EURAT
ETHICAL AND LEGAL ASPECTS OF TRANSLATIONAL MEDICINE

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Project Group EURAT

Ethical and Legal Aspects
of Translational Medicine

POSITION PAPER ON THE RETURN OF ADDITIONAL GENETIC FINDINGS IN MINORS

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FOREWORD BY PROF. DR. FRAUKE MELCHIOR

Whole genome analyses in the context of medical research and therapy have become increasingly significant in recent years. In important areas, the Heidelberg research landscape plays a pioneering role in the implementation of genome analyses in research, translation, and care. At the same time, this development is closely linked to a number of ethical and legal issues. As an interdisciplinary body of experts at Heidelberg University, the EURAT Group has dedicated its work to precisely these questions since 2011 and has since made a significant contribution to the development of responsible, ethically and legally sound biomedical practice. With its position papers "Cornerstones for an Ethically and Legally Informed Practice of Whole Genome Sequencing: Code of Conduct and Patient Consent Models" (2013), 2nd edition in 2015, and "On the Release of Raw Genomic Data to Patients and Study Participants" (2019), the EURAT Group has already published two important documents that provide applicable normative orientation and practical recommendations for action on important ethical and legal issues for genomic research, diagnostics, and treatment at Heidelberg University and Heidelberg University Hospital. With its third position paper presented here, the EURAT Group is devoting itself to a hitherto under-illuminated and at the same time very complex area: the handling of additional genetic findings in minors.

As one of the distinguishing features of this position paper, it places the best interest and rights of children at the center of its analyses and recommendations. Accordingly, the paper discusses, in particular, the extent to which the return of additional genetic findings entails positive or negative consequences for the best interest of the child. As a result, recommendations are presented that not only substantiate and define the framework for action in everyday research and treatment practice in a theory-based manner but also provide practical assistance. Therefore, the present statement also includes concrete patient information materials that can be used directly by researchers and treating physicians in the context of the patient information process with regard to additional genetic findings.

This current statement once again demonstrates the potential and relevance of interdisciplinary collaboration. In line with Heidelberg University's self-image as a comprehensive research university, the EURAT Group uses and combines a spectrum of subjects and disciplines in

order to integrate the broadest possible expertise and diverse perspectives in addressing important normative issues. I would like to thank the EURAT Group for its recent contribution, which will have practical benefits for many staff members of Heidelberg University and its partner institutions as well as stimulate the ethical-legal debate far beyond the university.

Prof. Dr. Frauke Melchior
Rector of Heidelberg University

Heidelberg, October 1, 2023

FOREWORD BY PROF. DR. INGO B. AUTENRIETH

In recent decades, genetic and genomic analysis methods such as whole genome sequencing have found their way into clinical diagnostics, thus enabling molecularly informed therapeutic strategies. Initiatives such as the *Modellvorhaben Genomsequenzierung* aim to make the benefits of genome sequencing available to more and more patients. Particularly in pediatrics, studies show that whole genome sequencing can make a significant contribution to diagnosing rare diseases and their genetic causes - such as developmental disorders in children - more quickly and accurately. This can help children, adolescents, and their families avoid long diagnostic odysseys and, in some cases, provide more targeted and often more effective treatment. For example, the Heidelberg INFORM program, in close collaboration with associated study groups, has shown that rapid genomic diagnostics is of great benefit, especially in children with cancer who have a high-risk disease or a relapse of the disease, when therapy based on tumor biology is possible. As part of these efforts, broad genomic diagnostics is now being rolled out to 12 European countries and Israel in a study context.

In addition to the information sought, genomic analyses can also reveal information regarding changes that are not directly related to the disease currently being treated but nevertheless have a health significance for patients. These so-called additional findings can be very useful for these patients. This is particularly true when it comes to identifying genetic risks for the development of a disease at an early stage and taking appropriate measures to minimize the risk. Early detection of such risks often allows better prevention. Therefore, in principle, it is obvious to consider additional findings in minors as valuable information in order to provide them with the best possible conditions for their future development. However, it is important to keep in mind that the return of additional genetic findings also entails risks for the patients. The decision on how to deal with additional findings in minors in individual cases usually lies within the parents' discretion. However, it is also the responsibility of the attending physicians to support parents in this decision-making process, always keeping the best interests of the child in mind. Specifically, this means appropriate options must be made available to parents regarding the return of different types of additional findings, as part of the informed consent process. This position paper provides specific recommendations and materials for the rationale and design of these options.

I very much welcome the fact that the EURAT Group analyzes the issue of handling additional genetic findings in minors with regard to ethical and legal aspects and provides physicians with concrete recommendations to support them in their daily work.

Prof. Dr. Ingo B. Autenrieth
Chairman of the Executive Board and Chief Medical Director
of Heidelberg University Hospital

Heidelberg, July 31, 2023

FOREWORD BY PROF. DR. DR. H.C. MICHAEL BAUMANN

The German Cancer Research Center (DKFZ) has one of the largest genome sequencing units in Europe. Genome sequencing is not only carried out in basic research, but rather DKFZ has been collaborating with physicians from hospitals for years to bring genome sequencing to translational research, i.e., to the interface between research and patient treatment. This is done in studies for adult cancer patients and for pediatric oncology with great scientific success. One example of this is DKFZ's strong commitment to the Hopp Children's Tumor Center (KiTZ) in Heidelberg.

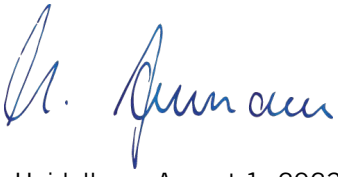
When analyzing genomic data, researchers may come across so-called additional findings: genetic alterations that go beyond the specific question regarding cancer diagnosis and may be important for the health of the people from whom the data originate. This also applies to pediatric cancer research. With regard to patients and study participants who are of age or capable of giving their full consent, the EURAT Group has already dealt with ethical questions concerning additional findings in the first EURAT statement "Cornerstones for an Ethically and Legally Informed Practice of Whole Genome Sequencing: Code of Conduct and Patient Consent Models" (2013/2015). The concrete reason for the founding of the EURAT Group and the first EURAT position paper was, notably, an additional finding that occurred during research analyses of the genome data of a minor patient. For this reason, too, it is very gratifying to see the EURAT Group is now addressing the issue of additional findings in minors in its new position paper.

We are aware of the responsibility to systematically ensure the careful handling of additional genetic findings in minors in (translational) biomedical research from the very beginning. However, this careful handling does not only mean protecting study participants from possible risks, which can undoubtedly be associated with the return of genetic knowledge. Instead, the return of additional findings is also an opportunity to generate a direct benefit for the study participants and not only - as is often the case in research - a benefit for future patients.

Regarding the question of how the risks and benefits of reporting additional findings are to be weighed against each other and what consequences result from this for the handling of the different types of additional findings, the EURAT Group provides valuable recommendations in its current position paper.

I would like to express my gratitude to the EURAT Group for this practical position paper, which is particularly committed to the rights of underage patients and study participants. It helps to promote and ensure responsible handling of their genetic information.

Prof. Dr. Dr. h.c. Michael Baumann
Chairman and Scientific Director the German Cancer Research Center



Heidelberg, August 1, 2023

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Editorial

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PREAMBLE

Responsible for the individual well-being and rights of minor patients and study participants, particularly their individual health well-being and health-related rights

Obligated to respect the right to informational self-determination of patients and study participants

In an effort to help empower underage patients and study participants to responsibly manage genetic predisposition knowledge

Recognizing the need to keep the burden of returning additional genetic findings within a range that is compatible with the primary responsibilities of researchers and physicians

With the intent to be proactive in providing a responsible approach to the additional genetic findings in minors for practice

Knowing that the acting persons are dependent on practical recommendations for action for the concrete and responsible implementation of the ethical and legal requirements

the EURAT Group issues the following position paper and recommendations for practice.

1 INTRODUCTION

In modern medicine, especially in the fields of oncology and rare diseases, genetic diagnostics have become increasingly important in recent years. This trend is expected to increase in the future due to the improved efficiency of the procedures and the associated decreasing costs.[1] In an effort to address this increasing importance of genetic and genomic analysis methods[2], the EURAT Group published *Cornerstones for an Ethically and Legally Informed Practice of Whole Genome Sequencing: Code of Conduct and Patient Consent Models (EURAT 2016)* in 2013 (second edition 2016) followed by the position paper *On the Release of Raw Genomic Data to Patients and Study Participants (EURAT 2019)*.[3] In these previous position papers by the EURAT Group, minors were explicitly excluded due to the special constellation of parents and children, the difficulty of determining the capacity of older children to give consent or make decisions, and the age-appropriate determination of the best interest of the child. Thus, the topic of returning any additional genetic findings has so far only been discussed by the EURAT Group with respect to adults capable of giving consent. The present position paper is now explicitly dedicated to the question of how to deal with additional genetic findings in minors both in the context of genetic diagnostics in a research-oriented clinical setting and in the context of a translational research setting, i.e., at the interface between research and care.

1.1 Background

Genetic diagnostics involves searching the human genome for variants that are relevant to the patient's current state of health or treatment. Human genetics uses genetic or genomic analyses in the diagnosis and treatment of diseases with a hereditary component. Whereas in the past only single genes or small gene panels could be investigated, due to the technical challenges and high costs, constant advances in sequencing technology and decreasing costs now enable the explorative investigation of large gene panels or even the sequencing of the entire exome

1 The costs of genetic and genomic diagnostics (at least in the area of rare and oncological diseases) will also be covered by health insurance from 2024. See also: https://gkv-spitzenverband.de/krankenversicherung/forschung_modellvorhaben/mv_genomsequenzierung/genomsequenzierung.jsp (last accessed on June 29, 2023)

2 In *genetic* analyses, individual genes are analyzed, while *genomic* analyses encompass the entire exome or genome. Both generate genetic knowledge, i.e., knowledge about genetic characteristics of the person concerned.

3 At first glance, the release of raw genomic data seems thematically related to the return of (genetic) additional findings. "In contrast to an actual, validated testing result (= finding), raw genomic data are not differentiated, specified, or interpreted regarding their specific medical and social significance for the individual participant. Raw data must therefore be clearly distinguished, on the one hand, from "results" or "findings" in the research context, and, in particular, from the final clinical stage of data processing, the quality-assured, validated findings [...]" (EURAT 2019) and thus, of (genetic) additional findings.

(Whole Exome Sequencing=WES) as well as the entire genome (Whole Genome Sequencing=WGS). This opens up completely new possibilities. WES and WGS have proven to be extremely efficient diagnostic methods, i.e., methods with a high "yield" – compared to conventional genetic diagnostic methods (Thevenon et al. 2016; Lionel et al. 2018). This is particularly important in the case of atypical forms of known syndromes, rare or novel diseases, and can often allow patients to avoid long diagnostic odysseys.

