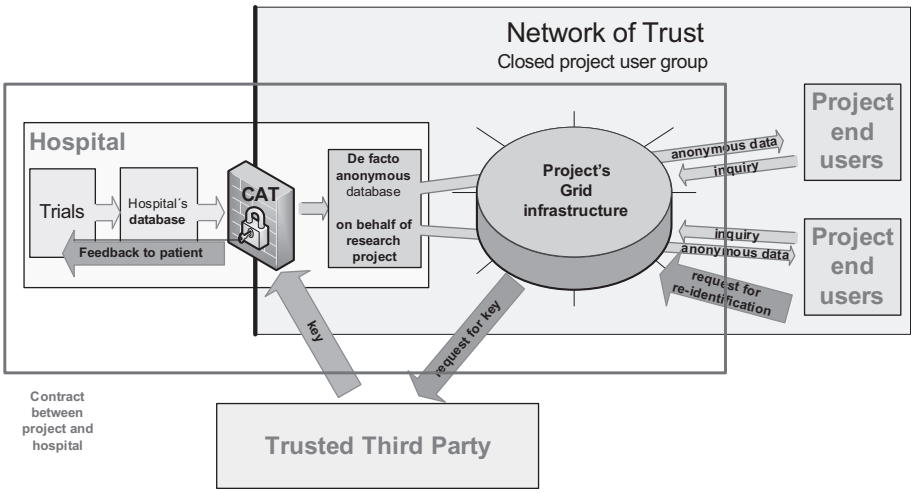

Figure 8: Contract with hospital within research networks

463 First, each data exporter, for example the hospital where patient data is collected, must have a contractual agreement with the research network concerning the data transfer. This contract rules in particular the obligation to de facto anonymise all data transferred to the project database. It also states that regarding the processing and storage of the patient's data within their own organisation the data exporters will be responsible for the compliance with data protection regulations and the procedures and policies provided by the research network. Additionally, the research network will commit the data exporters to guarantee for the fact that its employees (physicians, IT-staff, etc.) adhere to the procedures and policies provided by the framework. They have to make sure that access to the anonymous data is protected by the security mechanisms defined in the research network's Data Protection Framework. Taking into account the multitude of IT-infrastructures and different national legislations, the execution of these contracts will be both, of crucial and substantial importance.

464 Moreover, agreements with the end users are needed, which bind them to the data protection and data security policies of the research network.

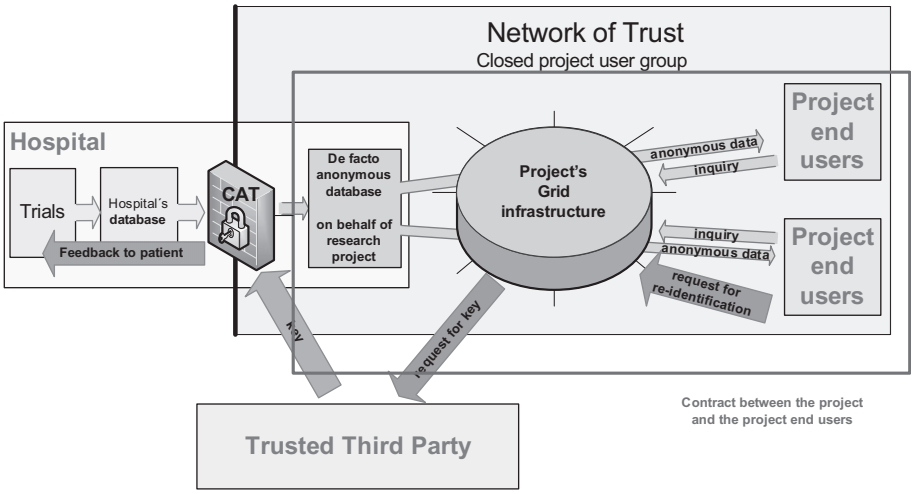

Figure 9: Contract with project end user within research networks

These contracts will be concluded with the Data Protection Authority and will in the first place set up regulations concerning the use of the data. 465

3.4.2.1. Contract between the Data Protection Authority and the data exporter (e.g. a hospital)

3.4.2.1.1. Guarantee of a "state-of- the-art" pseudonymisation. The contract has to ensure that only de facto anonymous genetic data will enter the research network. Technically this will be guaranteed by the implementation of a "state-of-the-art" pseudonymisation tool during the transfer procedure. The decision that has to be taken is: Whose sphere of responsibility shall be the functionality of the implemented pseudonymisation tool? Two solutions are thinkable: 466

The first option would be, the Data Protection Authority provides or has to agree on a specific pseudonymisation tool that the hospital implements. The second option would be to have the hospital to guarantee that it only transfers de facto anonymous data to the research project's database using whatever state-of-the-art pseudonymisation tool they like. 467

If the pseudonymisation tool does not work properly, for example due to a computer bug or human misconduct, and personal data is therefore processed within the research network, in both cases for the unlikely event of a damage the data subject might suffer (due to his genetic data being transferred to an insurance company for instance) in the first place the Data Protection Authority as data controller of the GRID infrastructure will be responsible. The critical difference between those two options is whether or not the Data Protection Authority could thereafter have recourse against the specific hospital (data exporter). 468

Of course both the Data Protection Authority and the hospital – whatever alternative will be chosen – could on their part subrogate against the software-producer finally, but whoever is liable with regard to this contract takes the risk of not to being able to subrogate against the producer. 469

3.4.2.1.2. Technically and organisationally separated project database. The project database is in most of the cases physically located at the data exporter, e.g. 470

at a hospital. A basic principle of the proposed Data Protection Framework is that only de facto anonymous data is processed within the research network. Therefore, it must be guaranteed that no project partner is able and allowed to identify the person to whom the data set refers. If the participant would be able and allowed to do so, the particular data sets would have to be qualified as personal data also for the Data Protection Authority. That is why it must be avoided that the data exporter is able to deanonymise the data transmitted by himself to the project database. Usually the data exporter would be able to de-anonymise the transferred data by matching them with his original data sets, which normally contain identifying characters. The proposed Data Protection Framework must rule out this possibility. Therefore, a clause must be introduced into the contract that the data exporter must ensure that, when project data is (permanently) stored at his organisation, it is technically and organisationally separated from other data. A matching procedure by the data exporter is ruled out because of the technical design of the project database and the dataflow.

471 Furthermore, it is also banned legally by the provision that the data exporter is not allowed to match any data transmitted to the research network with any original reference data sets.

472 These provisions are of crucial importance to guarantee that only de facto anonymous data is processed within the research network.

3.4.2.2. Contract between Data Protection Authority and end users

473 **3.4.2.2.1. Data controllers within genetic research networks.** The data controller is the person or organisation that determines the purposes and means of data processing.[436] Therefore, the question arises as to who or which entity will be the data controller within genetic research networks like ACGT.

474 This issue is very important for the compliance of the research network with current data protection legislation, as the data controller is the person or entity that has to ensure this compliance. As the compliance with current data protection legislation is crucial for the success of genetic research projects, this decision has to be made very carefully.

475 According to the Data Protection Directive, whenever personal data is processed there has to be a person or organisation responsible for this processing called "data controller". The data controller shall be a natural or legal person, public authority, agency or any other body which, alone or jointly with others, determines the purposes and means of the processing of personal data; where the purposes and means of processing are determined by national or Community laws or regulations, the data controller or the specific criteria for his nomination may be designated by national or Community law (see Article 2 lit d)).

476 The data controller has the duty to ensure that personal data is processed fairly and lawfully, in particular that personal data is only collected for specified, explicit and legitimate purposes and not further processed in a way incompatible with those purposes. Likewise the data controller has to make sure that the data is kept in a form which permits identification of data subjects for no longer than necessary for the purposes for which the data was collected or for which it is further processed. The data controller also has to implement appropriate technical and organisational

[436] See Bygrave 2003, p. 21; see also Art 2(d) of the EC Directive 95/46/EC

measures to protect personal data against accidental or unlawful destruction or accidental loss, alteration, unauthorised disclosure or access, in particular in cases in which the processing involves the transmission of data over a network.

Since it is the data controller who is liable for the legality of data processing and the fulfilment of the obligations towards the national data protection authority and the data subjects, it is essential that the data controller is always identifiable. If the data controller fails to fulfil his duties in accordance with the Directive and thus fails to respect the rights of data subjects, any person who has suffered damage as a result of such unlawful processing operation or of any act incompatible with the national provisions adopted pursuant to the Directive is entitled to receive compensation for the damage suffered from the data controller. However, the data controller may be exempted from this liability, in whole or in part, if he or she proves that he or she is not responsible for the event giving rise to the damage. 477

The first approach ensuring the needs described above would be to establish a legal body as the central data controller within the research network, who would be responsible for all the data processing within this network, whereas all other users (like the researchers) would only act as data processors for this legal body. A data processor is a natural or legal person, public authority, agency or any other body which processes personal data on behalf of the controller according to Article 2 lit. e of the Directive. The controller can determine, if at all, how and under what conditions the processor is allowed to process data on behalf of him or her (in a contract). The processor is only allowed to process data according to the instructions of the controller, who is legally responsible for the data processing carried out by the processor. 478

The central data controller would therefore be responsible for all the data processing within the research network and also for the processing of data received via the network by the end users. This approach would have several advantages: 479

Firstly, one entity would be responsible for all the processing transactions within the network. This entity would have the knowledge and the capacities to take care of all data protection issues. The entity would be an expert in the field of data protection within scientific research projects dealing with genetic data. Therefore, the entity would be able to ensure compliance of the data processing within the network with current data protection legislation. Secondly, from the data subjects' point of view, to have more than one data controller within the network makes it more complex to enforce their rights deriving from data protection law, as in case of violation of his rights, data subjects would need to find out against which particular data controller he or she would have to assert the claim. This approach would therefore perfectly ensure transparency and the possibility of data subjects to enforce their rights easily. 480

The end users (e.g. a researcher) would only act as a data processor in this approach. A data processor is defined in Article 2 lit. e of the Data Protection Directive as a natural or legal person, public authority, agency or any other body which processes personal data on behalf of the controller. This definition is commonly interpreted in a way that the data processor shall only act on instructions from the data controller (see Article 17 paragraph 3 of the Data Protection Directive). In research projects like ACGT the end users are researchers that, of course, have to decide on their own how they want to do their research and what means they want to use for it. That is why one could argue that the legal construction "data processor" is not in line with the scenario of genetic research networks. 481

482 But on the other hand one could argue that this construction was introduced to protect the privacy of a concerned data subject even though the data controller uses support of a third party in order to fulfil his or her duties.[437] Therefore, it introduces provisions guaranteeing transparency by stating that the responsibility remains with the data controller. This is why the data subject can claim his or her data protection rights (e.g. right of access) against the data controller even if the data is actually processed by the data processor. Considering this, one can argue that the construction of the "data processor" was introduced due to the same challenge we are facing in genetic research networks: protecting privacy and the rights of the data subjects by ensuring transparency. Because of that, there are good arguments that the model of data processor can also be used in this case. Still, as legal uncertainty remains, we decided in the research project ACGT to opt for the second approach, explained in the following.

483 **3.4.2.2.2. Data Protection Authority as central Data Protection Authority within the research network.** The second approach is to establish a legal entity[438] as a central data protection authority within the research network. In this scenario the Data Protection Authority is only the central data controller within the network's GRID infrastructure, whereas the end users are responsible for the data processing within their own entities. The end users are data controllers with regard to the data they receive via the research network. Being data controllers, the end users are responsible for the data processing within their organisations. They must therefore ensure to comply with data protection legislation, if applicable. This approach confers more responsibility on the end users, but also more freedom on how to deal with these obligations.

484 The advantage of this approach is that legal uncertainty linked with the first approach is smoothed out. As the end users are responsible for the data processing, they are of course free to choose how and with which means they want to process data received from the research network within the limits of data protection legislation and the limits of the contracts, which have to be concluded between the Data Protection Authority (on behalf of the research network) and the end users.

485 For the data subjects participating in the research project, this approach contains some disadvantages. If they want to execute a right deriving from data protection law (e.g. right of access) they have to claim the data controller. But in order to find out which end user processes their data, data subjects have to ask the Data Protection Authority first. Not untill then they can exercise their rights against the particular data controller (see **Error! Reference source not found.**). Besides, they need to find out on which territory the data controller is established, as the national data protection legislation of that state is applicable for any dispute regarding data protection law. Therefore, at first sight, this approach suffers intransparency.

[437] See Ehmann/Helfrich, Article 17 No. 9; Walz in Simitis, § 11 No. 1

[438] In ACGT: *Centre for Data Protection* (CDP), http://www.privacypeople.org/

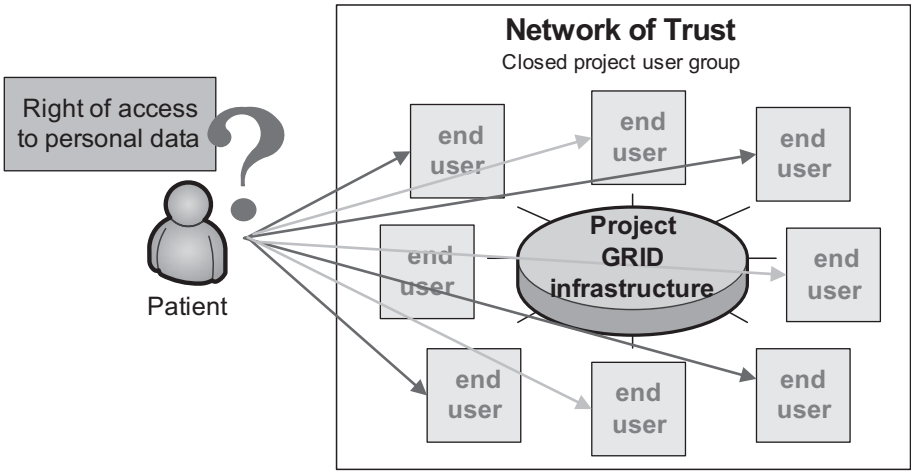

Figure 10: Right of access

As transparency is needed for ethical reasons and to convince patients to take part in the research project, this intransparency must be smoothed out by provisions stated in the contract between the Data Protection Authority and the end user. The data protection provision that the right of access (erasure etc.) can be exercised against the responsible data controller is binding law and cannot be modified by any contractual agreement. Therefore, the patient has always the possibility to exercise his rights deriving from data protection law against the particular data controller, in this case against the particular end user. 486

In order to remove intransparency, the Data Protection Authority must grant the data subject (e.g. the patient) additional rights: Patients will be able to exercise their rights deriving from data protection law not only against the end user but also against the Data Protection Authority. To enable the Data Protection Authority to fulfill these obligations, the end user is obliged to provide the Data Protection Authority with all necessary information. Patients can even sue the Data Protection Authority for any damage caused by any unlawful processing of his data by the end user. Of course, the end user will then have to compensate the Data Protection Authority for this damage. By introducing these provisions, the patient gets a central contact point for all data processing within the research network (see **Error! Reference source not found.**). Hence, the lack of transparency is removed. 487

This approach offers legal certainty in connection with transparency and usability. Therefore, we decided to follow this approach to establish the Data Protection Authority as central data protection authority within ACGT. 488

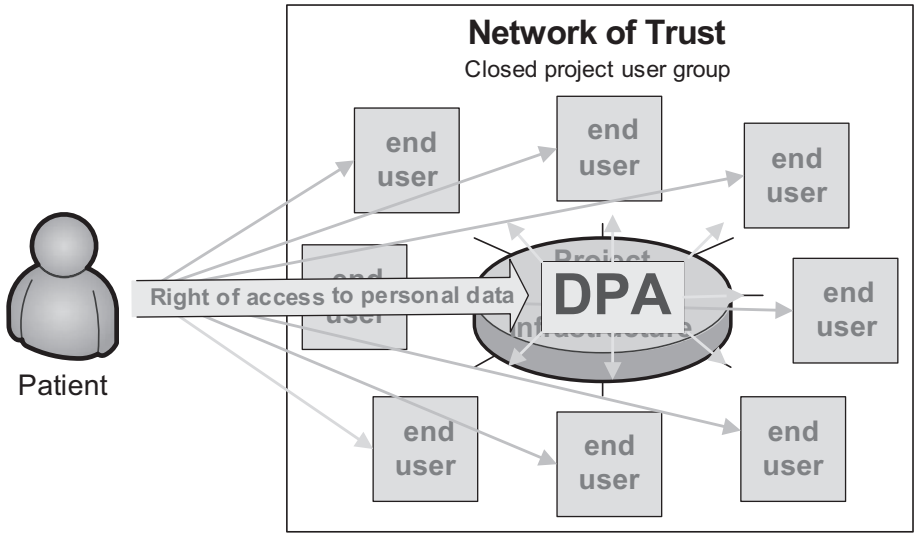

Figure 11: Right of access via Data Protection Authority

489 **3.4.2.2.3. Ensuring the context of anonymity.** But this approach must also be in line with the network's Data Protection Framework. The first pillar of the introduced Data Protection Framework is that only de facto anonymous data is processed within the closed user group of the project, so that the privacy of the participating patients is protected to the maximum extent as possible. If the data used in the network cannot be linked back to an individual person, data protection legislation (including the Data Protection Directive) is not applicable as the privacy of the concerned data subjects is not threatened.

490 But as already described, the used genetic data cannot be rendered anonymous in a way that no one can ever link the data back to the "owner", as genetic data is unique. By matching every genetic data set can be linked back to the concerned person, if a reference data set is available that contains identifying characters of the person, such as his name. Genetic data can therefore only be rendered de facto anonymous.

491 This is why we introduced the pseudonymisation procedure as part of the proposed Data Protection Framework: The genetic data set used in the research network contains only a pseudonym created by a software tool before the data is transmitted to the network and the link (from the pseudonym to the identifier) is stored at an independent Trusted Third Party. This kind of pseudonymised genetic data has also to be qualified as de facto anonymous data, which, as described above, has also to be qualified as anonymous data in a legal sense. In this case data protection legislation is not applicable, since the privacy of the concerned person is not threatened.

492 The very basic condition to qualify this kind of used data in the research network as de facto anonymous is a closed user group, meaning that all project participants (like the Data Protection Authority, the end users) and all people that have to be attributed to them (such as data processors) are not able to identify the concerned data subject with a proportionate amount of time, expense and labor. This closed user group has to be guaranteed by both: the technical design of the proposed Data Protection Framework (see above) and the legal framework.

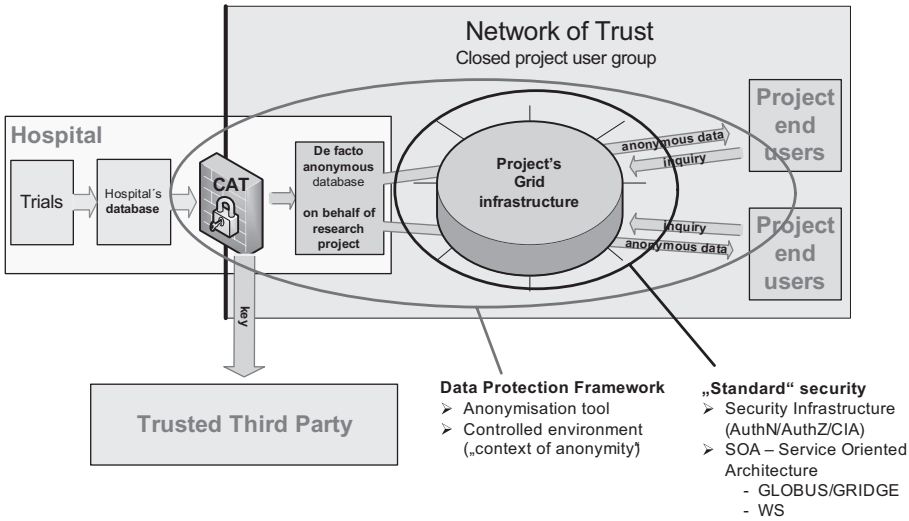

Figure 12: Security architecture

For the security architecture, there are two substantial conditions: Firstly, access is only granted to project participants having signed this contract. Secondly, the following provisions have to be introduced in this contract: 493

3.4.2.2.4. Separated database. To guarantee that only de facto anonymous data is processed within the research network, it is of great importance that data received from the network is separated technically and organisationally from data already stored at the end user, see: 0. 494

3.4.2.2.5. No matching. It is of vital importance that neither Data Protection Authority nor any of the end users carry out any matching procedures. With the help of these procedures the identity of the concerned patient could be determined, especially as the pseudonymised data sets often come from hospitals that are end users at the same time. These hospitals have of course a corresponding data set usually containing personal information of the patient. Therefore, they could identify the concerned patient just by carrying out such matching procedures. In order to guarantee that only de facto anonymous data is processed within the research network we have to guarantee that such matching procedures will not be done under any circumstance. Otherwise the genetic data within the research network would have to be qualified as personal data, as it would then be possible to identify the concerned patient with proportionate time, expense and labor. Consequently, data legislation would be applicable, so that the first pillar of the proposed Data Protection Framework would be swept away. 495

Another provision to be introduced into the contract is that no end user is allowed to publish any data received from the research project to any third party. As just described, de facto anonymous genetic data can be de-anonymised by matching procedures. These matching procedures cannot only be carried out by an end user himself (which is forbidden), but also by a third party, if it gets access to the genetic data set. 496

If such a clause would not exist, the end user might publish the data on the Internet, in a magazine or just transmit it to a third party. If a third party receiving 497

the data set from the Internet, a magazine or directly from the end user has a reference data set including identifying characters, this third party could also run a matching procedure and identify the concerned patient. For example, an insurance company could use such genetic data sets published on the internet to find out whether one of its clients suffers from cancer. A lot of life insurance companies already have databases containing genetic data of their customers. The privacy of the participating patients would be highly threatened. This scenario has to be prevented for ethical reasons. Thus, a clause which forbids any publication of data received from the research network must be introduced to the contract.

498 But this provision is also of vital importance for the first pillar of the proposed Data Protection Framework. Recital 26 of the Data Protection Directive states that to determine whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the controller or by any other person to identify the said person. According to the first pillar of the proposed Data Protection Framework, only de facto anonymous data may be used within the research project. If data sets would be published, all these data sets would have to be qualified as personal, as a third party, having a reference database, could easily identify the concerned patients. According to Recital 26 of the Data Protection Directive this knowledge would be attributable to the data controller and all end users as well. Since Data Protection Authority and the end users simply cannot know for which data sets a reference data set including identifying characters exists, all published data sets would need to be qualified as personal data to avoid liability. In other words: If any genetic data from the research network would be published, it would have to be qualified as personal data with the consequence that personal data would be processed within the research network so that data protection legislation would be applicable. The first pillar of the proposed Data Protection Framework would be swept away.

499 With these provisions and the technical design of the data flow a closed network user group and the context of anonymity of data processed within the research network can be guaranteed.

3.4.2.3. Second pillar and first fallback scenario: Informed Consent

500 The second pillar of the Data Protection Safety Net is to obtain informed consent of all patients participating in the research project. The consent of the data subject concerned is needed for various reasons. Firstly, whenever genetic data is transmitted to bodies outside of the research network or data is disclosed, the de facto anonymised data used in the research project has to be qualified as personal data. Therefore, permission for this processing operation would be needed. As a statutory legal basis is not available, the consent of the data subject (e.g. the concerned patient) would be required for that. Furthermore, consent might also be needed if genetic data shall be transferred to third countries. Such a transmission may take place if a researcher not participating in the research project wants to use the data for his research or if the research unit is not located within the EU. A disclosure may occur for example, if a researcher wants to publish an article in a medical magazine and the disclosure of genetic data is needed to demonstrate and verify his or her results.

501 Secondly, the consent is needed as a "fallback option". Although the proposed Data Protection Framework was developed to guarantee that only de facto anon-

ymous genetic data is used within the research network and that the project complies with current data protection legislation, it still might happen that personal genetic data is processed, for example, because an error occurred during the anonymisation process or due to human failure. For these unpredictable cases in which personal data is processed, permission is needed as well. And as, again, no statutory legal basis is available, the consent of the data subject is required to process this data and to ensure compliance with current data protection legislation.