Explorative analyses with the aid of WES or WGS are indeed beneficial to ensure a more accurate and faster diagnosis. At the same time, however, due to the large amount of data generated, the probability also increases that other genetic variants will be discovered in addition to primarily sought health-relevant information of the current disease (primary findings). These other genetic variants, which are not related to the original medical indication for the genomic analysis, may nevertheless be relevant for the (future) health status of the patient. These findings are called *additional genetic findings* (in the following: *additional findings*). A wide variety of additional findings can be detected with WES or WGS. Their frequency depends primarily on the extent of genetic or genomic sequencing and the bioinformatic filtering used (Schuol et al. 2015).[4] However, the still relatively high probability of additional findings makes it necessary to establish rules for dealing with them in practice, both in terms of adequately informing patients about the possibility of additional findings and about the question of which types of additional findings can and should be reported at all.

1.2 Scope of this position paper

This position paper offers assistance in designing the informed consent and return process regarding additional findings in minors in clinical diagnostics and at the interface between research and health care, such as in research programs in human genetics or translational oncology.[5] The interface between research and care is special terrain in that there are different legal bases for the two areas.[6] Additional findings from other collections of genetic or genomic data (e.g., commercial databases such as 23andMe) are explicitly not the scope of this position paper. In

[4] For WES, the percentage of additional findings is approximately 1-6% of those sequenced (Van Hout et al. 2020). Identified additional findings could be associated with cancer predispositions (1.38%), cardiovascular disease (0.87%), and dyslipidemia (eMerge Clinical Annotation Working Group 2020; Hart et al. 2019). Based on a recommended 76-gene list for pathogenic additional findings, it is estimated that at least 2.5- 3.0% of the population will have at least one of the additional findings on the list in their genome via WES/WGS when examined for WES (Miller et al. 2021).

[5] See, for example, the Pediatric Oncology Program, INdividualized Therapy FOr Relapsed Malignancies in Childhood (INFORM), https://www.gpoh.de/studienportal/pohkinderkrebsinfotherapiestudien/inform/index_ger.html (last accessed June 29, 2023) .

[6] For example, the Genetic Diagnostics Act (GenDG) applies in the context of care but has no relevance in research.

our recommendations (see Chapter 6), we first consider children incapable of giving consent, where the decision on the return of additional findings belongs to the parents. In the next step, we consider mature minors and their role in the decision regarding the return of additional findings.

1.3 Structure of this position paper

The present position paper is structured as follows: First, we briefly summarize the state of the literature on the return of additional findings in minors (Chapter 2). Then (Chapter 3), we explain terms that are important for understanding this position paper. In Chapter 4, we present the legal framework for the return of additional findings. In Chapter 5, we discuss ethical aspects that should be taken into account when considering the return of additional findings in minors. In Chapter 6, we present concrete recommendations regarding different categories of additional findings, which we practically illustrate in two case studies in Chapter 7. In Chapter 8, we present content for an information brochure on additional findings and their return both for parents (Chapter 8.1) and mature minors (Chapter 8.2). In Chapter 9, we propose both an information and a consent model text (again, each for parents and for mature minors) for dealing with additional findings in minors.

2 STATE OF THE LITERATURE

There has been a debate in the bioethical literature for several years regarding how to deal with genetic findings (both primary and additional) in minors generated in the context of pediatric *research* (Avard et al. 2011; Hens et al. 2011; Abdul-Karim et al. 2013; Knoppers et al. 2014; Holm et al. 2014; Senecal et al. 2015). Even though this debate focuses on the return of findings from pediatric *research*, not from the *treatment* context, it is relevant for us in that the authors elaborate ethically relevant aspects, which also need to be considered for the context of this position paper. In addition to the aforementioned literature, a few authors also deal with the question of returning additional findings in minors within the *clinical context* and develop recommendations on what kind of findings, in their opinion, must be reported and which must not (McCullough et al. 2015; Wilfond et al. 2015; Dondorp et al. 2021; Vears 2021).

The topic of returning additional findings in minors has not yet been dealt with in detail by the *major professional societies*. On the one hand, there are currently position papers on the handling of genetic testing in minors that focus primarily on the question of when and in what form it is appropriate to perform genetic testing in minors in the first place (Borry et al. 2009; Gendiagnostik-Kommission 2011; American Academy of Pediatrics 2013; Gesellschaft für Humangenetik 2013b; Botkin et al. 2015; Boycott et al. 2015; Vears et al. 2020; de Wert et al. 2021). The possibility of additional findings is discussed here, if at all, only in passing and very briefly. On the other hand, there are position papers on the handling of additional genetic findings that, however, do not address the specific context of minors in the necessary detail (Gesellschaft für Humangenetik 2013a; Green et al. 2013; ACMG 2015; Miller et al. 2021). The individual position papers have a great deal in common when it comes to naming the essential ethical and legal aspects and decision-making criteria, but they differ in some cases significantly in their handling and weighting and the resulting conclusions. This becomes clear, for example, when comparing the position paper of the German Society for Human Genetics (GfH) with the recommendations of the American College of Medical Genetics and Genomics (ACMG). While the GfH advocates, among other things, for the choice of a sequencing procedure associated with the lowest probability of the occurrence of additional findings (Gesellschaft für Humangenetik 2013a), the ACMG is primarily concerned with protecting patients from potential harm by

maximizing knowledge through an *active search* for additional findings (Green et al. 2013).

As mentioned above, the literature listed identifies relevant aspects that need to be considered when assessing whether additional findings in minors should be returned. Specifically, the following aspects are involved:

- The reliability (validity/quality) of the (additional) findings.
- The probability with which the genetic predisposition found leads to the onset of a disease.
- The severity of the disease in case of its outbreak.
- The relevance of the maturity of minors in question for the decision-making process regarding the return of additional findings.
- Considerations of the best interest of the child in the context of returning additional findings in minors
- The influence of the return of additional findings on the *still developing autonomy of the child*, in particular his or her future *right not to know*.
- The influence of the return of additional findings on the *child's right to an open (informational) future*.
- Potential benefits and potential harms to the health of minors from returning additional findings.
- The importance of additional findings in minors for their families.
- Parents' decision-making authority with respect to the return of additional findings in their children.

We will deal with these and other aspects that we regard as relevant in more detail in the next chapters.

3 EXPLANATION OF TERMS

Before we address the legal and ethical considerations of returning additional findings in minors, let us first explain the relevant terms and related concepts.

3.1 Additional finding

In the following, we use the term *additional finding* for a clinically validated finding that has arisen in the course of genetic or genomic analysis. An additional finding

1. is not related to the intended research question (i.e., in the treatment context: with the respective disease to be treated)
2. was *not* actively searched for,
3. has a potential significance for the health and/or reproduction of the person under investigation and, if applicable, his or her relatives.

In the literature, terms such as *unsolicited finding*, *incidental finding* or *secondary finding* are often used, sometimes synonymous with our term additional finding, sometimes with different connotations.[7] It is important for us to *clearly distinguish* the term "additional finding" used by us, on the one hand, from findings that were *actively searched for* and, on the other hand, from findings that are *directly related to the original research question* (even if they were not actively searched for).[8]

3.2 Type and relevance of the additional finding

3.2.1 Additional findings regarding medically treatable vs. additional findings regarding medically non-actionable diseases

Even though many different types of additional findings are conceivable in the context of genetic and genomic analyses, they can be roughly subdivided as follows:

- Additional findings that indicate a predisposition to a disease for which preventive programs and/or treatment options exist (and are in fact available) that have an impact on the length or quality of life (*additional findings regarding medically actionable diseases*),
- Additional findings regarding diseases for which no such preventive programs and/or treatment options exist (*additional findings regarding medically non-actionable diseases*).

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7 For a possible description of different types of non-primary findings, cf. Schuol et al. (2015).

8 An example of a finding in the latter category is that of a TP53 mutation discovered during tumor diagnosis. Although discovered unintentionally, this is not an **additional** finding according to our definition, since a TP53 mutation is associated with secondary malignancies during radiation and thus of great importance for the treatment of the patient's **current** illness.

However, the mere existence (and availability) of preventive programs and/or treatment options does not necessarily mean they are subsequently implemented. Factors such as the effectiveness and risks of the preventive programs and/or treatment options must always be weighed individually against other relevant aspects such as the probability of disease onset, as well as personal reasons (lifestyle, health awareness, etc.).

3.2.2 Relevance of additional findings

Within the context of assessing whether the return of additional findings is relevant for the children concerned and their families, the question of the actionability of the disease associated with the additional finding, which we call *medical relevance*, is crucial. However, the sole reference to the medical relevance of an additional finding does not go far enough, as an additional finding can also contain knowledge that is important for life planning, even if the corresponding disease is not medically actionable (according to the current scientific knowledge). Thus, if parents know that their child will sooner or later become seriously ill and require external care, they can make financial provisions for the child's care at an early stage. In addition to the child's life planning, the life planning of the parents and the rest of the family is sometimes affected by the return of additional genetic findings. This is the case, for example, when it comes to further family planning, which could possibly be adjusted in the light of knowledge about a possibly inherited genetic predisposition to disease (or even just the disease carrier status). In order to adequately represent this knowledge regarding life planning, we will speak in the following of the *life planning relevance* of additional findings in order to describe the relevance of the additional finding for the proactive future planning of the child and his or her family, taking into account the respective disease and its consequences.

3.3 Onset of disease and time for medical action

The term *onset of disease* describes the time at which a disease first manifests itself (early manifesting vs. late manifesting). In the case of an additional finding with regard to a medically actionable disease, however, it is obvious to attach particular importance to the point in time from which a beneficial prevention or treatment is possible and useful. In the case of additional findings regarding medically actionable diseases, it is therefore plausible to speak of the *time of need for medical action*. Both the time of *onset* and the *time of need for medical action* always refer to the earliest time (the earliest age of the affected person) at which the onset of the disease has been described. In both cases,

depending on the disease, this can be long before the onset of specific symptoms, which – as in the case of pancreatic carcinoma, for example – can appear very late in the course of the disease.

We distinguish between early (before the age of 18) and late (after the age of 18) onset of disease or time of need for medical action, respectively. The decision to distinguish between "early" and "late" at the time of coming of age is related to the legal consequences of coming of age, in particular the attribution of full legal capacity (see Chapter 4.2.3.2).

3.4 Disease carrier status

While additional findings can indicate a predisposition to a certain disease that is likely to occur at a later time, there are also additional findings that are not associated with a future onset of the disease in the person examined but which could lead to disease in any offspring of the person examined. A distinction is made between two types of this so-called *disease carrier status*, depending on whether the associated disease is inherited in an autosomal recessive or X-linked manner.

3.4.1 Autosomal recessive inheritance

In the case of autosomal recessive inheritance, the offspring of carriers are only at risk if the **other parent** is **also a carrier** for the same disease. 25% of the children of two carriers have a predisposition to the disease, while 50% of the children of these parents are only carriers themselves. If the **other parent** is **not a carrier**, there is only a small probability of a predisposition to the disease for the common offspring, e.g., due to a new mutation of the second gene copy. However, 50% of the children of a carrier are carriers themselves.

In our context, this means that if a child is found to be a carrier for an autosomal recessive predisposition, there is a *very high* probability that one of the parents may either also be a carrier for the disease in question or is himself of herself affected by the disease predisposition. There is also a *relevant* probability that any siblings may also be carriers of the said predisposition.