Furthermore, the consent of the data subject is needed from an ethical point of view. The data subject should be able to determine which data referring to her or him shall be processed by which processor and for what purposes. 502

Therefore, an informed consent of the data subject concerned is required for research projects, although the proposed Data Protection Framework shall guarantee the use of de facto anonymised data within the research network and the project's compliance with current data protection legislation. 503

3.4.2.3.1. Regulatory framework. *3.4.2.3.1.1. Definition.* Article 2 (h) of the Data Protection Directive defines the data subject's consent as any freely given specific and informed indication of her or his wishes by which the data subject signifies the agreement to personal data relating to him or her being processed. In other words, the Directive requires a declaration of intention made by the data subject concerned, which is given voluntarily, for a specific case in awareness of the factual situation. 504

3.4.2.3.1.2. Declaration of intention. A declaration of intention is an action being visible from outside for the addressee which, from an outside's point of view, can be seen as consent. 505

For sensitive data generally an *explicit* declaration is required (Article 8 paragraph 2a); otherwise, it is also accepted if consent is given by implied conduct. If the said person remains silent, this cannot be interpreted as consent. A specific form is not required. The declaration can be given orally, in writing or electronically.[439] 506

3.4.2.3.1.3. Freely given. The Directive requires the declaration of intention to be given freely. This means it has to be a self-determined action which is not led by external influences. The motivation of the person concerned, e.g. the question, whether the person concerned acts in his or her own interest or for the benefit of others, is irrelevant. The only relevant question is, whether the declaration is a product of a free decision. The wording "freely given indication" makes clear that the absence of external forces and threats of violence is not enough. The freedom of decision-making can also be restricted in a relation of dependence, which can make a consent invalid.[440] 507

3.4.2.3.1.4. For a specific case. According to the Directive, the declaration must relate to a specific case. That means that the data and activities in question must be specified as far as their content and extent is concerned. The requirements concerning the degree of specification are higher, the more rights and freedoms of the person concerned are affected. 508

An abstract consent to the processing of personal data is not possible. From the specific case and the situation must be clear, to which kind of personal data and to which activities the consent relates. This does not mean that the Data Protection 509

[439] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, p. 115
[440] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, p. 116

Directive makes it impossible to give consent which is valid for future research (see further under ■0).[441] This is of high importance for most studies as it can be difficult for researchers to anticipate all future uses of the data. During the course of a study new areas of interest may be highlighted or novel technologies may arise which could necessitate further analysis of the data.

510 *3.4.2.3.1.5. Informed indication.* Finally, the consent has to be given in awareness of the factual situation, which means it has to be an "informed consent". The Data Protection Directive requires that the data processor informs the person concerned adequately (Article 10 ff.).

511 The information to be given to the data subject is at least;
- the identity of the controller and of his representative, if any; and
- the purposes of the processing for which the data are intended.

512 Additional information, if necessary, with regard to the specific circumstances could concern;
- the recipients or categories of recipients of the data;
- whether replies to the questions are obligatory or voluntary; as well as
- the possible consequences of failure to reply; and
- the existence of the right of access to and the right to rectify the data concerning the data subject.

Wrong or incomplete information of the said person by the data processor makes the consent invalid.[442]

513 **3.4.2.3.2. Scope of the consent.** *3.4.2.3.2.1. Object of the consent/purpose specification/future research.* As stated above, the declaration must relate to a specific case. That means that the data and activities in question must be specified regarding their content and extent. The requirements concerning the degree of specification are higher, the more rights and freedoms of the person concerned are affected. An abstract consent to the processing of personal data is not possible.

514 The data subject concerned must be informed about the object and the kind of research which will be conducted with her or his data. This is the central requirement of all relevant regulations and recommendations concerning medical research. Nevertheless, most questions concerning the informed consent arise from this requirement.

515 For clinical studies, which usually have a clearly defined purpose, the object for which the consent is given is obvious. But when, as in research networks like ACGT, the aim of a research project is to set up a database in order to enable various research projects to be performed, the definition of the object is more difficult. Of course, these kinds of projects also focus on a specific area of research. However, there is an interest to use the data stored in that database for research purposes which are not known at the point of time of storage. Regarding this scenario, the question arises of how to define the object of a research project so that the data subject can give an informed consent, which is also valid for future research projects.

516 An option could be a far reaching definition of "specific case", e.g. medical research including genetic research. In this case a requirement would be that the person concerned will be informed about the uncertainty of the future use of his or her data. In consequence, this would mean that an informed consent can also be

[441] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, p. 115
[442] Dammann, Ulrich/Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, p. 116

reached by information about the uncertainty of the future use. The person concerned will be able to keep control of his or her data by the right to revocation and erasure.

Nevertheless, if the object is more specifically defined, e.g. a specific research question or research area, it will more certainly fulfil the generally accepted requirement to inform the said person about the intended use of his or her data appropriately. To mention a specific object however might result in the situation that if scientific research later requires an extension of the research question, the extended research object is not covered by the consent. 517

Therefore, it is recommended to ask the data subject concerned to consent to the specific project in question and further future projects. In conclusion, the data subject concerned should be informed as specifically as possible about the extent to which her or his personal data will be used. The information can relate to one or more specific research questions or to one or more research areas. 518

If the object is to set up a database for various research questions, which are not known at the point of time of storage, a more far reaching definition of the object in combinations with a right to erasure would be useful.[443] 519

To give an example: The presented research project ACGT defines its objectives as follows: 520

First, ACGT aims at generating new knowledge with respect to the characterisation, classification, prognosis of cancer and prediction of response, since prognostic and predictive markers are different. One of the goals is to compare the activity of genes in the tumours of patients who responded well to therapy with the activity of genes in the tumours of bad responders. 521

Second, it aims at establishing a new, computer based, interconnected infrastructure which helps research groups in different countries to access clinical, biological, and genomic data from cancer patients and to analyse and compare these data. 522

Ultimately, the project aims at facilitating data exchange and analysis, and contributing to a more precise description of different cancers, at the moment breast cancer and nephroblastoma. 523

3.4.2.3.2.2. Expected period of usage/temporal scope of the consent. An important principle of data protection legislation is that personal data has to be erased if it is not necessary anymore for the specified purpose it was collected for. In general, this means for an informed consent that the said person has to be informed about the point of time of erasure of his or her personal data. The intended duration of use has to be stated in the consent form. 524

However, there are no fixed limits on the time of storage to be found in European data protection legislation. As stated above, data protection legislation refers to the necessity of storage for the specified purpose the data was collected for.[444] 525

For a project aiming at setting up a database, the definition of the intended duration of use is naturally more difficult than in the case of a research question with a defined start and end. Also, for a database, a limited time of storage would be counterproductive as many studies rely on the long-term availability of the data. 526

[443] BMB-Projekt: Ein generisches Datenschutzkonzept für Biomaterialbanken, Version 1.0; April 2006, pp.31–33; Wellbrock, R, Biobanken für die Forschung – Zur Stellungnahme des Nationalen Ethikrates, Datenschutz und Datensicherheit, 2004 (9), pp. 563/564

[444] Nationaler Ethikrat, Biobanken für die Forschung, 2004, p. 61, http://www.ethikrat.org/dateien/pdf/Stellungnahme_Biobanken.pdf (accessed 5. February 2010)

527 However, from an ethical point of view, doubts have been raised concerning the applicability of the doctrine of informed consent for future research projects.[445] *Tiered consent* arranging different levels of authorisation in the consent procedure is proposed as being able to provide an appropriate solution. It offers to donors the possibility to authorise a broader or more restricted range of research to be done with their samples and data and time frame that may be used for research.[446] However, this model is difficult to handle in practice. Therefore, a model of consent referring to a *purpose of intermediate scope* (e.g.: clinico-genomic research on cancer) in the *context of a specific structure or project* (e.g.: ACGT) may be within the limits of ethical as well as legal considerations. This model also includes the general necessity to ask for reconsent if the scope of consent (e.g.: clinico-genomic research on cancer/ACGT project) will change and re-identifiable data will be used in further research projects.

528 Another problem occurs if the duration of a research project is limited. For example, the end of the ACGT research project will be in 2010. Due to this temporal limitation in the consent forms, the informed consent given by the patient expires in 2010 because the specified research setting of ACGT is then completed. Afterwards, ACGT is obliged to ask for reconsent because the scope of consent will change *or* to erase all personal data and to inform the data subject about the erasure.

529 However, it has to be taken into account that the data stored in the research network's database is de facto anonymous data and that the informed consent only relates to personal data. Therefore, when the consent expires, the link between the patient concerned and his or her data, which is needed to inform the patient about research results, has to be erased and the patient has to be informed about the erasure. What remains is a database consisting of anonymous genetic data.

530 The safeguards set up by proposed Data Protection Framework to prevent misuse and de-anonymisation of the genetic data must nevertheless remain in place, especially prohibition on publication and no transfer to third parties.

531 *3.4.2.3.2.3. Death of the patient.* Another problem arises in case of death of the person concerned. Data protection legislation is only applicable to living persons. But in Germany, for example, the basic right to protection of personal rights has its effects even after the death of the person concerned – with a declining intensity the more time passes after the death of the person concerned.[447] The doctor-patient confidentiality is also extended to the time after the death of the patient by German Criminal Law (§ 203 IV StGB). Therefore, a consent, defined purpose or access limitation given by the patient does not become invalid after his death. Relatives, heirs and other third persons can make arrangements in the medical field, if these arrangements comply with the wishes of the person concerned. The right to information might vest to the relatives of the person concerned, as far the information to be collected may be helpful to detect hereditary diseases or to answer questions of descent.[448]

532 Within the research network, as stated above, only de facto anonymous data will be used according to the proposed Data Protection Framework. If it is assumed that

[445] See 2.2

[446] See 2.4.1.2

[447] BVerfGE 65, 1; BVerfGE 30, 173, 194 "Mephisto"

[448] Datenschutz Berlin, Stellungnahme zu Fragen der Enquete-Kommission "Recht und Ethik der modernen Medizin" vom 19. 12. 2000, p. 7

the informed consent to participate in the research project given by the patient concerned does not become invalid after his or her death, the anonymous data stored in the project data bases can be stored even after the death of the patient. As a consequence, the question whether the right to erase the link can vest to the heir of the person concerned, does not affect the database itself.

3.4.2.3.2.4. Data transfer to third parties/third countries. As described, genetic data has to be regarded as personal data in case of transfer as the recipient might re-establish the link by using a matching procedure. Since the research network participants cannot know whether the recipient has a database to carry out such a matching procedure, the privacy of the data subject concerned may be at risk, so that data protection legislation such as the Data Protection Directive 95/46/EC must be applicable in order to provide sufficient protection for the data subjects concerned. Therefore, a permission is required if genetic data shall be transferred to third parties. As a statutory permission for the transfer is not available, the concerned data subject has to give his or her informed consent for the transfer of his or her genetic data. If the recipient is situated in a third country outside of the EU, additional rules and conditions for the transfer apply. 533

3.4.2.3.3. Consent of relatives needed? Another important issue in the context of the informed consent is the problem of who has to consent in case of genetic research. As explained, genetic data contains information not only about the concerned data subject, but also about his or her relatives. Whenever genetic data is examined, information can be gathered about the participating data subject him- or herself and also about his or her relatives. That is why not only the privacy of the data subject him- or herself is affected, but also the privacy of his or her relatives. This might mean that the relatives of the patient concerned might also have to consent to the genetic research. In other words, who is the data subject of the genetic data? 534

However, genetic research would be much more complicated if the consent from each relative is needed to examine only one set of genetic data. So, a conflict between the interests of research and the privacy of the concerned relatives occurs which has to be solved. 535

Article 2 lit (a) of the Data Protection Directive defines the data subject as an identified or identifiable natural person to whom information relates to. An identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity. 536

3.4.2.3.3.1. Additional information of relatives is collected. Whenever additional information of these relatives is collected together with the genetic data of the data subject, the consent of these relatives is also needed, as their genetic data is very similar to the data of the data subject and conclusions about these relatives could also be drawn from the data subject's data. The privacy of these relatives would be affected, so that an informed consent of the concerned relatives is needed.[449] But this provision must be interpreted restrictively. The consent is only needed of first-grade relatives (such as the parents or children), as only their data sets contain enough similarities to the data set of the data subject that their privacy is affected.[450] 537

[449] See Weichert, DuD 2002, p. 133 (138)
[450] See Weichert, DuD 2002, p. 133 (138)

In all other cases consent of the relatives is not needed because of the marginal similarities and the missing threat for their privacy. The interests of genetic research must prevail in these cases, as otherwise the improvement of genetic research would be put at risk, if not prevented. This interpretation corresponds also with the Data Protection Directive. Recital 26 states that in order to determine whether a person is identifiable, account should be taken of all the means likely to be reasonably used either by the controller or by any other person to identify the said person. Nobody would likely use any means reasonably to determine the relative of a patient if there are not enough similarities in the data sets to determine the relative and/or to draw any conclusions about them out of the available genetic data.

538 Therefore, only the data subject concerned has to be regarded as data subject of his or her genetic data, so that in general only the data subject has to give his or her informed consent. If additional information about first-grade relatives, that allows the identification of this relative, is collected together with the genetic data of the patient, then the informed consent of the relative concerned is also needed. Asking for that consent will necessarily oblige the physician to violate the legal requirement concerning medical confidential communication because he'll have to inform that concerned relative about the data subject's involvement to get an informed consent. Therefore, the data subject has to agree that his/her first grade relative is informed. Without this agreement and the consent of this relative, the genetic data of the data subject must not be processed.

539 *3.4.2.3.3.2. No additional information of relatives is collected.* If no additional information of first grade relatives is collected together with the genetic data of the data subject, no consent of these relatives is needed to process the genetic data of the data subject. Indeed, as just described, the genetic data of the data subject contains also information about first grade relatives, so that one could be of the opinion that a first grade relative has to consent to the processing of genetic data of another first grade relative, too. For example: the mother would have to consent to the processing of genetic data of her daughter, even if no additional information about the mother herself is processed as the daughter's genetic data contains information about the mother as well. And often a first grade relative is easily identifiable for a data controller. Hence the daughter's genetic data could be personal data of her mother as well, so that the data controller would need her consent to process the data.

540 But this interpretation would extend the scope of data protection law too much. The aim of data protection law is to protect the data subject's privacy and it's right to determine under what circumstances it's data may be processed. If the relative would not give his or her consent to the processing of the genetic data, the data subject could not determine self-determinedly about it's data. The aim of data protection law would be undermined. The interests of the data subject have to be ranked higher than the interests of the relative in case no additional information about them is processed together with the genetic data of the data subject.

541 **3.4.2.3.4. Consent of the minor data subject or person with intellectual disabilities needed?** Another important question is: Who has to consent if personal data of a minor data subject or of a data subject with intellectual disabilities is collected and/or processed? Do only the legal representatives of this data subject have to consent or the minor/intellectually disabled data subject concerned too? Minor and intellectually disabled data subject are, for example, vulnerable, because

they do not have achieved physical and psychological maturity (yet). Therefore, they are not able to assess the consequences of their decisions in each case. That is why minors and people with intellectual disabilities have to be protected by law. In almost every European country a person does not become fully contractually capable until the age of 18 and intellectually disabled persons must be represented by their legal representatives to conclude contracts. Nevertheless, the consent forms used in genetic research projects have to be adapted to national legislation in each Member State if the law in this State states that also people under the age of 18 or intellectually disabled people can validly consent to the processing of their personal data.

But such strict legal rules do not (and cannot) respect the fact sufficiently that 542
becoming an adult with all corresponding rights is also a process. Furthermore, there are also huge differences between people suffering from intellectual disabilities. One minor data subject may assess the consequences of giving his consent to the processing of his or her personal data, another may not. The same applies to intellectually disabled data subjects.

To avoid liability the data controller should always acquire consent of the legal 543
representatives of the minor or intellectually disabled data subject. Furthermore, the data controller should also acquire assent of the minor or intellectually disabled data subject so that the interests of these data subjects are respected best.

That is why for example the World Medical Association recommends that: 544
"When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative."[451]

In conclusion, it is not obligatory from a legal point of view to acquire consent 545
from a minor or intellectual disabled data subject if their personal data shall be processed, but, on the other side, it is not forbidden to do so. From an ethical point of view it is highly recommendable to acquire consent from a minor or intellectually disabled patient as well whenever this patient is or seems able to assess the consequences of his decision. This solution involves the data subject in the project and to protect his or her interests and privacy best.[452]

3.4.2.3.5. The right to withdraw and right to erasure. Each data subject has the 546
right to withdraw his or her consent. According to Article 12 lit b of the Directive, the stored personal data of the data subject concerned must be erased.

If the data concerned is stored in an anonymised form, it is, as discussed above, 547
not personal data anymore, because the link to the patient concerned is not known to the researchers working with the data stored in the database.

According to the proposed Data Protection Framework, the participating hospi- 548
tals will transmit pseudonymised patient data to the project's databases. For the researchers working with the data, it is de facto anonymous data. The link between the data and the patient, which can transform the de facto anonymous data into personal data, is exclusively held by the Trusted Third Party.

---

[451] See paragraph 25 of the World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, last added in Seoul 2008, available at: http://www.wma.net/en/30publications/10policies/b3/index.html (5. February 2010)

[452] See for the consent of children: Working Document 1/2008 of the Article 29 Data Protection Working Party, available at: http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/2008/wp147_en.pdf (accessed 5. February 2010)

549 When the patient concerned signs the consent form to take part in the research project, he or she consents to the anonymisation and the processing of his or her data.

550 As within the research network all data is de facto anonymous and, hence not personal data, the patient concerned has no right to erasure of her or his data. Nevertheless, he or she has a claim to erase the link which is held by the Trusted Third Party. The request of withdraw or another exercise of patient's right will be formulated to the attending doctor or directly to the Data Protection Authority. But this right does not affect the database itself. Therefore, the de facto anonymous data stored in the project's database can still be used for the research within the network. However, when the patient concerned has withdrawn his or her consent, the data can no longer be disclosed or transferred to third parties, as for these processing operations an informed consent of the concerned data subject is needed. Nevertheless, the processing operations for which consent is needed already took place with valid consent. Therefore, they have still to be regarded as lawful operations. Only the future processing of the concerned data is forbidden when the consent is withdrawn by the data subject and the consent is needed for the lawfulness of the processing.[453] Therefore, the transfer and the disclosure of the concerned data would no longer be lawful, whereas all other data processing operations, such as the use of the genetic data, would still be lawful as the genetic data within the research network has to be regarded as anonymous data and no consent is needed for the processing of anonymous data.

3.4.2.4. The right to know and the duty of notification

551 Each patient taking part in the research project would like to decide whether or not he wants to be informed about the results of the research that is carried out with his or her genetic data. Therefore, it has to be examined whether the patient has a statutory right to know or not to know these results.

552 According to Article 12 of the Directive, each data subject has the right to know from the data controller if personal data is processed, for what purposes it is processed, what categories of data are concerned and who the recipient(s) of the data is/are. But this right to know is only guaranteed by the Directive, if the Directive is applicable at all.

553 As described, genetic data within the research network is pseudonymised and has to be regarded as de facto anonymised data, so that the Directive is not applicable. Therefore, the data subject has no statutory right to know what happens with his or her genetic data within the research network, as long as the data is not disclosed or transferred, since the quality of the genetic data changes in these cases. In these cases the genetic data has to be regarded as personal data, so that the data subject concerned might have the right to know the described facts.

554 Even in these cases, it is questionable whether the data subject has such a statutory right, as Article 13 paragraph 2 of the Directive states an important exemption. According to that and subject to adequate legal safeguards, Member States may, if there is clearly no risk of breaching the privacy of the data subject, restrict the rights provided for in Article 12 by legislative measures regarding the following cases: (1) when data is processed solely for purposes of scientific research,

[453] See Ehmann/Helfrich, EG-Datenschutzrichtlinie, Article 12 marginal number 72 f

or (2) is kept in personal form for a period which does not exceed the period necessary for the sole purpose of creating statistics.

In the proposed scenario there might be no risk of breaching the privacy of the data subject, as the genetic data is pseudonymised and has to be regarded as de facto anonymous data. But in case of disclosure or transfer of genetic data, the risk of breaching the privacy of the data subject cannot be excluded as a recipient might re-establish the link and de-anonymise the genetic data by using a matching procedure. Therefore, the exemption stated in Article 13 paragraph 2 of the Directive is not applicable whenever genetic data is disclosed or transferred, so that the data subject has a statutory right according to Article 12 to know from the data controller if personal data is processed, for what purposes they are processed, which categories of data are concerned and who the recipient(s) of the data is/are. 555

But this right does not include a statutory right to get to know the results of the research done with the genetic data of the data subject concerned anyway.[454] 556

According to Article 10 no. 2 of the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Convention on Human Rights and Biomedicine), everyone is entitled to know any information collected about his or her health. In this context, genetic data has to be regarded as information about health.[455] But this right only grants access to the collected data or not to be informed about the collected data and not to results of a research as well. That is why this statutory right does not entitle the concerned patient to know the results of the research that was carried out with his or her data.[456] 557

It has also to be taken into account that a right to know these results might be developed from the personal rights of the concerned data subject.[457] The concerned data subject has the right to be informed by the data controller or data processor about his or her genetic disposition.[458] This genetic disposition and the consequences have to be explained to the data subject by an expert, so that the data subject understands what a particular genetic disposition means for him or her. As this knowledge might cause harm to the data subject, he or she must also have the right not to know these results, since the data subject as a person must be able to choose what he or she wants to know about himself or herself and what facts he or she doesn't want to know, as it is granted by the personal rights. 558

One opinion even grants the data subject concerned the right to be informed about how the research with the genetic data was carried out and what means were used for the analysis, otherwise the researcher would have too much power over the patient as nobody else would be able to verify the analysis.[459] Another argument for that opinion is that Article 12 lit. a of the Data Protection Directive states the right of the data subject to obtain from the controller the knowledge of the logic involved in any automatic processing of data concerning him or her at least in the case of the automated decisions referred to in Article 15 (1). 559

[454] See Antonow, p. 90; Simitis/Dammann, EG-Datenschutzrichtlinie, Article 12 marginal number 4
[455] Antonow, p. 80
[456] Compare Antonow, p. 80
[457] See Weichert, DuD 2002, p. 133 (141), Wellbrock, CR 1989, p. 204 (209)
[458] See for example: Weichert, DuD 2002, p. 133 (141)
[459] Weichert, DuD 2002, p. 133 (142)

560 But this right of knowledge must be limited because the researcher has intellectual property rights regarding the tools and means used for the analysis. Therefore, he or she cannot be forced to publish them just because of that rule.[460] In conclusion, the concerned data subject has no statutory right to be informed about the tools and means used for the analysis of his or her genetic data.

561 Furthermore, it can be doubted that a data subject participating in a research project like ACGT has a statutory right of (non) knowledge that can only be concluded from his or her personal rights. As only de facto anonymous data will be used during the research within the research network, the personal rights may not be applicable in this case.

562 Therefore, a contractual right should guarantee the participating data subjects in research networks like ACGT to be informed about their genetic disposition. This right should be included in the contract the patient has to conclude with the research network before entering the trial. Furthermore, this right should not only be a pull procedure. The research project should also inform the patient (if he or she wants that), whenever results are achieved that could be important for the treatment of the patient. The patient would also be granted a right of notification then. So, whenever a researcher achieves results from which patients having a certain genetic disposition could benefit, other patients with the same disposition should be searched in the research network's database and informed about the research results, if they so choose.

563 The participating patients can exercise the right of information by asking the Data Protection Authority directly or via their attending physician. The Data Protection Authority will then, together with the Trusted Third Party and the end users, provide the requested information to the attending physician, who can inform the participating patient and explain the results to him or her. It is of vital importance for research networks like ACGT to guarantee these patient's rights, as a lot more patients will take part in these projects in this case. Also for dissemination purposes it must be recommended to grant the participating patients these rights.

3.4.2.5. Third Pillar and second fallback scenario: Exceptions for genetic research in national legislations

564 It is very unlikely, but there might be cases that for a specific patient the de facto anonymisation fails (e.g. because of additional knowledge or because of a failure during the anonymisation process) and no valid informed consent at all exists or the consent does not cover the specific use of the data. Here, the particular applicable national legislation has to be analysed with regard to an exemption according to Article 8 paragraph 4 Directive 95/46/EC. National exemptions form the third pillar of the proposed Data Protection Safety Net and serve as a second fallback scenario.

565 As mentioned above, under 3.2.1.3.2., Member States may, for reasons of substantial public interest, lay down further exemptions from the general prohibition on processing sensitive data, e.g. scientific research, see Recital (34).

566 Generally, this exemption is applicable to genetic research projects but Member States are free to implement such an exemption. Whether the Member State, whose

[460] See Antonow 2006, p. 90

law is applicable for the data processing operation in question, has introduced such an exemption in its national law, has to be analysed for each Member State individually. However, this analysis ought to be made by the Data Protection Authority for each individual case as those national provisions differ from one Member State to the other and can change all the time.