3.4.2 X-linked inheritance

If a woman who is a carrier for an X-linked disease reproduces, 50% of her male offspring will have the corresponding pathogenic variant, which can lead to the onset of disease in them. 50% of the female offspring of the same woman are themselves carriers.

This means for our context: If a girl is diagnosed as a carrier for an X-linked disease, there is a 50% probability for future male offspring to inherit the corresponding *pathogenic variant*. If the girl has inherited the corresponding mutation from her mother, it further follows that there is a 50% probability for her (future) brothers to have inherited (or to inherit) the corresponding *pathogenic variant*.

As the remarks on disease carrier status show, this is a complex phenomenon with different implications for different family members and offspring, which should always be taken into account in subsequent considerations on the possible involvement of family members (Chapter 5.10).

4 LEGAL ASPECTS

4.1 Scope of application of the GenDG for translational research

The German Gene Diagnostics Act (GenDG)[9] came into effect on February 10, 2010 and is therefore of a more recent nature.[10] In view of the advancing technological developments in sequencing the human genome, legislators wanted to strengthen the guarantee of human dignity (Section 1 (1) of the German Basic Law (GG)) and citizens' right to informational self-determination (Section 2 (1) in conjunction with Section 1 (1) GG), since genetic or genomic[11] data are special personal health data relevant to the identity of the individual and may contain health-related information about third parties (relatives).[12] Pursuant to Section 1 (1) GenDG, the scope of the Act is limited to genetic examinations and genetic analyses carried out in this context and the samples and data obtained from them. According to Section 3 Nos. 1 and 4 GenDG, this applies exclusively to examinations that seek to determine inherited genetic characteristics and does not extend to those regarding acquired (i.e., somatic) mutations. According to Section 2 (2) No. 1 GenDG, it does not apply in particular "to examinations and analyses and the handling of genetic samples and data for research purposes" (translation by the authors). In the course of the legislative process, some lawmakers noted that there was a need for differentiation and regulation with regard to a research privilege.[13] Legislators deliberately avoided including such amendments.[14] It is unclear for the norm addressee how the – fundamentally diverse – concept of research is to be understood,[15] since the GenDG has dispensed with a legal definition. Whether the medical project constitutes "research" is the deciding factor whether the GenDG can be applied.[16] The explanatory memorandum to the Act states that Section 2 (2) No. 1 GenDG relates to genetic research with a focus on investigating the causal factors of human characteristics in general; it does not aim to implement specific measures regarding individual persons.[17] It has been pointed out by academia that this cannot

9 Law on Genetic Testing in Humans (Genetic Diagnostics Act – GenDG) of July 31, 2009 (BGBl. I pp. 2529, 3672).

10 On the evolution of the nearly thirty-year long debate over the codification of human genetic testing, cf. *Meyer* (2016), pp. 86-126.

11 Since the GenDG does not differentiate between genetic and genomic data and analyses (see footnote 2 in this document), this Chapter 4 will always refer to genetic data and analyses and will refrain from differentiating between them and genomic data and analyses.

12 BT-Drs. 16/10532, p. 1.

13 BT-Drs. 16/12713, p. 34.

14 BT-Dr. 16/10532, p. 45; BT-Dr. 16/10582, p. 1.

15 This question is raised by *Linoh und Rosenau* (2020) e.g., in terms of scope (basic research, applied research in the context of a clinical trial, "cure trials"), type (public or private), and funding aspect (budget or third-party funding); In-depth *Fleischer* (2018), pp. 208ff.

16 *Linoh und Rosenau* (2020) (2); *Fleischer* (2018), p. 204.

17 BT-Dr. 16/10532, p. 20; also *Erbs/Kohlhaas/Häberle* Nebengesetze GenDG § 2 Rn. 4.

be the (sole) criterion for the purpose of research.[18] The constitutionally mandated principle of certainty (Section 103 (2) GG, Section 3 German Act on Regulatory Offences (OWiG)) – with reference to the provisions on prosecutions and fines laid out in Sections 25 and 26 GenDG – and the scope of protection of the fundamental right of scientific freedom (Section 5 (3) GG) require an interpretation of the concept of research to ensure that "any serious, methodically ordered and planned search for objective truth" is covered.[19]

According to the wording of Section 2 (2) No. 1 GenDG, the deciding factor is the "research *purpose*" (translation by the authors). In the literature, a normative assessment has emerged: If the research purpose is the main purpose in a genetic examination, the exemption regulation of Section 2 (2) No. 1 GenDG should apply; if, on the other hand, medical treatment is the main purpose, the GenDG then applies.[20] The legal boundary between research and treatment is sometimes difficult, as for quite some time now there has been an interface between research and therapeutic purposes.[21] A distinction is predominantly made between curative, therapeutic, and scientific experiments.[22] As a result, curative and therapeutic experiments are to be subject to the GenDG, whereas purely scientific experiments are not.[23] This outcome corresponds at least to the intention of legislators to leave science unregulated – until legislation on biobanks is drawn up.[24] In contrast, the legal difficulties in differentiating the applicability of the GenDG raises the question whether, from the outset, the investigation (also) pursues concrete medical purposes with respect to the person to be tested; the merely vague possibility that the research project could possibly result in findings for the treatment of the patient is not sufficient to directly apply the law given the high requirements of Section 103 (2) GG and Section 3 OWiG.[25]

Whether translational research and research programs in human genetics fall within the scope of the GenDG can only be determined based on their purpose. Particularly in translational research, the differenti-

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18 *Linoh und Rosenau* (2020) (2); *Vossenkuhl* (2013), p. 111; *Sosnitza und Op den Camp* (2011) (402); *Meyer* (2016), p. 352.
19 *Linoh und Rosenau* (2020) (2), translation by the authors.
20 All things being equal, *Linoh und Rosenau* (2020) (5) give priority to freedom of research.
21 *Fleischer* (2018), p. 204; Hart (2016) (672ff.).
22 *Meyer* (2016), pp. 350ff.
23 *Meyer* (2016), p. 354; *Sandberger*, Guidance for the Ethics Committee's Evaluation of Clinical Trials in Genetic Research, p. 1. (https://www.medizin.uni-tuebingen.de/files/download/YQOdMDrv9lE0n6J05on-jp4L7/genetische%20Forschung%20Nov2020.pdf last accessed June 30, 2023).
24 *Linoh und Rosenau* (2020) (5); *Spickhoff/Fenger* Medizinrecht GenDG § 2 Rn. 1.
25 *Fleischer* (2018), p. 211.

ation between "general research" and "concrete measures" confronts the user and (potential) subject of the law with the question of how to classify the use of individual patient results for scientific purposes.[26] Translational research is the interface between basic experimental research and clinical care of patients.[27] The intended link between research and therapy aims for a rapid transfer of research results to clinical application and of clinical issues to research.[28] Translational research thus represents an interface between applied diagnostic medicine and experimental research. On the one hand, there is a research interest, on the other hand, there is at least also a treatment interest. It is true that translational research also includes studies that aim to improve the treatment of *future* (i.e., not yet individualized) patients.[29] In this case, the research purpose should regularly be in the foreground and the applicability exemption of Section 1 (2) No. 1 GenDG should apply. Accordingly, translational research does not exclusively serve a "research purpose" as defined by the GenDG. However, if *concrete* and individualized medical purposes (concerning the person being tested) are also pursued from the outset, the provisions of the GenDG should also be observed.[30] Whether the treatment purpose lays in the fore- or background must be determined on a case-by-case basis according to the design of the research project.

Insofar as human genetic diagnostics (sequencing of exome and genome = WES/WGS) in an oncological setting is primarily concerned with tumor characterization for the purpose of gaining data with clinical relevance, "additional findings" occurring in this context – initially independent of any subsequent scientific utilization[31] – are an "additional" product of a planned curative treatment, since originally there was a medical indication for performing the genetic examination. This "excess information" is a by-product of the actual genetic examination, and its possible occurrence was thoroughly considered by lawmakers.[32] Accordingly, human genetic diagnostics does not pursue any overriding "research purpose" within the meaning of Section 2 (2) No. 1 GenDG but rather aims to achieve an overriding treatment purpose, so that the GenDG applies.[33]

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26 *Fleischer* (2018), p. 207.

27 Charité Universitätsmedizin Berlin (available online at: https://ifa.charite.de/translationale_forschung/ last accessed on 30 June 2023).

28 *Hart* (2016) (672 f.); Charité Universitätsmedizin Berlin (available online at: https://ifa.charite.de/translationale_forschung/ last accessed June 30, 2023).

29 For these studies, the consent forms therefore state that their results will have no impact on the treatment of the respective donors.

30 *Fleischer* (2018), p. 211.

31 *Linoh und Rosenau* (2020) (6) on changing the purpose of study results (from treatment to research), which are governed by the provisions of the GDPR and state data protection laws.

32 *Fleischer* (2018), p. 74; BT-Drs. 16/10532, p. 27.

33 *Fleischer* (2018), p. 211 supports the applicability of the GenDG in case of pure research studies with subjects which are to be informed of additional findings.

4.2 Genetic examinations (Section 3 No. 7 GenDG and Section 3 No. 8 GenDG)

4.2.1 Diagnostic and predictive tests

Genetic testing can have multiple objectives, which are legally defined. According to Section 3 No. 1 GenDG, a genetic examination is a genetic analysis aimed at determining genetic characteristics or clarifying prenatal risks, including the assessment of the respective results. According to Section 3 No. 4 GenDG, genetic characteristics are inherited genetic information or genetic information acquired from humans during fertilization or up to the time of birth. This genetic material can provide information about existing and future diseases and is therefore an important indicator for therapeutic measures and the shaping of patients' lives.

According to Section 3 No. 6 GenDG, a distinction is made between diagnostic and predictive genetic examinations. Predictive testing is performed on a person who has no symptoms of a disease, by checking whether a mutation is present that indicates a predisposition to a disease.[34] Diagnostic testing, on the other hand, is performed on a person who already has the disease to confirm or reject a previously suspected diagnosis.[35] In medical practice, difficulties can sometimes arise when differentiating between diagnostic and predictive examinations, which is why the legal distinction is considered problematic.[36]

According to Section 3 No. 7 GenDG, various objectives can be pursued within the framework of diagnostic examinations: clarifying the existence of a disease or health disorder (lit. a) or of genetic characteristics that, together with the influence of certain external factors or foreign substances, can trigger a disease or health disorder (lit. b), the diagnostic workup with regard to the presence of genetic characteristics that can influence the effect of a drug (lit. c; so-called pharmacogenetic examination), or to the presence of genetic characteristics that can completely or partially prevent the occurrence of a possible disease or health disorder (lit. d).

According to Section 3 No. 8 GenDG, the aim of predictive examinations is to investigate the existence of a disease or health disorder that will only occur in the future (lit. a) or of a predisposition for diseases or health disorders in offspring (lit. b; so-called carrier status).

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[34] BT-Drs. 14/9020, p. 120; *Fleischer* (2018), p. 112; *Spickhoff/Fenger Medizinrecht GenDG § 3 Rn. 6.*
[35] BT-Drs. 14/9020, p. 120; *Fleischer* (2018), pp. 110f.; *Spickhoff/Fenger Medizinrecht GenDG § 3 Rn. 6.*
[36] *Fleischer* (2018), pp. 112ff.

4.2.2 Legal requirements for medical conduct before and after genetic testing (Sections 9, 10, 11 GenDG)

In view of the relevance of affected legal positions, the genetic examination must be transparent for the person examined before and after the testing. For this reason, the attending physicians are obliged or authorized (depending on the treatment constellation) to inform the person examined about the nature, significance, and scope of the genetic examination before obtaining consent (Sections 8 and 9 GenDG), to offer or perform genetic counseling unless a waiver is provided (Section 10 GenDG) and, within appropriate limits, to communicate the results (Section 11 GenDG).

Patient information requirements (Section 9 GenDG)[37] serve the free and self-determined decision-making development of the person concerned. All or part of the patient information may be waived in accordance with the generally recognized right to waive information.[38] The content of the patient information must be documented in writing in accordance with Section 9 (3). The extent of the information is to be oriented on the provisions laid out in Section 9 (2). This includes in particular:

- the purpose, nature, extent, and significance of the genetic examination, including the results that can be obtained with the intended genetic examination tool within the scope of the purpose of the examination; this also includes the significance of the examined genetic characteristics for a disease or health disorder, as well as the possibilities for avoiding, preventing, or treating said disease or disorder (No. 1),
- health risks associated with knowledge of the result of the genetic examination and with obtaining the genetic sample required for this purpose for the person concerned, and in the case of pregnant women health risks associated with prenatal genetic examinations and with obtaining the genetic sample required for this purpose for the embryo or fetus (No. 2),
- the intended use of the genetic sample and of the test or analytical results (No. 3),
- the right of the data subject to withdraw consent at any time (No. 4),
- the right of the data subject not to know, including the right not to take note of the results of the investigation or parts thereof but rather to have them destroyed (No. 5),

[37] In-depth *Meyer* (2016), pp. 157-162.
[38] BT-Drs. 16/10532, p. 27.

- in the case of a serial genetic screening, informing the persons concerned of the result of the evaluation of the screening by the Genetic Diagnostics Commission in accordance with Section 16 (2) No. 6.

Information should also extend – beyond the wording – to unsolicited "additional findings", in order to obtain (legal) certainty for the subsequent consent (Section 8 GenDG) and the communication of the results (Section 11 GenDG). Since, in principle, it is not possible to provide specific information about genetic variants that are not actively sought, commissions and academia recommend categorizing or typifying the types of additional findings.[39]

The provision of **Section 10 GenDG** regulates the requirement for **genetic counselling to** be offered and carried out by physicians qualified to provide genetic counselling (cf. Section 7 (3) GenDG).[40] In the case of diagnostic examinations (Section 10 (1) GenDG), counselling should in principle be offered after the results of the examination are available.[41] Whenever non-treatable diseases or health disorders are identified, the offer of counselling is obligatory (Section 10 (1) sentence 2 GenDG). In the case of predictive examinations (Section 10 (2) GenDG), physicians are in any case obliged to actually provide (and not only offer) counseling both before the examination and after the examination results are available, insofar as the person concerned has not waived this obligation in writing after being informed of the contents of the counseling.[42] This gradation takes into account the intrusive relevance of the respective examination.[43] The counseling requirements are concretized by Section 23 (2) No. 3 of the GEKO guideline; in particular, physical and psychological offers of help are also covered by this. The deciding factor is that genetic counseling does not have the quality of patient information from a legal standpoint.[44]

Genetic counseling is intended to be "non-directive", i.e., it should provide information without steering the decision in a particular direction in order to comply with the right not to know.[45] The provision in Section 10 (3) sentence 3 GenDG stipulates that in the case of suspected (or already diagnosed) diseases, physicians should recommend to the persons examined to suggest to their genetic relatives that they

39 Exemplary *Fleischer* (2018), p. 87.
40 In-depth *Meyer* (2016), pp. 162-171.
41 This is not necessary, for instance, "if consultation beyond mere communication of the analysis result is not required with regard to implications for the data subject"; BT-Drs. 16/10532, p. 28 (translation by the authors).
42 BT-Drs. 16/10532, p. 28.
43 BT-Drs. 16/10532, p. 28.
44 BT-Drs. 16/10532, p. 28.
45 BT-Drs. 16/10532, p. 28.

undergo genetic counseling.[46] According to the wording of the law and the explanatory memorandum, the forwarding of information is exclusively within the "sphere of influence" of the person examined.

Communication of the test results (Section 11 GenDG)[47] – also referred to as return of said results – may only be made by the responsible medical person (or by the person providing genetic counselling in accordance with Section 10 GenDG) to the person tested (Section 11 (1) GenDG) unless an institution has been entrusted with the evaluation (Section 11 (2) GenDG) or the person concerned has expressly consented to communication to third parties – in writing or electronically (Section 11 (3) GenDG). As a deciding factor, the communication shall be omitted if the data subject has decided that the results are to be destroyed (Section 8 (1) sentence 1 GenDG) or if they have revoked their consent (Section 8 (2), (4) GenDG).

4.2.3 Incapacitated persons in the GenDG

In principle, all persons of legal age and capacity enjoy a right of self-determination that they are free to exercise with regard to the performance of a genetic examination. This applies, in particular, to the mandatory consent required for genetic testing and collection of the sample in accordance with Section 8 (1) GenDG, since the medical intervention interferes – among others – with the right to physical integrity and the collection of genetic material interferes with the general personality rights.

Various problems arise if the examination is to be performed on a person who is incapable of giving consent. This is based on the fact that the responsibility of the person concerned has not yet developed (in full). Consent regulates the responsibility for the impairment of one's own legal interests.[48] In the legal literature, it is assumed that persons incapable of giving consent are unable to grasp the value or status of the legal assets and interests in question, the consequences and risks arising from the decision to give consent, and the equally suitable but less burdensome means available (incapacity for knowledge) or are unable to act in accordance with the knowledge gained in each case (incapacity for self-direction).[49]

First of all, it must be determined who is deemed capable of giving consent within the meaning of the GenDG and who is not. Section 14 (1) GenDG is based on the aforementioned definition and, according to

[46] BT-Drs. 16/10532, p. 29.
[47] In-depth *Meyer* (2016), pp. 171-175.
[48] *Amelung* (1992).
[49] Cf. *Amelung* (1992) (552ff).

its wording, includes "all persons who are incapable of recognizing the nature, significance, and scope of the genetic examination and of directing their will accordingly" (translation by the authors).

4.2.3.1 Scale of the assessment

Whether someone is *incapable of giving consent* is not determined by a specific age limit, but by the ability to understand and consent to the specific intended examination; the ability to give consent does not therefore require the patient to be of age.[50] According to the guidelines of the GEKO Commission, the determination of the capacity to consent must be assessed and documented by the responsible medical person in each individual case, taking into account the personal development of the patient and the nature and significance of the genetic examination (which is regularly more difficult to convey than a "normal" treatment).[51] This is therefore a case-by-case decision.

4.2.3.2 Minors or children/youth

(1) Comparison with legal capacity

First of all, it is clear that minors or children must be regarded as incapable of giving consent due to their lack of legal capacity (Section 104 No. 1 of the German Civil Code (BGB)). A declaration of intent in general business transactions would be void anyway (Section 105 (1) BGB). Minors with limited legal capacity (Section 106 BGB), on the other hand, could be considered capable of giving consent, since their legal declarations already have partial (limited) effect (Sections 107-110 BGB). Hence, a 7- to 17-year-old child could be aware of the significance and implications of a genetic examination and act accordingly. However, the capacity to consent must be distinguished from the capacity to enter into legal contracts, e.g., a diagnostic contract.[52] Applying the rigid standards of the German Civil Code would be incompatible with the idea of context-dependent individual decision-making envisaged by legislators.

(2) Differentiation according to decision maturity

According to the GEKO guideline, *incapacity to consent* should end for adolescents at the latest when they reach the age of 18, which conversely means that, depending on their development and maturity, minors may already have the *capacity to consent.*[53] This is plausible, since the developmental stage of the same adolescent at the age of 16 or 17 probably

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50 BT-Drs. 16/10532, p. 30; *Erbs/Kohlhaas/Häberle Nebengesetze GenDG § 14 Rn. 1; Meyer* (2016), p. 54.

51 Guideline of the Gene Diagnostics Commission (GEKO) on genetic examinations in persons incapable of giving consent in accordance with Section 14 in conjunction with Section 23 (1) no. 1c GenDG (version of July 26, 2011; with effect on July 27, 2011), BGesBl. 2011 (54), p. 1257.

52 *Prütting/Stockter* Medizinrecht § 14, marginal no. 26; see already footnote 12.

53 Guideline of the Gene Diagnostics Commission (GEKO) on genetic examinations in persons incapable of giving consent in accordance with Section 14 in conjunction with Section 23 (1) no. 1c GenDG (version of July 26, 2011; with effect on July 27, 2011), BGesBl. 2011 (54), p. 1257.

differs only marginally from that at the age of 18. Section 14 (1) GenDG is based on whether the person in question is "capable of recognizing the nature, significance, and scope of the genetic examination and of directing his or her will accordingly" (translation by the authors).

It is assumed at times that children under the age of 14 lack the ability to discern.[54] At first glance, this definition seems arbitrary, but it is already based on other understandable legal considerations, such as the exclusion rule in Section 5 of the German Act on the Religious Education of Children (KErzG). Nevertheless, the individual case and thus the respective individual ability to discern must be taken into account here as well, and each individual case must be assessed when dealing with children under 14 years of age – although the result will probably be negative on a regular basis.

(3) Other non-consenting persons

As the reference in Section 14 (3) sentence 3 GenDG to Section 1902 (2), (3) BGB shows, not only minors but also persons under care who are of full age may be deemed incapable of giving consent.[55] Recurring reasons for this are mental illnesses or disabilities. Depending on the severity of the condition, the capacity to consent may even be excluded per se due to the deviation from the normal state if a certain "maturity" cannot be achieved.

4.2.4 Interim result

The capacity to consent must be determined by the responsible medical figure on a case-by-case basis, taking into account the personal development of the respective patient and the nature and significance of the genetic examination. Unless there are indications to the contrary, it can generally be assumed that persons who have reached the age of majority are capable of giving consent, whereas persons under the age of 14 are often (but not always) incapable of giving consent. However, a case-by-case assessment is required, which must be carried out all the more carefully as the person approaches the age of 18.

4.3 Genetic examinations of persons incapable of giving consent (Section 14 GenDG)

4.3.1 Self-interested genetic testing (Section 14 (1) GenDG)

Section 14 (1) GenDG exclusively permits diagnostic or predictive genetic testing, including the collection of a genetic sample required

[54] *Prütting/Stockter* Medizinrecht § 14 marginal no. 29. *Laufs/Katzenmeier/Lipp*, Arztrecht, XIII marginal no. 108 still requires the consent of the (representative) parents for curative and research interventions on minors capable of giving consent.