4. Legal conclusion

As shown above, it is possible to create a framework that takes into consideration both the needs of modern scientific genetic research projects such as ACGT and the needs of the data subjects participating in those research projects regarding data protection and privacy. Only if these two conditions are met, such research projects can succeed. In order to protect the individual rights of data subjects who donate data, genetic research projects have to take several ethical and legal requirements into account. First of all, also from a legal point of view, donors have to be provided with adequate information to consent voluntarily and explicitly to data sampling, storage and usage (informed consent). The given information has to be comprehensive and understandable and should at least include the main intentions of the research project and the range of possible uses of data, measures taken to protect donors' personal rights, the possible risks and benefits, and further implications of participation. 567

Not only the donors, but also the authorised users of the research project's network structure have to be informed and conclude contracts with the central Data Protection Authority on behalf of the project before getting access. They should declare that they will meet the requested standards of the project regarding the protection of data and privacy. 568

Regarding the disclosure of research results, the particular research project has to make sure that general study findings are accessible for donors. Furthermore, donors have the legal right to access data stored about her or him on request. Therefore, the implementation of this right requires an organisational structure that is suitable to reply on donors' request. 569

One of the main ethical and legal challenges in a genetic research project is the sensitivity and vulnerability of genetic data. Besides, genetic data has some special characteristics: it is not possible to render genetic data completely anonymous. As it is unique it can only be rendered de facto anonymous. This is the big difference to normal, conventional data. This is also the big challenge for the application of data protection regulation. 570

As described above, it is possible to keep the data flow in major parts outside of the scope of the Data Protection Directive 95/46/EC, if certain conditions are fulfilled. Such data is de facto anonymous data which can be regarded as anonymous data within the meaning of the Data Protection Directive. Following that, the Data Protection Directive is applicable whenever the particular data controller has the link from the genetic data to the concerned data subject or whenever he can obtain this link with legal means. 571

Furthermore, the Directive is applicable if a third party could establish this link. Therefore, the genetic data has to be regarded as personal data in the case of disclosure or transfer to the outside of the closed project user group, as the privacy of the concerned data subject is affected in this case as well. In case of all other data processing, for example use and storage, the Data Protection Directive is not applicable, provided that the data controller does not have the link and does not have legal access to it. 572

573 Following these legal considerations, a Data Protection Framework was created, as described in part 0, to ensure the compliance of the research project with data protection regulation. The main parts are the establishment of a internal Data Protection Authority within the project, a pseudonymisation procedure, the introduction of a Trusted Third Party, binding contracts between each project participant or end user with the central Data Protection Authority and finally an informed consent of each patient for ethical reasons on the one hand and, on the other hand the unlikely case, that we will have personal data in some situations. If this architecture is implemented in the research project, participating researchers could do their research without having big obstacles because of data protection reasons. They could concentrate on their scientific research so that this architecture would ensure and improve the efficiency of the research project.

574 In the Data Protection Authority established experts from all relevant professions within the research project can be represented, for example legal, technical and medical experts. That would guarantee the needed expertise to ensure the success of research project. This central Data Protection Authority must be empowered by the project to conclude binding contracts regarding data protection and to act as the responsible entity regarding data protection (including acting as the data controller within the project) on behalf of the project.

575 Furthermore, one or several Trusted Third Parties would need to be chosen by the central Data Protection Authority to hold the link between the data subject and his or her genetic data to be processed within the research project and to assist the project in case a re-identification of a data subject is needed.

576 Besides, contracts between the Data Protection Authority on behalf of the project and the hospitals and the participating research entities must be concluded to ensure compliance of these parties with data protection regulations and the research project's policies to keep the data de facto anonymous.

577 The fulfilment of these conditions is a crucial factor for the compliance of the particular research project with current data protection regulation, which is itself of vital importance for the success and acceptance of the project. The compliance of all partners, end-users and the Data Protection Authority has to be verified very carefully to guarantee the data subjects' privacy and to ensure compliance with data protection law.

578 As shown above, it is possible with this proposed Data Protection Framework to ensure compliance of the genetic research project with current data protection regulation while efficient scientific research is guaranteed at the same time. Therefore the implementation of the elaborated framework and the compliance with it should be followed is high priority. By implementing this Framework the needs of the researchers, hospitals and data subjects can be satisfied at the same time so that this Data Protection Framework can be an important part to lead the genetic research project to success.

5. References

Abramovitch R, Freedman J L, Henry K et al (1995): Children's capacity to agree to psychological research: knowledge of risks and benefits and voluntariness, *Ethics and Behavior,* 5 (1), 25–48

Agard A, Hermeren G, Herlitz J (2001): Patients' experiences of intervention trials on the treatment of myocardial infarction: is it time to adjust the informed consent procedure to the patient's capacity? *Heart (British Cardiac Society)*, 86 (6), 632–637

Alderson P (1993): Children's consent to surgery, Buckingham: Open University Press

Alderson P, Goodey C (1998): Theories of consent, *British Medical Journal*, 317, 1313–1315

Alston B (2005): Blood rights: The body and information privacy, *Journal of Medical Law*, 12 (4), 426–440

American Academy of Pediatrics (AAP, 1995): Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations, *Pediatrics*, 2, 286–294

American Society of Clinical Oncology Policy Statement Update (ASCO 2003): Genetic Testing for Cancer Susceptibility, *Journal of Clinical Oncology*, 21 (12), 2397–2406

Andorno R (2004): The right not to know: an autonomy based approach, *Journal of Medical Ethics*, 30, 435–439

Antoine M (2001): Le Commerce électronique européen sur les rails? Analyse et propositions de mises en œuvre de la Directive sur le commerce électronique, Bruxelles: Bruylant

Antonow K (2006): Der rechtliche Rahmen der Zulässigkeit für Biobanken zu Forschungszwecken, Baden-Baden: Nomos Verlagsgesellschaft

Ashcroft R (2000): The ethics of reusing archived tissue for research, *Neuropathology and Applied Neurobiology*, 26, 408–411

Bamberg M, Budwig N (1992): Terapeutic misconceptions: when the voices of caring and research are misconstrued as the voice of curing, *Ethics and Behavior*, 2 (3), 165–184

Banks T M (2000): Misusing informed consent: a critique of limitations on research subjects' access to genetic research results, *Saskatchewan Law Review*, 63 (2), 539–80

Beauchamp T L, Childress J F (2001): Principles of biomedical ethics, New York: Oxford University Press (5th edition)

Benkendorf J L, Reutenauer J E, Hughes C A, Eads N, Willison J, Powers M, Lerman C (1997): Patients' attitudes about autonomy and confidentiality in genetic testing for breast-ovarian cancer susceptibility, *American Journal of Medical Genetics*, 73, 296–303

Benkner S, Berti G, Engelbrecht G, Fingberg J, Kohring G, Middleton S E, Schmidt R (2005): GEMSS: Grid-infrastructure for medical service provision, *Methods of Information in Medicine*, 2 (44), 177–181

Bernstein M (2005): Fully informed consent is impossible in surgical clinical trials, *Canadian Journal of Surgery*, 48 (4), 271–272

Bevan E G, Chee L C, McGhee S M, McInnes G T (1993): Patients attitudes to participation in clinical trials, *British Journal of Clinical Pharmacology*, 35, 204–207

Bjorn E, Rossel P, Holm S (1999): Can the written information to research subjects be improved? – an empirical study, *Journal of Medical Ethics*, 25, 263–267

Bottorff J L, Ratner P A, Balneaves L G, Richardson C G, McCullum M, Hack T, Chalmers K, Buxton J (2002): Women's interest in genetic testing for breast cancer risk: the influence of sociodemographics and knowledge, *Cancer Epidemiology, Biomarkers and Prevention,* 11, 89–95

Brühann U (2004): Die Veröffentlichung personenbezogener Daten im Internet als Datenschutzproblem, *Datenschutz und Datensicherheit*, 4, 201–209

Buchanan A, McPherson E, Brody B A, Califano A, Kahn J, McCullough N, Robertson J A) (2002): Pharmacogenetics: ethical and regulatory issues in research and clinical practice, Consortium on Pharmacogenetics. Report of the Consortium on Pharmacogenetics: Findings and Recommendations

Bundesdatenschutzgesetz (1990):, http://bundesrecht.juris.de/bdsg_1990/index.html, accessed 15. 9. 2009

Bunin G R, Kazak A E, Mitelman O (1996): Informing subjects of epidemiologic study results: Children's Cancer Group, *Pediatrics,* 97, 486–491

Burgess E, Singhal N, Amin H et al (2003): Consent for clinical research in the neonatal intensive care unit: a retrospective survey and a prospective study, *Archives of Disease in Childhood: Fetal and Neonatal Edition*, 88 (4), F280–285, discussion F285–286

Burke W, Diekema D (2006): Ethical issues arising from the participation of children in genetic research, *The Journal of Pediatrics*, 149, 34–38

Bygrave L (2002): Data Protection Law, London: Kluwer Law International

Bygrave L (2003): The body as data? Reflections on the relationship of data privacy law with the human body, www.privacy.vic.gov.au/privacy/web.nsf/download/CF51D885BA101AAC-CA256E050012CBA5/$FILE/Byg, assessed 22. 9. 2009

Byrne D J, Napier A, Cuschieri A (1988): How informed is signed consent? *British Medical Journal*, 296, 839–840

Case P (2003): Confidence matters: the rise and fall of informational autonomy in medical law, *Medical Law Review*, 11 (2), 208–236

Cassileth B R, Lusk E J, Miller D S et al (1982): Attitudes toward clinical trials among patients and the public, *Journal of the American Medical Association*, 248 (8), 968–970

Caulfield T, Upshur R E G, Daar A (2003): DNA databanks and consent: a suggested policy option involving an authorization model, *BMC Medical Ethics*, 4, 1–4

Chen D T, Rosenstein D L, Muthappan P, Hilsenbeck S G, Miller F G, Emanuel E J, Wendler D (2005): Research with stored biological samples. What do research participants want? *Archives of Internal Medicine*, 165, 652–655

Clarke A, Richards M, Kerzin-Storrar L, Halliday J, Young M A, Simpson S A, Featherstone K, Forrest K, Lucassen A, Morrison P J, Quarrell O W, Stewart H (2005): Genetic professionals' reports of nondisclosure of genetic risk information within families, *European Journal of Human Genetics*, 13 (5), 556–562

Clayton E W (1998): What should the law say about disclosure of genetic information to relatives? *Journal of Health Care Law and Policy,* 1, 373–390

Clayton E W (2005): Informed consent and biobanks, *The Journal of Law, Medicine and Ethics*, 33, 15–21

Clayton E W, Ross L F (2006): Implications of disclosing individual results of clinical research, *Journal of the American Medical Association*, 295 (37), 37–38

Clayton E W, Steinberg K, Khoury M J, Thomson E, Andrews L, Kahn M J E, Kopelman L, Weiss J O (1995): Informed consent for genetic research on stored tissue samples, *Journal of the American Medical Association*, 274 (22), 1786–1792

Corrigan O (2003): Empty ethics: the problem with informed consent, *Sociology of Health and Illness*, 25 (3), 768–792

Council for International Organizations of Medical Sciences (CIOMS, 2002): International ethical guidelines for biomedical research involving human subjects, Geneva, www.cioms.ch/frame_guidelines_nov_2002.htm, accessed 15. 9. 2009

Council of Europe (1997): Convention No. 164 of the Council of Europe for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: Convention on Human Rights and Biomedicine, Oviedo, http://conventions.coe.int/Treaty/Commun/QueVoulezVous.asp?NT=164&CM=8&DF=15/09/2009&CL=ENG, accessed 15. 9. 2009

Council of Europe (2005): Additional protocol to the Convention on Human Rights and Biomedicine, concerning biomedical research, Strasbourg, http://conventions.coe.int/Treaty/en/Treaties/Html/195.htm, accessed 15. 9. 2009

Council of Europe (2006): Recommendation 2006/4 of the Committee of Ministers to member states on research on biological materials of human origin, adopted by the Committee of Ministers on March 15, 2006, https://wcd.coe.int/ViewDoc.jsp?id=977859, assessed 15. 9. 2009

Cousins G M H, Ring L, Conroy R, Kay E, Croke D T D (2005): Public Perceptions of Biomedical Research. A survey of the general population in Ireland, Dublin: Royal College of Surgeons in Ireland and Health Research Board

Dahl M, Wiesemann C (2001): Forschung an Minderjährigen im internationalen Vergleich: Bilanz und Zwischenperspektiven, *Ethik in der Medizin,* 13, 87–110

Dammann U, Simitis S (1997): EG-Datenschutzrichtlinie, Baden-Baden: Nomos Verlagsgesellschaft
Data Protection Working Party (2004): Article 29, working document on genetic data, http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/2004/wp91_en.pdf, assessed 15. 9. 2009
Dawson A, Spencer S A (2005): Informing children and parents about research, *Archives of Disease in Childhood*, 90, 233–235
De Melo-Martín I, Ho A. (2008): Beyond informed consent: the therapeutic misconception and trust, *Journal of Medical Ethics*, 34 (3), 202–205
De Montgolfier S, Moutel G, Duchange N, Theodorou I, Herve C, Leport C, APROCO Study Group (2002): Ethical reflections on pharmacogenetics and DNA banking in a cohort of HIV-infected patients, *Pharmacogenetics*, 12 (9), 667–675
Dinnett E M, Mungall M M, Gordon C, Ronald E S, Gaw A (2006): Offering results to research participants, *British Medical Journal (Clinical research edition)*, 332, 549–550
Dixon-Woods M, Jackson C, Windridge K C, Kenyon S (2006): Receiving a summary of the results of a trial: qualitative study of participants' views, *British Medical Journal (Clinical research edition),* 332, 206–210
Dorn L D, Susman E J, Fletcher J C (1995): Informed consent in children and adolescents: age, maturation and psychological state, *Journal of Adolescence Health*, 16, 185–190
Dressler L G, Juengst E T (2006): Thresholds and boundaries in the disclosure of individual genetic research results, *American Journal of Bioethics,* 6, 18–20, author reply W10–12
Durfy S J, Bowen D J, McTiernan A, Sporleder J, Burke W (1999): Attitudes and interest in genetic testing for breast and ovarian cancer susceptibility in diverse groups of women in western Washington, *Cancer Epidemiology, Biomarkers and Prevention*, 8, 369–375