[55] Clarifying also *Amelung* (1992) (558).

for this purpose from a person incapable of giving consent if it opens up possibilities for prevention or therapeutic intervention with regard to a disease or health disorder or if treatment with a drug is envisaged whose effect is influenced by the genetic characteristics (No. 1).[56] The decisive factor here is the *direct benefit* for the person incapable of giving consent,[57] i.e., the examination must provide a concrete advantage (through verifying or falsifying a medical hypothesis). The examination must also be communicated as clearly as possible to the person unable to consent, and he or she must not refuse both the examination and the collection of samples (No. 2).[58] Furthermore, the examination must be associated with as few risks and burdens as possible (No. 3) and the legal representative must have consented after comprehensive patient information (Section 9 GenDG) and genetic counselling (Section 10 GenDG) (Section 8 (1) GenDG) (No. 4).

4.3.2 Family-beneficial genetic examinations (Section 14 (2) GenDG)

An exception is made to the principle of direct benefit for the person incapable of giving consent in Section 14 (2) GenDG in favor of *family benefit.*[59] At the same time, the requirements are greater. A genetic examination of a person incapable of giving consent should also be possible if, in the case of a genetically related person planning a pregnancy it is not possible to clarify in any other way whether a particular genetically determined disease or health disorder may occur in a future offspring of the genetically related person (No. 1). According to the explanatory memorandum, this practice, which is accepted in principle, should be possible if a hereditary disease is already known in the family; however, this should be limited to "rare cases" in which the examination is indispensable.[60] An intervention for the benefit of the *reproduction of family members*, that only indirectly serves the person incapable of consent (for the purpose of preserving family ties) is only permitted by law if the prerequisites according to (1) Nos. 2 and 4 are met (No. 2); the person incapable of consent is likely to be only slightly affected in terms of health and not beyond the risks generally associated with obtaining the genetic sample required for this purpose (No. 3); and the person is unlikely to be physically or psychologically burdened by the result of the examination (No. 4).[61]

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56 *Spickhoff/Fenger* GenDG § 14 marginal no. 1; *Fenger* (2010) (58).
57 BT-Drs. 16/10532, p. 30.
58 *Meyer* (2016), p. 514.
59 On the scope of the constitutional and private law concept of the best interest of the child in more detail *Meyer* (2016), pp. 212-223.
60 BT-Drs. 16/10532, p. 31.
61 *Meyer* (2016), p. 518 requires that an impairment must not occur with a probability bordering on certainty, either at present or in the future.

4.3.3 Diverging views on consent

If the parents disagree among themselves or the child (exercising their "veto" right) and the parents disagree on the performance of genetic testing, a family court may be called upon to make a decision.[62]

4.3.4 Problems with incapacitated persons

Whereas information and consent prior to genetic testing require the participation of the legal representative (Section 14 (1) No. 4 GenDG) and of the person incapable of giving consent (Section 14 (1) No. 2 GenDG), the notification of findings (Section 11 GenDG) is an act performed unilaterally by the physicians. In principle, the notification of findings is limited to the results of the examination objective. In the case of so-called additional findings, the question of "whether" and "how" to return them arises in the event of positive findings. In the case of "parent-child" constellations, there are three factors in particular that must be taken into account.

4.3.4.1 Parental decision primacy

Provided minors are not capable of giving consent, the parents will decide within the scope of their personal care (cf. Sections 1626, 1627 BGB) not only on consent to genetic testing but also on the return of additional findings. Much like the return of findings in general (Section 11 GenDG), additional findings are returned the parents as legal representatives of their child.[63] Although the parents can generally grant or refuse such return, it is not possible to provide specific information (Section 9 GenDG) on these findings in advance, as they are by definition unknown at the time as unforeseen findings that only arise as a result of the examination itself. The highest guideline for the parents' decision-making competence is the orientation towards the best interest of the child. It is problematic that before the child has reached (full) capacity to consent, an externally determined decision is made for him or her that may contradict his or her later decisions and may even be irreparable once the additional findings have come to light.

4.3.4.2 Genetic involvement of parents and recipients of recommendations within the meaning of Section 10 (3) sentence 4 GenDG

In the "parent-child" structure, a fundamental genetic involvement of the parents may exist in the case of direct descent (this is described in more detail in Chapter 5.10). The problem is that parents may be (un)consciously guided by this notion when deciding on the return of

[62] For more details, see *Spickhoff/Fenger* GenDG Section 14 marginal no. 1; *Prütting/Stockter* Medizinrecht Section 14 marginal no. 58.

[63] *Prütting/Stockter Medizinrecht § 14 Rn. 104*; *Meyer* (2016), p. 514.

additional findings or, if they refuse the return, there may be unknown risks of disease for themselves or other descendants, which then go undetected.

In the case of genetic involvement of the parents of a child who is incapable of giving consent, the provisions of Sections 10 and 11 GenDG play a decisive role: Given the child's incapacity to give consent, findings must generally be returned to the parents (who are authorized to represent the child, Sections 11, 14 (1) Sentence 1 GenDG). In addition, the recommendation laid out in Section 10 (3) sentence 4 GenDG for the person examined to suggest any potentially affected genetic relatives to undergo genetic counseling is in such cases given directly to the parents instead of the minor. However, these are supposed to be the very recipients of this suggestion. The "chain of recommendation" is thus effectively dissolved, i.e., the parents indirectly learn of the likelihood of their own person being affected during the counseling interview concerning the examined minor. Consequently, in this constellation, the physicians have a right to recommend genetic testing on the parents.

4.3.4.3 Probability statements

Given their probabilistic nature, additional findings only provide information on the probability of occurrence (penetrance), timing, and expected severity (expressivity) of a disease. Accordingly, they do not provide absolute certainty but can only make relative statements.[64] Such information (Section 9 GenDG) is essential, as parents and the children concerned have a comprehensive right to this.[65] False-negative results, i.e., overlooked mutations, could provide false "certainty" and false-positive results would cause unnecessary concern. This necessarily applies exclusively to predispositions and carrier status, as previously diagnosed diseases have already occurred. If findings on predispositions and carrier statuses are returned, decision making based on prognoses can clash with the rights of the genetically affected persons not to know and their life planning (as it is shaped without knowledge of the additional findings).

4.3.5 Differentiation in the case of medically actionable diseases: Time for medical action

In the context of additional findings, a further differentiation is necessary. In the case of medically actionable diseases, the time of need for medical action is relevant. In this respect, a distinction is made between diseases with an early need for medical action (Child/Early-Onset) and

[64] For more details, see Chapter 5.2 below.
[65] *Schönke/Schröder/Sternberg*-Lieben § 223 marginal no. 41f with further references.

diseases with a late need for medical action (Adult/Late-Onset).[66] In the context of medical actionability, the deciding factor in practice – especially for the decision on the return of additional findings – is when an initial preventive or therapeutic treatment measure could be carried out. In terms of the *right to life and physical integrity of* the person concerned, it is important not to let this point in time pass, but at best to take action – possibly also in order to avoid the risk of criminal liability.

This differentiation is also relevant in the context of genetic examinations of persons incapable of giving consent according to Section 14 (1) GenDG: For the examination of medically non-actionable diseases with a late onset and a lack of acute symptoms, such examinations are excluded according to the GEKO guideline, since the *right not to know and* the *right to future autonomy of decision of the* child are to be favored even against a contrary urgent wish of the parents.[67] Additional findings may nevertheless indicate such a disease, since they are not the purpose of the investigation but rather an ancillary diagnosis.

This indicates a clear ethical position of the GEKO with regard to late manifesting diseases:

If no acute prevention or intervention option is available, the right not to know prevails.

If therapeutic measures are unlikely to be successful (medically non-actionable disease), the right not to know prevails.

4.3.6 Legal positions and balancing parameters

For problematic cases in which there are divergent opinions regarding the return of an additional finding (both on the part of the parents or the child and on the part of the physicians), it is necessary in the context of a balancing process to take the conflicting interests into consideration and ultimately to weigh them against each other.

4.3.6.1 The right to life and physical integrity

First and foremost is the right to life and physical integrity pursuant to Article 2 (2) sentence 1 GG, which is undoubtedly of fundamental importance. It includes, among other things, both the biological-physical existence from the time of birth until the occurrence of death,[68] as

[66] See the definition in chapter 3.3.

[67] Guideline of the Gene Diagnostics Commission (GEKO) on genetic testing in persons incapable of giving consent according to § 14 in conjunction with Section 23 (1) no. 1c GenDG (version of July 26, 2011; effective on July 27, 2011), BGesBl. 2011 (54), p. 1259.

[68] BVerfGE 115, 118 (139) = NJW 2006, 751 (753).

well as the protection against diseases and infirmities.[69] If an acute illness or a predisposition of the child is detected (and thus with a certain probability a predisposition in the parents as well) these rights are to be considered by physicians deciding on the return of additional findings, i.e., in principle, imminent or threatening dangers for the persons are to be averted. Survival interests are fundamentally paramount. Particularly in the case of those who are incapable of giving consent, the right to determine one's own physical integrity becomes part of their legal representatives' duty of care. These representatives are ultimately given the authority to make decisions on behalf of the child, since the child is not yet (fully) able to discern, judge and control it's own actions.[70]

4.3.6.2 The right to informational self-determination

Section 1 GenDG prominently emphasizes the state's obligation to safeguard the right to informational self-determination. This right is an "independent manifestation" of the general right of personality under Article 2 (1) in conjunction with Article 1 (1) GG.[71] It "takes account of threats to and violations of personality that arise from information-related measures under the conditions of modern data processing" (translation by the authors).[72] This also includes the guarantee for the individual person to decide for him- or herself (or, if necessary, through the intermediary of persons with custody rights) on the disclosure and dissemination of his or her genetic data and to be able to exclude third parties from gaining knowledge of it,[73] i.e., a power of disposition. In the field of modern human genetics, the "right of the person concerned not to take note of the test result or parts thereof but to have it destroyed" (translation by the authors), as recognized in Section 9 (2) No. 5 GenDG, can be seen as a further manifestation of this.

4.3.6.3 The right not to know one's own genetic predisposition

While the right to informational self-determination in genetics is intended to protect the area of external perception, the right to know or not to know concerns self-knowledge.[74] In the context of family law disputes, the German *Federal Constitutional Court* has thus far only recognized the right to know one's own parentage. Regarding the scope of the general right of personality, it issued the following opinion: "Understanding and development of individuality are, however, closely connected with knowledge of the factors constitutive of it. These include, among others,

69 BVerfGE 56, 54 (74) = NJW 1981, 1655 (1656).
70 *Meyer* (2016), p. 36.
71 *Jarass/Pieroth* GG-Kommentar Art. 2 Rn. 40.
72 BVerfGE 130, 151 (183) = NJW 2012, 1419 (1423).
73 *Meyer* (2016), p. 41.
74 *Fleischer* (2018), p. 48.

descent. It not only determines the genetic makeup of the individual and thus helps to shape his personality. Independently of this, it also occupies a key position in the consciousness of the individual for finding individuality and self-image. In this respect, the personality value of knowledge also does not depend on the degree of enlightenment that biology is currently able to provide about the hereditary disposition of the human being, which may be significant for the shaping of his life" (translation by the authors).[75] From this, the *Federal Court of Justice* derived the "right not to know one's own genetic predisposition" from the general right of personality (Art. 2 (1) in conjunction with Art. 1 (1) GG) in a judicial development of the law in a medical malpractice case, since the need for protection of personality also exists in view of modern developments – such as human diagnostics – and the dangers associated with them.[76] The "right not to know one's own genetic predisposition" is intended to protect the individual from gaining knowledge of genetic information concerning him or her that is significant for his or her personal future without wanting to do so.[77] This further development of the law has been confirmed in principle in academia, although this new right is in part also derived from the right to informational self-determination.[78] Not knowing one's own genetics, in particular the genetically determined predisposition to disease, is a central component of one's own personality, lifestyle, and life planning.[79] This primarily concerns knowledge of genetic anomalies or deviations from the norm, which are the basis for diseases or can indicate predisposition to diseases. The "right not to know" was included *expressis verbis in* Section 9 (2) No. 5 GenDG. The GenDG thus serves not only to protect genetic information but also to protect *against* genetic information.[80]

Two opposite interests can thus be identified. On the one hand, the right to receive information (right to know) and, on the other, the right to reject "imposed" information (right not to know).[81] In its landmark decision, the *Federal Court of Justice* expressly left open the question of whether the right not to know is already impaired when a person is told that he or she may be a carrier of a hereditary disease.[82] The surprising and unwanted information from a genetic analysis may represent a par-

75 BVerfGE 79, 256 (268) = NJW 1989, 891; BVerfG JuS 2007, 472 (474), where, on the other hand, the existence of the right not to know one's own parentage is doubted.
76 BGH NJW 2014, 2190 (2191) with reference to BVerfGE 79, 256 (268) = NJW 1989, 891.
77 BGH NJW 2014, 2190 (2191).
78 Damm (2012) (707, 709); *Damm* (2014) (140 et seq.); *Duttge* (2010) (35 ff.); *Taupitz* (1998) (592 ff.); *Kern/Hahn*, GenDG, Section 1 marginal no. 15; *Meyer* (2016), p. 43; *Fleischer* (2018), p. 49; Final Report of the Enquete Commission "Law and Ethics of Modern Medicine, BT-Drs. 14/9020, pp. 132f.
79 BGH NJW 2014, 2190 (2191).
80 *Fleischer* (2018), p. 49.
81 *Damm* (2012) (709); *Meyer* (2016), pp. 44f.
82 BGH NJW 2014, 2190 (2191f.); differently OLG Koblenz, MedR 2014, 168 ff., which assumed a violation by notification of the 50% carrier probability of a related third party with Chorea-Huntington.

ticular threat to the right not to know. The greater the difference between growing knowledge on the one hand and limited therapeutic options for action on the other, the greater the threat is considered to be.[83] However, the Sixth Civil Senate of the German *Federal Court of Justice* at least indicates a tendency not to assume that the right not to know has been violated, since a free decision against receiving certain information presupposes that the person concerned is aware of information that he or she could potentially learn about.[84]

A decision on the disclosure of information on additional findings to the person examined (genetic diseases of the child or hereditary involvement of the parents) should be documented as part of the information and consent provided by the attending physicians (Section 9 (3) GenDG).[85] According to the wording of Section 9 (2) (5) GenDG, the "person concerned" has the right not to know. Due to the reference to consent in Section 9 (1) GenDG, this is to be exercised by the legal representatives, i.e., the parents on behalf of the child incapable of giving consent, according to the conception of the law. The child incapable of giving consent is indeed an independent bearer of fundamental rights,[86] but due to his or her immature stage of development the child is factually prevented from exercising the right in accordance with its intrinsic content.[87] In the case of hereditary illnesses of the child, the parents also have an independent right not to know about their own – affected – hereditary information. Accordingly, it is possible in principle that they may refuse to disclose information about the child's additional findings to themselves by invoking this right.

4.3.6.4 The right to future decisional autonomy

From the fact that the parents exercise the child's right not to know on behalf of the child when deciding on the return of any (additional) findings, it should follow that this right at the time of the child's incapacity to consent is in the nature of a right to future autonomy[88] in decision-making.[89] This right takes account of the fact that the decision for the child is made by the parents and thus necessarily relevant factors

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83 Cf. Enquete Commission of the Bundestag, BT-Drs. 14/9020, p. 121; *Vossenkuhl* (2013), p. 16.

84 *Taupitz* (1998) (597); BGH NJW 2014, 2190 (2191).

85 For example, with an explicit declaration of consent as in the project "INFORM – INdividualized Therapy FOr Relapsed Malignancies in Childhood": "We want to be informed about clinically useful results concerning our child's tumor disease at the current time that indicate a hereditary component of the tumor disease" (translation by the authors).

86 *Jarass/Pieroth GG-Kommentar Art. 2 Rn. 56.*

87 In-depth *Laufs/Katzenmeier/Lipp, Arzttrecht, XIII. marginal no. 106ff.*

88 Among other things, it is also understood as the will of the child within the framework of the best interest of the child, according to *Grüneberg/Götz* § 1666 Rn. 9.

89 Cf. also Guideline of the Gene Diagnostics Commission (GEKO) on genetic examinations in persons incapable of giving consent pursuant to Section 14 in conjunction with Section 23 (1) no. 1c GenDG (version of July 26, 2011; effective on July 27, 2011), BGesBl. 2011 (54), p. 1257 (1259f.).

(e.g. about lifestyle, life planning, and reproductive desire of the future fully developed individual) are not (and cannot be) included. This right can therefore be regarded as the nucleus of the right to know or not to know of the child who is still incapable of giving consent and must be included as a legal position when shaping the options for the return of additional findings.

4.3.6.5 The best interest of the child (Section 14 (3) GenDG)

The external determination of the decision is compensated for by the orientation towards the *best interest of the child,* to which the parents are obliged (Section 14 (3) sentence 3 GenDG with its reference to Section 1627 BGB). It is true that Section 14 GenDG refers exclusively to the decision as to whether a genetic examination should be carried out at all. However, the provisions on parental care under Sections 1626 and 1629 BGB apply comprehensively, so that they are also applicable to the return of additional findings within the scope of general personal care. The best interest of the child is an indeterminate legal concept that is to be concretized by courts on the basis of specific child welfare criteria and development standards.[90] According to medical ethicist *Wiesemann,* the best interest of the child is an ethical concept that requires threefold normative evaluations: the moral position of the child, first, in comparison to the future adult; second, in comparison to his or her parents and family; and, third, with respect to objective values based essentially on general, social agreements.[91] In assessing the best interest of the person incapable of giving consent, the representative must, from a legal standpoint, take into account both the subjective view of the child and objective normative viewpoints (e.g., future prospects).[92] Accordingly, the determination of the best interest of the child is undoubtedly a case-by-case decision involving various perspective factors. These are influenced by the parents, their socio-economic status, values, and behavior and thus represent both an opportunity and a life risk for the child.[93]

One legal limit for the exercise of parental care is the *risk to the welfare of the child,* as the state has a duty to guard against danger in this respect (Section 1666 BGB).[94] A risk to the child's welfare exists in the event of a present danger that, without intervention, makes considerable harm almost certain.[95] The more serious the threat of harm, the

[90] *Grüneberg/Götz § 1666 Rn. 7.*
[91] *Wiesemann* (2016) (242). *Similarly Coester* (1983), pp. 135ff.
[92] BT-Drs. 16/10532, p. 32.
[93] For example, BVerfGE FamRZ 10, 713.
[94] For example, BVerfGE FamRZ 12, 1127.
[95] For example, BVerfGE FamRZ 15, 112; also explicitly *Laufs/Katzenmeier/Lipp,* Arzttrecht, XIII, marginal no. 106ff. for research and curative interventions.

less stringent the requirements for the probability of harm occurring.[96] Accordingly, it can basically be stated that the threat to the child's welfare (in the case of tumor diseases, particularly with regard to the child's life) is to be assessed depending on the probability of occurrence as well as the estimated severity of a disease or predisposition and indicates the increased need for action on the part of the physician.

4.3.6.6 Other consideration parameters

For the handling of a diagnosis from an additional finding, there are further parameters that must be included in the consideration of a conflict regarding the return of an additional finding. These parameters are partly (in)direct ethical consequences[97] of the legal positions described.

(1) Treatment relevance

First of all, actionability is important. In the case of a medically actionable disease, preventive programs or treatment options exist (and are in fact available) that have an impact on the length or quality of life.[98] Basically, a distinction can be made here between medically actionable and medically non-actionable diseases. Only in the case of medically actionable diseases do therapeutic measures offer a promising benefit. However, for therapeutic measures the affected person must first have been informed of the additional findings (and consented to treatment). In legal terms, treatment relevance directly opens access to the right to life and physical integrity (which includes a person's physical and mental health) and thus also to healing or alleviation of symptoms. Failure to act threatens to restrict this right.

(2) Life planning and reproductive relevance

In the same way, the relevance to life planning and reproduction must be included as a factor in the decision-making process. This includes the possible consequences for the affected person's lifestyle, life planning, and family planning as a result of the return of an additional finding.[99] The person should have the right to shape his or her life with the knowledge of the disease or predisposition, i.e., with a health status deviating from the "normal case", in a manner that takes into account their individuality and their own expectations. This can create added value in terms of quality of life, both in the case of medically non-actionable and medically actionable diseases.

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96 *Grüneberg/Götz* § 1666 Rn. 8 with examples.
97 See chapter 5 for more details.
98 See definition in chapter 3.2.
99 See definition in chapter 3.2.

(3) Psychological distress or autonomy promotion through knowledge
Knowledge of the genetic alteration will have a significant influence on the person affected. This is also likely to be true for treatable (medically actionable) diseases, but probably most so for medically non-actionable diseases. On the one hand, a psychological burden caused by the knowledge of the disease, predisposition, or carrier status is possible to such an extent that the affected person is deprived of quality of life as a result. Whether this is the rule is unclear. The empirical study base is limited here.[100] On the other hand, the knowledge of a medically (non-)actionable disease can also promote autonomy.[101] Thus, a more conscious planning of time combined with the strengthening of family bonds or the self-identity of the affected person is conceivable. Some people perceive this possibility in such a way that during the time when the potential illness has not yet developed, activities can be carried out that would no longer be possible after the onset of the illness.[102]

4.3.7 Legal risks

In addition to the aforementioned legal considerations and other assessment parameters, any legal risks must be explored with regard to a physician's decision to return additional findings. There are liability risks to be considered in the area of medical confidentiality and notification obligations, whereby the constellation of imposed additional findings must be distinguished from the failure to provide the return in the case of additional findings regarding medically actionable diseases.

4.3.7.1 Unsolicited findings "imposed" or communicated without justification

The problem area of "imposed" additional findings relates to situations in which the parents are not even offered a decision on the return of additional findings prior to the genetic examination of the minor and the physicians virtually "impose" these findings on them. This can be equated, for example, with situations under Section 11 (4) GenDG concerning additional findings, i.e., notification despite the decision to destroy and despite revocation of consent to notification. In such cases, there is therefore a lack of information and consent.