Ehmann E, Helfrich M (1999): EG-Datenschutzrichtlinie, Koeln: Dr. Otto Schmidt
Eriksson S, Helgesson G (2005): Potential harms, anonymization, and the right to withdraw consent to biobank research, *European Journal of Human Genetics*, 13, 1071–1076
EU (2001): Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, Luxembourg, http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf, accessed 15. 9. 2009
EU (2004): Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, Strasbourg, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:EN:PDF, assessed 15. 9. 2009
EU (2006): Directive 2006/86/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells, Strasbourg, http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_294/l_29420061025en00320050.pdf, assessed 15. 9. 2009
Evans HM (2004): Should patients be allowed to veto their participation in clinical research? *Journal of Medical Ethics*, 30, 198–203

Faden R R, Beauchamp T L (1986): A history and theory of informed consent. New York: Oxford University Press
Ferguson P R (2002): Patients' perceptions of information provided in clinical trials, *Journal of Medical Ethics*, 28 (1), 45–48
Fernandez C V, Weijer C (2006): Obligations in offering to disclose genetic research results, *American Journal of Bioethics*, 6, 44–46
Fernandez C V, Kodish E, Taweel S, Shurin S, Weijer C, Children's Oncology Group (2003a): Disclosure of the right of research participants to receive research results: an analysis of consent forms in the Children's Oncology Group, *Cancer*, 97 (11), 2904–2909
Fernandez C V, Kodish E, Weijer C (2003b): Informing study participants of research results: an ethical imperative, *IRB: Ethics and Human Research*, 25, 12–19
Fernandez C V, Kodish E, Shurin S, Weijer C (2003c): Offering to return results to research participants: attitudes and needs of principal investigators in the Children's Oncology Group, *American Journal of Pediatric Hematology/Oncology*, 25, 704–708

Fernandez C V, Skedgel C, Weijer C (2004): Considerations and costs of disclosing study findings to research participants, Canadian Medical Association Journal, 170, 1417–1419

Fernandez C V, Shurin S, Kodish E (2006): Providing research participants with findings from completed cancer-related clinical trials – not quite as simple as it sounds, *Cancer*, 107 (6), 1419–1420

Fernandez C V, Santor D, Meijer C, Strahlendorf C, Moghrabi A, Pentz R, Gao J, Kodish E (2007): The return of research results to participants: Pilot questionnaire of adolescents and parents of children with cancer, *Pediatric Blood and Cancer*, 48 (4), 441–446

Fox R C (1990): The Evolution of American bioethics: a sociological perspective, Weisz G (ed): *Social science perspectives on medical ethics*, Dordrecht: Kluwer, 201–217

Gallet M, Aupetit J F, Servan E, Lestaevel M, Lopez M, Chassoux G (1994): Informed consent, what information is left after a therapeutic trial? *Archives des Maladies du Coeur et des Vaisseaux*, 87, 39–45

Geller G, Tambor E S, Bernhardt B A, Chase G A, Hofman K J, Faden R R, Holtzman N A (1993): Physicians' attitudes toward disclosure of genetic information to third parties, *Journal of Law, Medicine and Ethics*, 21, 238–240

Gola P, Schomerus R (2007): BDSG Bundesdatenschutzgesetz Kommentar, Muencenh: C.H. Beck (9th edition)

Goodson M L, Vernon B G (2004): A study of public opinion on the use of tissue samples from living subjects for clinical research, *Journal of Clinical Pathology*, 57 (2),135–138

Gotay C C (2001): Perceptions of informed consent by participants in a prostate cancer prevention study, *Cancer Epidemiology, Biomarkers and Prevention*, 10, 1097–1099

Green R M, Thomas A M (1997): Whose Gene Is It? A Case Discussion About Familial Conflict over Genetic Testing for Breast Cancer, *Journal of Genetic Counseling*, 6 (2), 245–254

Grossman S A, Piantodosi S, Covahey C (1994): Are informed consent forms that describe clinical oncology research protocols readable by most patients and their families? *Journal of Clinical Oncology*, 12, 2211–22115

Hansson M G (2005): Building on relationships of trust in biobank research, *Journal of Medical Ethics*, 31, 415–418

Hansson M G, Dillner J, Bartram C R, Carlson J A, Helgesson G (2006): Should donors be allowed to give broad consent to future biobank research? *Lancet Oncology*, 7, 266–269

Harth S C, Thong Y H (1990): Sociodemographic and motivational characteristics of parents who volunteer their children for clinical research: a controlled study, *British Medical Journal*, 300, 1372–1375

Harth S C, Thong Y H (1995): Parental perceptions and attitudes about informed consent in clinical research involving children, *Social Science and Medicine*, 41 (12), 1647–1651

Hoeren T, Sieber U (2009): Handbuch Multimedia-Recht, Muenchen: C.H. Beck, supplemental set 23

Hoeyer K, Olofsson B O, Mjorndal T, Lynoe N (2004): Informed consent and biobanks: a population-based study of attitudes towards tissue donation for genetic research, *Scandinavian Journal of Public Health*, 32, 224–229

Hoeyer K, Olofsson B O, Mjörndal T, Lynoe N (2005): The ethics of research using biobanks. Reason to question the importance attributed to informed consent, *Archives of Internal Medicine*, 165, 97–100

HUGO Ethics Committee (1998): Statement on DNA sampling: control and access, February 1998, http://www.hugo-international.org/img/dna_1998.pdf, assessed 15. 9. 2009

Hunter A G, Sharpe N, Mullen M, Meschino W S (2001): Ethical, legal, and practical concerns about recontacting patients to inform them of new information: the case in medical genetics. *American Journal of Medical Genetics*, 103 (4), 265–276

Jacobsen P B, Valdimarsdottier H B, Brown K L, Offit K (1997): Decision-making about genetic testing among women at familial risk for breast cancer, *Psychosomatic Medicine*, 59, 459–466

Janofsky J, Starfield B (1981): Assessment of risk in research on children, *Journal of Pediatrics*, 98 (5), 842–846

Jepson R G, Hewison J, Thompson A G H, Weller D (2005): How should we measure informed choice? The case of cancer screening, *Journal of Medical Ethics*, 31, 192–196

Joffe S, Cook E F, Cleary P D, Clark J W, Weeks J C (2001): Quality of informed consent in cancer clinical trials: a crossectional survey, *Lance*t, 358, 1772–1777

Kaphingst K A, Janoff J M, Harris L N, Emmons K M (2006): Views of female breast cancer patients who donated biologic samples regarding storage and use of samples for genetic research, *Clinical Genetics*, 69, 393–398

Kapp M B (2006): Ethical and legal issues in research involving human subjects: do you want a piece of me? *Journal of Clinical Pathology*, 59, 335–339

Kilian W, Heussen B (2009): Computerrechts-Handbuch, Muenchen: C.H. Beck, supplemental set 27

Kjaergaard L L, Kruse A Y, Krogsgaard K, Gluud C N, Mortensen E L, Gottschau A, Bjerg A M (1998): Outpatients' knowledge about and attitude towards clinical research and randomized clinical trials. The INFO Trial Group, *Danish Medical Bulletin*, 45, 439–443

Klitzman R (2006): Questions, complexities, and limitations in disclosing individual genetic results, *American Journal of Bioethics*, 6 (6), 34–36

Knoppers, B M (2001): Duty to recontact: A legal harbinger? *American Journal for Medical Genetics*, 103 (4), 265–276

Knoppers B M, Joly Y, Simard J, Durocher, F (2006): The emergence of an ethical duty to disclose genetic research results: international perspectives, *European Journal of Human Genetics*, 14, 1170–1178

Knyrim R, Momeni D (2003): Datenschutz bei klinischen Prüfungen und medizinischen Studien, *Recht der Medizin*, 3, 68–71

Kodish E D, Pentz R D, Noll R B, Ruccione K, Buckley J, Lange B J (1998): Informed Consent in the Childrens Cancer Group. Results of preliminary research, *Cance*r, 82 (12), 2467–2481

Kollek R (2006): Schritte zur internationalen Verständigung über bioethische Fragen, Deutscher UNESCO-Kommission (eds): *Allgemeine Erklärung über Bioethik und Menschenrechte. Wegweiser für die Internationalisierung der Bioethik*, Bonn: Koellen, 37–49

Kollek R (2009): Informed consent. Comment on Article 6, Ten Have H A M J, Jean M S (eds): *Universal Declaration on Bioethics and Human Rights. Background, principles and application*. Paris: UNESCO Publishing (Ethics series), 123–138

Kollek R, Lemke T (2008): Der medizinische Blick in die Zukunft. Gesellschaftliche Implikationen prädiktiver Gentests, Frankfurt a. M.: Campus

Koocher G, De Maso D (1990): Children's competence to consent to medical procedures. *Pediatrician*, 17, 68–73

Kottow M (2004): The battering of informed consent, *Journal of Medical Ethics*, 30, 565–569

Kruse A Y, Kjaergard L L, Krogsgaard K, Gluud C, Mortensen E, Gottschau A, Bjerg A (2000): A randomized trial assessing the impact of written information on outpatients' knowledge about and attitude toward randomized clinical trials: The INFO trial group, *Controlled clinical trials* 21, 223–240

Kurz R (2003): Ethik in der pädiatrischen Forschung, *Monatsschrift Kinderheilkunde*, 12, 1276–1281

Kuther T L (2003): Medical decision-making and minors: issues of consent and assent, *Adolescence,* 38 (150), 343–358

Lehmann L S, Weeks J C, Klar N, Biener L, Garber J E (2000): Disclosure of familial genetic information: perceptions of the duty to inform, *The American Journal of Medicine,* 109, 705–711

Leikin S (1993): Minors' assent, consent, or dissent to medical research, *IRB: A Review of Human Subjects Research*, 15 (2), 1–7

Lemke T (2004): Genetische Diskriminierung in Deutschland – Eine explorative Studie am Beispiel der Huntington-Krankheit, *Soziale Welt*, 56, 417–439

Lemke T (2006): Die Polizei der Gene: Formen und Felder genetischer Diskriminierung. Frankfurt a. M.: Campus

Levi R B, Marsick R, Drotar D, Kodish E D (2000): Diagnosis, disclosure, and informed consent: learning from parents of children with cancer, *American Journal of Pediatric Hematology/ Oncology*, 22 (1), 3–12

Levine R J (1996): Research involving children as subjects. Thomasma D C, Kushner T (eds): *Birth to Death. Science and Bioethics*, Cambridge: Cambridge University Press, 270–282

Lohaus A, Albrecht R, Seyberth H W (2002): Einwilligungsfähigkeit bei Kindern. Ergebnisse einer empirischen Studie und zukünftige Forschungsperspektiven, *Monatliche Kinderheilkunde*, 12, 1502–1507

Ludman E J, Curry S J, Hoffman E, Taplin S (1999): Women's knowledge and attitudes about genetic testing for breast cancer susceptibility, *Effective Clinical Practice*, 2, 158–162

Luttenberger N, Kollek R, Reischl J, Stürzebecher S (2006): Design of Individual Donor Feedback Processes in Biobank Research, *Proceedings of the Jahrestagung der Gesellschaft für Informatik. Lecture Notes in Informatics (LNI)*, Heidelberg: Springer, 722–728

Maede, C D, Howser D M (1992): Consent forms: How to determine and improve their readability, *Oncology Nursing Forum*, 19, 1523–1528

Manolio, T A (2006): Taking our obligations to research participants seriously: disclosing individual results of genetic research, *American Journal of Bioethics*, 6 (6), 32–34

Markman M (2006): Providing research participants with findings from completed cancer-related clinical trials – not quite as simple as it sounds, *Cancer*, 106 (7), 1421–1424

Mason S A, Allmark P J (2000): Obtaining informed consent to neonatal randomised controlled trials: interviews with parents and clinicians in the Euricon study, *Lancet*, 356, 2045–2051

McCollum A T, Schwartz A H (1969): Pediatric research hospitalization: its meaning to parents, *Pediatric Research*, 3 (3), 199–204

McQuillan G M, Porter K S, Agelli Met al (2003): Consent for genetic research in a general population: the NHANES experience, *Genetics in Medicine*, 5 (1), 35–42

Medical Research Council (MRC, 2004): Human Tissue Bill. Views of the Medical Research Council, London: Medical Research Council

Meltzer L A (2006): Undesirable implications of disclosing individual genetic results to research participants, *American Journal of Bioethics*, 6 (6), 28–30; author reply W10-2