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100 See chapter 5.15.3.

101 *Kern* (2012) (353) for the disposition of the incurable disease Huntington's disease with the assumption that it is better to know that one does not have the disease than to remain in the unknown.

102 Cf. SPIEGEL-ONLINE article v. 13.10.2022: "They should see the world with their own eyes: Four years ago, Edith Lemay and her husband received a shattering diagnosis: three of their four children will probably soon no longer be able to see. On a trip around the world, the Canadian family wants to create visual memories." (translation by the authors, available online for a fee at: https://www.spiegel.de/reise/fernweh/familien-reise-mit-erblindenden-kindern-sie-sollen-die-welt-mit-eigenen-augen-sehen-a-487a2910-1271-4e74-b808-a7d781e89982, last accessed 6/29/2023).

(1) Criminal liability according to Section 203 (1) No. 1 German Criminal Code (StGB)

The physicians providing the information may be liable to prosecution for breach of private secrets pursuant to Section 203 (1) No. 1 of the German Criminal Code (StGB) if they have disclosed another person's secret without authorization, namely a secret belonging to the personal sphere of life that has been entrusted to them or made known to them when exercising their profession. Private secrets, which include the results of genetic examinations, are protected by the criminal provision of Section 203 StGB[103] and, from the perspective of physicians, another person's sphere of life – namely the patient's – is affected.[104] The unauthorized nature results from the lack of consent.[105]

However, it is questionable whether this case is really covered by the criminal provision. Disclosure is any release of facts from the circle of those in the know or those called to know[106], i.e., to a third party.[107] It is questionable whether the communication to the patient or the patient's legal representatives constitutes such disclosure. These are not third parties within the doctor-patient relationship. The core issue here is the scope of the duty of confidentiality, i.e., whether Section 203 StGB also protects the right of the person concerned not to know or only protects the secret from being known to third parties.[108]

Based on the systematic position of Section 203 StGB in the overall context (Section 15: "Violation of the personal sphere of life and secrecy"), it is predominantly assumed that only disclosure to third parties, but not unauthorized communication to the person affected by the secret and his or her custodial representatives, should be covered.[109] This assessment goes hand in hand with the protective purpose of Section 203 StGB, the private right of disposal over certain information,[110] which determines that the persons concerned must in principle decide for themselves when and within what limits personal facts of life are to be *published.*[111] However, this should logically presuppose that they have knowledge of their own information. Section 203 StGB therefore does not protect the right of the patients concerned not to know and does not apply to additional findings that are "imposed" on them or communicated without authorization.

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103 *Erbs/Kohlhaas/Häberle* GenDG § 11 marginal no. 2.
104 Schönke/Schröder/Eisele StGB § 203 marginal no. 8; MüKo-StGB/*Cierniak/Niehaus* StGB § 203 marginal no. 29; *Spickhoff/Knauer/Brose* Medizinrecht StGB §§ 203-205 marginal no. 4.
105 *Fischer* StGB § 203 Rn. 63ff.
106 LK-StGB/*Schünemann* § 203 marginal no. 41.
107 *Fischer* StGB § 203 marginal no. 33.
108 *Erbs/Kohlhaas/Häberle* GenDG § 11 marginal no. 2.
109 LK-StGB/*Schünemann* § 203 Rn. 43 with further references; SK-StGB/*Hoyer* § 203 Rn. 31.
110 SK-StGB/*Hoyer* § 203 Rn. 1.
111 Cf. OLG Hamburg NStZ 1998, 358.

(6) Civil law claims

The parents themselves (or on behalf of the child) could assert civil claims against the unauthorized doctors. Claims for damages or compensation for pain and suffering due to psychological distress or illness caused by knowledge of the genetic alteration could be considered.

Previous case law

Thus, in a decision regarding predictive genetic diagnostics in the family unit and liability law, the *Federal Court of Justice* left it open whether the 'right not to know one's own genetic predisposition is already impaired by the fact that a person is given the indication that he or she is 'possibly a carrier of a hereditary disease'.[112] No decision has been made in this regard.

The case concerned a man suffering from Huntington's disease (which is incurable), who had released his attending physician (the defendant) from the duty of confidentiality. The doctor informed the divorced wife – at the man's request – that there was a 50% probability that the children would get the disease. The women (claimant) – who was not affected by the genetic defect herself – suffered psychological damage as a result of the knowledge of the children's likelihood of getting the disease. She claimed non-material damages in court.

The lower court found a claim based on liability pursuant to Section 823 (1) BGB, since the physician had had no justification for informing the claimant about a genetic defect causing an incurable disease.[113] The *Higher Regional Court* spoke of an "unlawful act on the part of the defendant solely by informing the claimant at least at an inopportune time" (translation by the authors), although the father affected by the disease had released the doctor from his duty of confidentiality to inform the mother of his children about their genetic predisposition. Providing the information to the child's mother, who did not want to know, was also not justified by the Gene Diagnostics Act, the guideline of the Gene Diagnostics Commission or a hypothetical consent, because a doctor also has to respect the "right not to know" of the divorced wife.[114] The *Federal Court of Justice* overturned the judgment of the *Higher Regional Court* on the one hand because the notification of a serious illness of the children remains a general risk of life and is not covered by the protec-

[112] BGH NJW 2014, 2190 (2191f.).

[113] Worth reading: OLG Koblenz, Urt. v. 31.7.2013 – 5 U 1427/12, (OLG Koblenz 2014, 168ff.) mAnm. Damm; OLG Koblenz, decision of 1.2.2012 – 5W 63/12, (OLG Koblenz 2012, 742ff.) mAnm. Damm. In the first instance, the Bad Kreuznach Regional Court (judgment of November 2, 2012 – 3 O 306/11, BeckRS 2014, 11535) still saw a justification of the physician.

[114] OLG Koblenz (2014) (editor's leading sentence); op. cit. Kern (2012).

tive purpose of Section 823 (1) BGB, and on the other hand because the claimant as mother had asserted precisely not her own right not to know (with regard to her own genetic predisposition) but that of her children.

Despite certain differences between this case and the constellation presented here (e.g., examination of an adult symptomatic male instead of a (still healthy) child, primary instead of additional findings, release from the duty of confidentiality instead of completely unauthorized communication), it can be assumed here that such claims for damages will be recognized in principle because of the particular significance of the right not to know. The *Federal Court of Justice* rejected a claim primarily because of the specific features of this individual case. This means there is a civil liability risk in cases of unauthorized return of unsolicited findings.

Application to the example case

In the case of genetic testing of a minor, a treatment contract is concluded between the parents acting on behalf of the child and the treating physicians. The unauthorized communication could constitute a breach of a duty of consideration pursuant to Sections 280 (1), 241 (2) BGB. Necessary prerequisites are, in particular, a substantiated pathological condition exceeding the materiality threshold (keyword: so-called shock damage), which is causally and objectively attributable to the unauthorized communication. Since both the child and the parents are entitled to a right not to know (Article 2(1) in conjunction with Article 1(1) GG), this can be asserted by the person who alleges the psychological damage based on knowledge of his or her own genetic abnormality. The *Federal Court of Justice* has expressly left open the question of impairment, i.e., breach of duty within the meaning of Section 241 (2) BGB or infringement of legal interests within the meaning of Section 823 (1) BGB. However, if the causal chain between unauthorized communication and psychological damage is concluded upon medically, it follows that an act of violation would have to be affirmed. The assumption of a general life risk must be ruled out if, contrary to medical prudence, such findings are "imposed" on patients in a completely surprising manner. Whether the physicians acted intentionally or negligently is irrelevant because of Section 276 (1) BGB. In the context of a possible exclusion of illegality, the parents' express consent to the communication of the additional findings must be denied if this consent is lacking (for example, also due to a lack of inquiry about this). A hypothetical consent would have to deal with the decisive conflict between the right not to know and the right to life or physical integrity. However, this would probably only be

the case if there were a corresponding relevance to treatment in the event of an existing risk to life or limb.

The risks described here must be taken into account in the information process and can be minimized by explicitly asking for consent regarding the return of additional findings before the start of the examination.

4.3.7.2 Penal failure to return unsolicited findings regarding medically actionable diseases

On the other hand, physicians may face criminal charges if they fail to return additional findings regarding medical actionable diseases. Assuming that a criminal liability would only exist if a physical condition were to decline but which could in principle be improved, only constellations with promising intervention possibilities (through prevention or treatment) are covered here. In the case of other diseases, the failure to return can no longer have a concrete effect on the decline of the condition.

In order to underscore this point, reference is made to a situation in which an additional finding indicates a predisposition to a life-threatening but medically actionable disease in the child with an early need for medical action. The parents decide in advance they do not to want to be informed about additional findings, and the physicians do not inform them accordingly.

(1) Criminal liability according to Section 323c (1) StGB

An omitted assistance in accordance with Section 323c (1) StGB comes into consideration.

Accident

Omitted assistance requires, as a concrete endangerment offense, that an accident takes place,[115] i.e., a suddenly occurring event that entails considerable danger for an individual legal asset.[116] A mere illness as such is not sufficient for this.[117] A threatening rapid aggravation of the illness is crucial.[118] With regard to the element of "suddenness", which is not to be tied to excessively high conditions, the focus shall not be on the past course of the disease but rather on the presence of the danger.[119] Thus, a deterioration in a state of health that occurs as expected

[115] Generally dismissive of "chance finds" is *Fleischer* (2018), p. 219.
[116] Disputed jurisprudence e.g., BGHSt 3, 65 (66) = NJW 1952, 1062; 6, 147 (152) = NJW 1954, 1049; 11, 135 = NJW 1958, 390.
[117] *Fischer* StGB § 323c marginal no. 6.
[118] MüKo-StGB/*Freund/Koch* § 323c marginal no. 25; *Lackner/Kühl/Heger/Heger* StGB § 323c marginal no. 2; BeckOK StGB/von *Heintschel-Heinegg StGB* § 323c marginal no. 8.
[119] *Schönke/Schröder/Hecker StGB § 323c marginal no. 6.*

is not "sudden" within the meaning of Section 323c StGB.[120]
A hereditary predisposition does not fulfill this requirement. Depending on the course of the disease, certain hereditary diseases will, among other things, lead to a more rapid worsening of the state of health, so that a distinction would have to be made between different hereditary diseases. It is necessary that this aggravation of the condition is imminent or has already occurred. Based on Section 16 StGB, the duty to act depends on the time of the return in question. Therefore, the example outlined here does not amount to an accident.

Interim result
In principle, a risk of criminal liability for physicians pursuant to Section 323c (1) StGB can be ruled out in case of failure to return additional findings that are not present, i.e., have not manifested.

(2) Punishable omission regarding the protection of life and limb according to Sections 212, 223ff., 13 StGB
If the omission leads to bodily injury due to deterioration of the child's state of health or even to death, criminal liability by omission in accordance with Section 13 StGB may also be considered. In this context, legal issues arise especially with regard to the guarantor status[121] of persons involved in the genetic examination and in case of parents waiving their right to the return (of findings).