Merz J F, Sankar P, Taube S E, Livolsi V (1997): Use of Human Tissues in Research: Clarifying Clinican and Researcher Roles and Information Flows, *Journal of Investigative Medicine*, 45 (5), 252–257

Metschke R, Wellbrock R (2002): Datenschutz in Wissenschaft und Forschung (Berlin: Materialien zum Datenschutz), www.**datenschutz-berlin**.de/attachments/47/**Materialien**28.pdf, accessed 16. 9. 2009

Miller F A, Christensen R, Giacomini M, Robert J S (2008a): Duty to disclose what? Querying the putative obligation to return research results to participants, Journal of Medical Ethics,, 4 (3), 210–213

Miller F A, Giacomini M, Ahern C, Robert J S, De Laat S (2008b): When research seems like clinical care: a qualitative study of the communication of individual cancer genetic research results, *BMC Medical Ethics*, 9, 4

Miyata H, Tachimori H, Takahashi M, Saito T, Kai I (2004): Disclosure of cancer diagnosis and prognosis: a survey of the general public's attitudes towards doctors and family holding discretionary powers, *BMC Medical Ethics*, 5 (7), 1–6

Moutel G, Duchange N, Raffi F, Sharara L I, Theodorou I, Noel V, De Montgolfier S, Callies I, Bricaire F, Herve C, Leport C (2005): Communication of pharmacogenetic research results to HIV-infected treated patients: standpoints of professionals and patients, *European Journal Human Genetics*, 13, 1055–1062

National Bioethics Advisory Commission (NBAC 1999): Research involving human biological materials: ethical issues and policy guidance: Vol 2, Report and Recommendations of the National Bioethics Advisory Commission. Rockville, Md: National Bioethics Advisory Commission

Nationaler Ethikrat (2005): Prädiktive Gesundheitsinformationen bei Einstellungsuntersuchungen, Stellungnahme, Berlin, www.ethikrat.org/stellungnahmen/pdf/Stellungnahme_PGI_Einstellungsuntersuchungen.pdf, assessed 16. 9. 2009

Nationaler Ethikrat (2007): Prädiktive Gesundheitsinformationen beim Abschluss von Versicherungen, Stellungnahme, Berlin, www.ethikrat.org/stellungnahmen/pdf/Stellungnahme_PGI_Versicherungen.pdf, assessed 16. 9. 2009

Nicholson R (1991): The ethics of research with children, Brazier M, Lobjoit M (eds): *Protecting the vulnerable autonomy and consent in health care*, London: Routledge, 10–21

O'Brien J, Chantler C (2003): Confidentiality and the duties of care, *Journal of Medical Ethics*, 29, 36–40

Office of the Victorian Commissioner, Melbourne (2003): 8 September 2003, www.privacy.vic.gov.au/dir100/priweb.nsf, accessed 15. 9. 2009

Olechnowicz J Q, Eder M, Simon C et al (2002): Assent Observed: Children's Involvement in Leukemia Treatment and Research Discussions, *Pediatrics*, 109, 806–814

O'Neill O (2003): Some limits of informed consent, *Journal of Medical Ethics*, 29, 4–7

O'Neill O (2004): Informed consent and public health, *Philosophical transactions of the Royal Society of London: Series B: Biological sciences*, 359, 1133–1136

O'Neill S C, Brewer N T, Lillie S E, Morrill E F, Dees E C, Carey L A, Rimer B K (2007): Women's interest in gene expression analysis for breast cancer recurrence risk, *Journal of Clinical Oncology*, 25, 4628–4634

Ondrusek N, Abramovitch R, Pencharz P, Koren G (1998): Empirical examination of the ability of children to consent to clinical research, *Journal of Medical Ethics*, 24, 158–165

Olver I N, Buchanan L, Laidlaw C, Poulton G (1995): The adequacy of consent forms for informing patients entering oncological clinical trials, *Annals of Oncology*, 6, 867–870

Ormond K E (2006): Disclosing genetic research results: examples from practice, *Americal Journal of Bioethics*, 6, 30–32

Ossorio P N (2006): Letting the gene out of the bottle: a comment on returning individual research results to participants, American Journal of Bioethics, 6 (6), 24–25; author reply W10-2

Parker M, Lucassen A (2003): Concern for families and individuals in clinical genetics, *Journal for Medical Ethics*, 29, 70–73

Partridge A H, Winer E P (2002): Informing clinical trial participants about study results, *Journal of the American Medical Association*, 288, 363–365

Partridge A H, Burstein H J, Gelman R S, Marcom P K, Winer E P (2003): Do patients participating in clinical trials want to know study results? *Journal of the National Cancer Institute*, 95, 491–492

Partridge A H, Hackett N, Blood E, Gelman R, Joffe S, Bauer-Wu S, Knudsen K, Emmons K, Collyar D, Schilsky R L, Winer E P (2004): Oncology physician and nurse practices and attitudes regarding offering clinical trial results to study participants, *Journal of the National Cancer Institute*, 96, 629–632

Partridge A H, Wong J S, Knudsen K, Gelman R, Sampson E, Gadd M, Bishop K L, Harris J R, Winer E P (2005): Offering participants results of a clinical trial: sharing results of a negative study, *Lancet*, 365, 963–964

Pelias M K (2004): Research in human genetics: the tension between doing no harm and personal autonomy, *Clinical Genetics*, 67, 1–5

Pentz R D, Billot L, Wendler D (2006): Research on stored biological samples. Views of African American and white American cancer patients, *American Journal of Medical Genetics,* 140A, 733–739

Plantinga L, Natowicz M R, Kass N E et al (2003): Disclosure, confidentiality, and families: experiences and attitudes of those with genetic versus nongenetic medical conditions, *American Journal of Medical Genetics: Part C, Seminars in medical genetics*, 119 (1), 51–59

Pope J E, Tingey D P, Arnold J M et al (2003): Are subjects satisfied with the informed consent process? A survey of research participants, *The Journal of Rheumatology,* 30 (4), 815–824

Poullet Y, Herveg J (2007): Which Major Legal Concerns in Future e-Health? *The Information Society: Innovation, Legitimacy, Ethics and Democracy in Honor of Professor Jaques Berleur s.j., collection International Federation for Information Processing*, 233, 159–170

Press N, Browner C H (1995): Risk, autonomy and responsibility: informed consent, *Hastings Center Report*, 25, 9–12

Pullman D, Hodgkinson K (2006): Genetic knowledge and moral responsibility: ambiguity at the interface of genetic research and clinical practice, *Clinical Genetics*, 69, 199–203

Ravitsky V, Wilfond B S (2006): Disclosing individual genetic results to research participants, *American Journal of Bioethics*, 6, 8–17

Redeker K, Karpenstein U (2001): Über Nutzen und Notwendigkeit, Gesetze zu begründen, *Neue Juristische Wochenschrift*, 39, 2825–2831

Renegar G, Webster C J, Stuerzebecher S, Harty L, Ide S E, Balkite B, Rogalski-Salter T A, Cohen N, Spear B B, Barnes D M, Brazell C (2006): Returning genetic research results: points to consider, *Bioethics*, 20 (1), 24–36

Reymond M A, Steinert R, Escorrou J, Fourtanier G (2002): Ethical, legal, and economic issues raised by the use of human tissue in postgenomic research, *Digestive Diseases*, 20, 257–265

Reymond M A, Alla A S, Steinert R, Eder F, Halangk W, Lippert H (2003): Informed Consent for Molecular-Based Diagnostic and Prognostic Studies in the Cancer Patient, *Digestive Diseases*, 21, 351–356

Richards M P, Ponder M, Pharoah P et al (2003): Issues of consent and feedback in a genetic epidemiological study of women with breast cancer, *Journal of Medical Ethics*, 29 (2), 93–96

Rigby H, Fernandez C V (2005): Providing research results to study participants: support versus practice of researchers presenting at the American Society of Hematology annual meeting, *Blood*, 106, 1199–1202

Roßnagel A, Scholz P (2000): Datenschutz durch Anonymität und Pseudonymität-Rechtsfolgen der Verwendung anonymer und pseudonymer Daten, *Multimedia und Recht*, 12, 721–731

Royal College of Paediatrics (2000): Guidelines for the ethical conduct of medical research involving children, developed by the Ethics Advisory Committee, *Archives of Disease in Childhood*, 82, 177–182

Sade R M (2002): Research on Stored Biological Samples is Still Research, *Archive of International Medicine*, 162, 1439–1440

Saeltzer G (2004): Sind diese Daten personenbezogen oder nicht? *Datenschutz und Datensicherheit*, 4, 218–227

Sass H M (1998): Genotyping in clinical trials – towards a principle of informed request, *Journal of Medicine and Philosophy*, 23 (3), 288–296

Satin D J (2005): More realism about informed consent, *Journal of Laboratory and Clinical Medicine*, 145, 292–294

Scherer D G (1991): The capacities of minors to exercise voluntariness in medical treatment decisions, *Law and Human Behavior*, 15 (4), 431–449

Schulz C J, Riddle M P, Valdimirsdottir H B, Abramson D H, Sklar C A (2003): Impact on survivors of retinoblastoma when informed of study results on risk of second cancers, *Medical and Pediatric Oncology*, 41, 36–43

Shalowitz D I, Miller F G (2005): Disclosing Individual Results of Clinical Research. Implication of Respect for Participants, *Journal of the American Medical Association*, 294, 737–740

Shalowitz D I, Miller F G (2006): Implications of Disclosing Individual Results of Clinical Research, Letter, *Journal of the American Medical Association*, 295, 37

Shalowitz D I, Miller F G (2008): Communicating the results of clinical research to participants: attitudes, practices, and future directions, *PLoS Medicine*, 5, e91

Simitis S (ed) (2006): Bundesdatenschutzgesetz, Baden-Baden: Nomos (6th edition)

Smith K (2000): Genetic testing of the general population: ethical and informatic concerns, *Critical Reviews in Biomedical Engineering*, 28 (3–4), 557–561

Snowden C, Garcia J, Elbourne D (1998): Reactions of participants to the results of a randomised controlled trial: Exploratory study, *British Medical Journal (Clinical Research Edition)*, 317, 21–26

Stegmayr B, Asplund K (2002): Informed consent for genetic research on blood stored for more than a decade: a population based study, *British Medical Journal (Clinical Research Edition)*, 325, 634–635

Stockter U (2008): Das Verbot genetischer Diskriminierung und das Recht auf Achtung der Individualität. Gendiagnostik als Anlass für gleichheits- und persönlichkeitsrechtliche Erwägungen zum Umgang mit prognostischen und anderen statistischen Daten. Berlin: Duncker und Humblot.

Struewing J P, Lerman C, Kase R G, Giambarresi T R, Tucker M A (1995): Anticipated uptake and impact of genetic testing in hereditary breast and ovarian cancer families, *Cancer Epidemiology, Biomarkers and Prevention*, 4, 169–173

Susman E J, Dorn L D, Fletcher J C (1992): Participation in biomedical research: the consent process as viewed by children, adolescents, young adults, and physicians, *Journal of Pediatrics*, 121 (4), 547–552

Tait A R, Voepel-Lewis T, Malviya S (2003a): Do they understand? (part I): parental consent for children participating in clinical anesthesia and surgery research, *Anesthesiology,* 98 (3), 603–608

Tait A R, Voepel-Lewis T, Malviya S (2003b): Do they understand? (part II): assent of children participating in clinical anesthesia and surgery research, *Anesthesiology*, 98 (3), 609–614

Tarnowski K J, Allen D M, Mayhall C, Kelly P A (1990): Readability of pediatric biomedical research informed consent forms, *Pediatrics,* 85 (1), 58–62

Trouet, C (2004): New European guidelines for the use of stored human biological materials in biomedical research, *Journal of Medical Ethics*, 30, 99–103

UNESCO (1997): International Declaration on the Human Genome, Records of the General Conference, 29nd session, Paris, http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html, assessed 19. 9. 2009

UNESCO (2003): International Declaration on Human Genetic Data, Resolution adopted on the report of Commission III at the 20th plenary meeting, on 16 October 2003, Records of the General Conference, 32nd session, Paris, http://portal.unesco.org/en/ev.php-URL_ID=17720&URL_DO=DO_TOPIC&URL_SECTION=201.html, assessed 19. 9. 2009

UNESCO (2005): Universal Declaration on Bioethics and Human Rights, Resolution adopted by acclamation on 19 October 2005, by the 33rd session of the General Conference of UNESCO, Paris, http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html, accessed 19. 9. 2009

United State Department of Health and Human Services (US-DHHS 2005): Public Welfare Department of Health and Human Services, part 46, protection of human subjects, June 23, 2005, http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm, accessed 19. 9. 2009

Van den Boer-van den Berg H M A, Maat-Kievit, A A (2001): The whole truth and nothing but the truth, but what is the truth? *Journal of Medical Genetics*, 38, 39–42

Van Eecke P (2001): Electronic health care services and the E-commerce Directive, Dumortier J, Robben F, Taeymans M (eds): *A Decade of research @ the crossroads of law and ICT*, Bruxelles: De Boeck and Larcier, 365–380

Van Stuijvenberg M, Suur M H, De Vos S et al (1998): Informed consent, parental awareness, and reasons for participating in a randomised controlled study, *Archives of disease in childhood*, 79 (2), 120–125

Vollmann J, Winau R (1996): Informed consent in human experimentation before the Nuremberg Code, *British Medical Journal*, 313, 1445–1449

Wade C H, Kalfoglou A L (2006): When do genetic researchers have a duty to recontact study participants? *American Journal of Bioethics*, 6, 26–27

Weichert T (2002): Gentests und Persönlichkeitsrecht. Datenschutz und Datenhoheit. Vortrag im Rahmen des Wintersymposiums des Instituts für Recht und Politik und der Heinrich-Böll-Stiftung: Von der Durchsichtigkeit des Menschen – Rechtsprobleme der Gendiagnostik, Berlin, www.datenschutzzentrum.de/material/themen/gendatei/gentests.htm, accessed 19. 9. 2009

Weichert T (2002): DuD, Der Schutz genetischer Information, 3, 133–145

Wellbrock, R (1989): CR, Genomanalyse und das informationelle Selbstbestimmungsrecht, 3, 204–210

Wellbrock R (2003): Datenschutzrechtliche Aspekte des Aufbaus von Biobanken für Forschungszwecke, *Medizinrecht*, 21 (2), 77–82

Wellbrock, R (2004): Biobanken für die Forschung, DuD, 9, 561–565

Wellbrock R (2007): Generische Datenschutzmodelle für Biomaterialbanken, *Datenschutz und Datensicherheit*, 31, 17–21

Wendler D, Emanuel E (2002): The debate over research on stored biological samples. What do sources think? *Archives of Internal Medicine*, 162, 1457–1462

Wendler D, Pentz R (2007): How does the collection of genetic test results affect research participants? *American Journal of Medical Genetics*, 143A, 1733–1738

Wendler D, Prasad K, Wilfond B (2002): Does the current consent process minimize the risks of genetics research? *American Journal of Medical Genetics*, 113, 258–262

Wertz D C (1999): Archived specimen: A platform of discussion, *Community Genetics*, 2, 51–60

Wertz D C, Fletcher J C, Mulvihill J J (1990): Medical geneticists confront ethical dilemmas: cross-cultural comparisons among 18 nations, *American Journal of Human Genetics*, 46, 1200–1213

Williams E D (2001): Informed consent in genetic research, *Croatian Medical Journal*, 42 (4), 451–457

Wolpe P (1998): The triumph of autonomy in American bioethics. A sociological review, Devries R, Subedi J (eds): *Bioethics and society: sociological investigations and the enterprise of bioethics*, Englewood Cliff: Prentice Hall, 38–59

World Health Organisation (WHO 2003): Genetic databases: assessing the benefits and the impact on human and patient rights, Geneva: World Health Organisation

World Medical Association (WMA 1964): Declaration of Helsinki (Ethical Principles for Medical research Involving Human Subjects), adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, as amended by various WMA General Assemblies, last amendment Seoul 2008, www.wma.net/e/policy/b3.htm, assessed 19. 9. 2009

World Medical Association (WMA 2008): Declaration of Helsinki. Ethical principles for medical research involving human subjects, in the version of Seoul 2008, www.wma.net/e/ethicsunit/helsinki.htm, accessed 19. 9. 2009

Yuval R, Halon D A, Merdler A, Khader N, Karkabi B, Uziel K, et al (2000): Patient comprehension and reaction to participating in a double-blind randomized clinical trial (ISIS-4) in acute myocardial infarction, *Archives of Internal Medicine*, 160 (8), 1142–1146

Zlotnik S R, Reid L, Essue B, Gibson J, Marzinotto V, Daneman D (2005): Dissemination to Research Subjects: Operationalizing Investigator Accountability, *Accountability in Research*, 12, 1–16

6. Appendix 1– legal terminology

Anonymous data/ Rendering anonymous	Rendering anonymous means the modification of personal data so that the information concerning personal or material circumstances can no longer or only with a disproportionate amount of time, expense and labour be attributed to an identified or identifiable individual. Personal data that was anonymised is no longer "personal data" in the legal sense. It will have to be an aim to have as much anonymised data within ACGT as possible and reasonable.
Confidentiality	Persons employed in data processing shall not collect, process or use personal data without authorisation (confidentiality). On taking up their duties such persons shall be required to give an undertaking to maintain such confidentiality. This undertaking shall continue to be valid after termination of their activity. Any person acting under the authority of the controller or of the processor, including the processor himself, who has access to personal data must not process them except on instructions from the controller, unless he is required to do so by law. Researchers participating in the project are therefore only allowed to collect, process and use personal data of a patient in compliance with the patient's informed consent. They are not allowed to disclose any data unless they are authorised by the particular patient.
Consent	The data subject's consent means any express indication of his wishes by which the data subject signifies his agreement to personal data relating to him being processed, on condition he has available information about the purposes of the processing, the data or categories of data concerned, the recipient of the personal data, and the name and address of the controller and of his representative if any. The data subject's consent must be freely given and specific, and may be withdrawn by the data subject at any time. If the data subject is incapable of a free decision or domestic laws don't permit the data subject to act on his/her own behalf, consent is required of the person recognised as legally entitled to act in the interest of the data subject or of an authority or any person or body provided for by law. An informed consent of the particular patient is a vital requirement in order to collect and use the data needed for the research project lawfully, though it is not the only possibility. The processing of personal data can also be permitted expressively by law. If the data subject is a minor, the informed consent of the legally entitled persons (cfr. Legal representative), normally the minor's parents, is needed.
Data controller	The controller is, according to the Data Protection Directive 95/46 EC, the natural or legal person who alone, or jointly with others, determines the purposes and means of the processing of personal data. He is responsible for complying with data protection legislation and can be held liable in case of violation.
Data processor	Data processor shall mean a natural or legal person, public authority, agency or any other body which processes personal data on behalf of the controller who is liable for the legality of the processing and the fulfillment of the obligations towards the national data protection authority and the data subjects.

Data reduction/Data economy (Minimality) .... Personal data must not be excessive in relation to the purposes for which they are collected and/or further processed. It is therefore not allowed to process any data unless the data is necessary to achieve the purpose mentioned for which the data are collected and further processed. In cases where the processing of data is needed, only as little personal data as possible should be processed. The processed personal data has to be erased or anonymised once they are no longer required for the purposes for which they have been kept.
For genetic research projects this means that it is only allowed to process (collect, use etc.) this kind of personal data of a patient that is needed for this project.

Data Subject ..... The data subject is the subject of personal data, i. e. an identified or identifiable person whom the personal data refers to. An identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity.
Regularly the patient, whose genetic data is collected and used for the research project, will be the data subject.

Hospital ..... Hospitals are health institutions where patients are treated.

Legal representative ..... The legal representative(s) is/are the person(s) who has/have the power by law or legal decision to decide for a minor patient (or equivalent status).

Legitimacy of data processing ..... The collection, processing and use of personal data is only lawful,
1. if permitted by law or
2. if the data subject has consented to the processing of his data.

This is the basic rule of data protection law.
If personal data is processed at least one of these conditions must be fulfilled.

Modification ..... Modification means the alteration of the substance of stored personal data.

Obtaining/Collecting ..... Obtaining/collecting is the acquisition of data on the data subject.

Organisational measures ..... Organisational measures, combined with technical measures, must ensure an appropriate level of security of the data processing, taking into account the state of the art and the costs of their implementation in relation to the risks inherent in the processing and the nature of the data to be protected. Appropriate organisational measures shall be taken by the controller against accidental loss, destruction or alteration of, or damage to, personal data and against unauthorised or unlawful processing of personal data, in particular where the processing involves the transmission of data over a network, and against all other unlawful forms of processing. The controller must, where processing is carried out on his behalf, choose a processor providing sufficient guarantees in respect of the technical security measures and organisational measures governing the processing to be carried out, and must ensure compliance with those measures.
Such appropriate organisational measures to ensure the confidentiality, integrity and accuracy of processed data should be for example:
- control of the entrance to installations
- access control
- authorisation control
- transmission control
- input control

– job control
– availability control

Such organisational measures have to be taken by all the participants of the research project processing personal data.

Patient ..... The patient is the person who is suffering from a certain disease. As his genetic data is processed within the genetic research project, he will be regarded as data subject in most of the cases.

Personal data ..... Personal data means any information relating to an identified or identifiable natural person ('data subject'). An identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity. Therefore a set of date collected under a certain number or sign "patient xxx", "tissue YYY" can be personal data.

Physician ..... The physician is the natural person who is in charge of the patient's treatment.

Processing ..... Processing, according to Directive 95/46/EC, shall mean any operation or set of operations which is performed upon personal data, whether or not by automatic means such as collection, recording, organisation, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, blocking, erasure or destruction.

Pseudonymising ..... Pseudonymising means replacing a person's name and other identifying characteristics with a label in order to preclude identification of the data subject or to render such identification substantially difficult.

Purpose ..... The purposes for processing of personal data must be adequate, relevant and not excessive in relation to the purposes for which they are collected and/or further processed.

The purposes must be specified, explicit and legitimate. Personal data must be not further processed in a way incompatible with those purposes

.

Recipient ..... The recipient is, according to Directive 95/46/EC, a natural or legal person, public authority, agency or any other body to whom data are disclosed, whether a third party or not.

Sensitive (personal data)/ Special categories of data — Sensitive personal data is personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and data concerning health (genetic data) or sex life. Member States shall prohibit the processing of these data, except in explicitly stated exceptions.

Storage ..... Storage means the entry, recording or preservation of personal data on a storage medium so that they can be processed or used again.

Third Party ..... The Third Party is, according to Directive 95/46/EC, any natural or legal person, public authority, agency or any other body other than the data subject, the controller, the processor and the persons who, under the direct authority of the controller or the processor, are authorised to process the data;

Transfer (also to Third Countries) ..... Transfer means the disclosure to a third party of personal data stored or obtained by means of data processing either

a) through transmission of the data to the third party or
b) through the third party inspecting or retrieving data held ready for inspection or retrieval.

The transfer to a third country of personal data which is undergoing processing or is intended for processing after transfer may take place

	only if the third country in question ensures an adequate level of protection, according to Directive 95/46/EC. If the third country does not ensure an adequate level of protection, a transfer of personal data is only allowed under the conditions established in Article 26 of the Directive.
Trusted Third Party	The Trusted Third Party is a security authority that performs the security related functions and cryptography methods. Institutions, public authorities or companies which offer trust services can be Trusted Third Parties. Within genetic research projects Trusted Third Parties can keep the link between a pseudonym and the corresponding clear name of a patient. In most of the cases the link will be a software algorithm decoding the pseudonym. The security, cryptographic and pseudonymisation measures shall ensure a level of security appropriate to the risks represented by the processing and the nature of the sensitive data to be protected.

7. Appendix 2 – relevant regulation

European level:
Article 3, 7, 8 of the Charter of Fundamental Rights of the European Union
The Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data
Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices
Article 8 of the Convention of the Council No. 5 for the protection of human rights and fundamental freedoms
Convention No. 108 of the Council of Europe for the protection of individuals with regard to automatic processing of personal data
Convention No. 164 of the Council of Europe for the protection of human rights and dignity of the human being with regard to the application of biology and medicine (Convention on Human Rights and Biomedicine)

Recommendations:
Council of Europe, Recommendation No. R(97)5 on the protection of medical data adopted of 13 February 1997
Council of Europe, Recommendation on human rights and biomedicine, concerning biomedical research, Strasbourg 25th of January 2005

Relevant International Instruments and Documents:
Additional Protocol to the Convention on human rights and biomedicine concerning biomedical research
World Medical Association Declaration of Helsinki
UNESCO Universal Declaration on Human Genome and Human Rights
UNESCO International Declaration of Human Genetic Data
UNESCO Declaration on Bioethics and Human Rights

Article 29 Data Protection Working Party:
Opinion 6/2000 on the Human Genome and Privacy
Working Document on Genetic Data (WP91)
Opinion 4/2007 on the concept of personal data
Working Document 1/2008 on the protection of children's personal data

Other relevant documents:
Opinion of the European Group on Ethics in science and new technologies to the European Commission, No. 11, 21 July 1998
International Guidelines for biomedical research involving human subjects (prepared by the Council for International Organisations of Medical Sciences in collaboration with the World Health Organisation)