Guarantor obligation
Treating physicians
By virtue of (actual and/or contractual) assumption of responsibility, the attending physicians have a legal obligation to act on behalf of their patients (guarantor obligation), since they have expressly or impliedly committed themselves to prevent certain dangers and have thus effectively assumed corresponding obligations.[122] They are thus fundamentally obliged to prevent injuries and death to the patient. This does not apply, however, to genetic relatives of the patient who have no treatment relationship with the physicians in question.

Researching physicians
The internal organization of (university) hospitals and associated research centers is of essential importance in the case of researching physicians due to their lack of patient contact. Non-treating physicians may also have duties of care, e.g., whoever cooperates with the treating

[120] *Schuhr in Spickhoff, Medizinrecht, § 323c StGB Rn. 19.*
[121] Generally rejected for researchers involved in a data analysis for "chance finds" of subjects: *Fleischer* (2018), p. 219.
[122] MüKo-StGB/*Freund* § 13 marginal no. 173.

physicians as head of a drug trial or comparative therapy studies.[123] This may result in a duty to carry out interim evaluations and to inform patients of their results.[124] A legal duty of compliance may exist in particular for researching physicians in the context of translational research if their collaboration is closely linked to clinical diagnostics on patients. The involvement with human genetic material also speaks in favor of a duty of compliance due to its particular sensitivity.

Non-physicians

Hospital, nursing, or non-medical staff may also have a guarantor's duty, insofar as they actually perform a protective function[125] and thereby create a situation of trust for the person at risk.[126] This must be determined according to the individual case, i.e., according to the extent to which the person is involved with the genetic examination and is responsible for it.

Justification of the omission

If the individual at risk waives his or her right to assistance in a legally effective manner, the illegality of the omission can be resolved.[127] This involves consent to a concrete result of injury or death. Effective consent requires the protected legal good to be of a disposable nature and that no vices of consent nor violations of moral principles are immanent to the consent itself.[128] The legally protected good of physical integrity is a disposable legal interest in the German legal system, but only within the limits of the common decency (see Section 228 StGB). In principle, the legally protected right to life is only disposable for the bearer of the legal interest, and even then, within narrow limits (Section 216 StGB, Sections 1901a ff. BGB).[129] For the parents of a child (as another bearer of legal rights), on the other hand, the child's life is not disposable. They cannot effectively consent to a homicide by refusing to receive additional findings.

In the case of a comprehensive information process, which already points out in advance the possibility of additional findings and possible serious consequences for life and/or limb, it can be assumed that – were the parents to comprehensively refuse the receipt of additional findings – the limits for legally effective consent would be exceeded.

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123 NK-StGB/Gaede § 13 marginal no. 39. BGH NStZ 2001, 188 for head of a transfusion center in which blood was contaminated.
124 NK-StGB/*Gaede* § 13 marginal no. 39.
125 OLG Celle NJW 1961, 1939 (1940).
126 OLG Düsseldorf NJW 1991, 2979 (2980).
127 Standard in *Fischer StGB § 323c Rn. 32f.*
128 *Fischer StGB Vor § 32 Rn. 3b, 3c.*
129 MüKo-StGB/*Schlehofer* Vor § 32 Rn. 156ff. with further references on the development of the self-determination of dying.

Interim result

In the area of the above examined omission offenses, the effectiveness of consent in cases of serious damage to health or even death must be rejected accordingly. A risk of criminal liability on the part of the treating physicians exists in cases of failure to return additional findings despite acute danger to life. This ultimately depends on the specific individual case. However, the crucial point will be the effectiveness of the consent (Section 8 GenDG) and thus the scope of the informative discussion that took place beforehand (e.g., to what extent was attention drawn to possible health impairments as a result of the refusal to receive additional findings?).

4.4 Overriding parental will as an exercise of medical notification duties?

It has now been established that in the event of failure to return additional findings – even if this is the wish of the persons authorized to care for the patient – there is still a risk of both civil and criminal liability for the physicians, which, however, is highly dependent on the individual case; it is therefore necessary to differentiate between various scenarios. This way, conclusions can be drawn as to how the legal risks for the medical staff can be countered by the best possible design of the return process and in particular – in advance – of the informed consent process.

4.4.1 Additional findings in the case of minors and lack of consent for return

4.4.1.1 Additional findings regarding medically actionable diseases

The first question concerns a situation in which additional findings regarding a medically actionable disease are collected during the examination of a child who is incapable of giving consent but whose parents have not previously given consent for the return of such findings.

- In the case of predispositions to **early manifesting**, serious diseases that are **treatable** (i.e., medically actionable diseases with the early need for medical action), the child's right to life and physical integrity will regularly prevail. Due to the probable early onset and the relevance of treatment, chances of survival for the child must be ensured – even against the parental will. The parents' right not to know must be set aside wherever there is an acute risk to the child's welfare. The same applies to the right not to know, which the parents only exercise on behalf of the child. The right to later decision-making autonomy, including the child's own life planning, is preserved only if the child survives. Procedurally, this could be done

in such a way that the parents are to be informed of the need for information with the indication that immediate action is required. If there is no response, the family court is to be notified with the indication that there is a risk to the child's life. This applies in any case for researching physicians.

- In the case of predispositions to **late manifesting** diseases of the child, the right not to know regularly prevails due to the lack of present danger for the child. It is preferable to allow the child's capacity to consent to develop but to take precautions for later information. **Return of additional findings** is necessary in the case of **medically actionable diseases** with a **late need for medical action** from the onset of treatment relevance and the earliest therapeutic option in terms of the right to life and physical integrity of the (then) adult. At this point, physicians should develop time parameters depending on the disease and the individual case.
- **(Delayed) return of additional findings** to the adult who is now capable of giving consent must respect the scope of the right not to know. Is the right already violated when it is communicated that there are findings? Or only when the specific findings are communicated? *Taupitz* argues that a free decision not to receive certain information presupposes that the person concerned knows that there is information of which he or she could take note.[130] This, however, is a basic problem of the dimensions of human knowledge: the right not to know is supposed to relieve the right holder psychologically as a right of defense. The mere knowledge that findings (of whatever kind) exist can cause a psychological burden. Automatic return of (additional) findings to the adult who is now capable of giving consent may already interfere with their right not to know. However, the adult's perception of the autonomous decision is not possible otherwise. This issue must be given due consideration when contacting the adult by formulating the request as carefully as possible.
- **Assigning** the parents with the task of informing the child about the mere presence of findings when he or she has reached the capacity to consent must be viewed ambivalently. One very obvious issue might be that the parents simply forget to do this, resulting in a health hazard (for which the physician is responsible in the first place) for the (now) adult.

4.4.1.2 Additional findings regarding medically non-actionable diseases

The second constellation differs from the first only in that an additional finding now regards a medically non-actionable disease.

[130] *Taupitz* (1998) (597); discussion also in *Kern* (2003), pp. 65f.

- In the case of predispositions to **medically non-actionable** diseases with **early onset**, the weighing shifts because of the elimination of treatment relevance. There is no preventable danger to the child. The return of additional findings might be psychologically stressful or autonomy-enhancing. The right of the parents and the child not to know weighs heavily. In the event of a declared refusal to accept additional findings, such will shall generally prevail. However, it would be tantamount to schematization if the right not to know were to prevail in every conflict situation.[131]
- The same applies to predispositions to **medically non-actionable** diseases with **late onset**. Additional findings can be returned to allow for the exercise of the adult's decision-making autonomy and with regard to the adult's life and reproductive planning.

4.4.2 Case: the child as carrier

A further issue arises if the child has a disease carrier status as this can become relevant in the context of reproduction (family planning). The GfH (Society for Human Genetics) recommends that tests should not be performed on children if there are no clinical symptoms and they would only be relevant for the reproductive planning of the future adult.[132] Does this mean that genetic disease carrier statuses should not be reported if they are additional findings?

At this point, a distinction must first be made. If the sole purpose of the examination is to obtain information about the disease carrier status for the sake of reproductive planning of the carrier, an examination is not currently necessary because the child is (probably) not yet planning to reproduce. The medical intervention would therefore not be proportionate. If, on the other hand, a genetic examination with a different purpose reveals the existence of a disease carrier status, the situation is different. The additional information obtained is now already available without further medical intervention.

The return of additional findings regarding a disease carrier status must be made while weighing the rights of the child to later decision-making autonomy on the one hand and life/family planning on the other. The return of additional findings regarding a disease carrier status at an early age is obviously of no use to the child at the present time, so that the

[131] BMBF-Projektgruppe "Recht auf Nichtwissen" (2016) (400, 404); *Fleischer* (2018), pp. 81, 224, who proposes a contractual regulation on categorization of different diseases for "accidental findings."

[132] Cf. Guideline of the Gene Diagnostics Commission (GEKO) on genetic examinations in persons incapable of giving consent pursuant to Section 14 in conjunction with Section 23 (1) no. 1c GenDG (version of July 26, 2011; effective on July 27, 2011), BGesBl. 2011 (54), p. 1257 (1259).

right to later decision-making autonomy or current ignorance prevails. The closer biological family planning approaches, the more valuable this information is for the (adolescent) child. In this respect, these findings are comparable to late manifesting diseases. These findings only become relevant after the patients reach a certain age. However, the indirect benefit of the knowledge in the case of a possible involvement of the parents and the consequences for their families and life planning must also be taken into account. In this respect, a reasonable procedure would be to offer the return of the information regarding the disease carrier status if such information is also relevant and useful for relatives.

4.4.3 Additional findings of probable concern to parents of a child incapable of consenting and their refusal to receive information

Here, the focus is on the genetic involvement of the parents (see also Chapter 5.10 about the relevance of the additional finding for parents and siblings). In light of the fact that the parents will have already reached adulthood by the time of the examination, the focus will regularly no longer be on early-onset diseases, but primarily on late-onset diseases. In these cases, a balance must be struck between the parents' right not to know on the one hand and their right to life and physical integrity on the other.

- The information provided (Section 9 GenDG) prior to genetic testing regarding possible additional findings should include a reference to possible genetic involvement of the parents. If the parents refuse to receive these additional findings, they have exercised their own right not to know, which must be taken into account. In the case of a predisposition for **medically non-actionable diseases**, the right not to know must be respected. The parents have deliberately chosen not to be informed regarding their own life planning and reproductive relevance.
- In the case of a predisposition of **medically actionable diseases**, attention should nevertheless be paid to a possible risk to the parents (or further descendants), even if the probability of outbreak is low. In this case, instead of a response, a solution is often sought by means of genetic counseling (Section 10 (3) sentence 4 GenDG).[133] Although this is expressly only a recommendation,[134] it largely preserves the right not to know if the procedure is objective and non-directive and still offers prevention and therapy options. In cases of doubt, the child's right not to know also reaches its limits here if constitutionally protected rights of third parties (the parents) – namely physical integrity – are concretely endangered.[135]

[133] *Prütting/Stockter Medizinrecht § 14 Rn. 7.*
[134] *Kern* (2012) (353).
[135] BMBF-Projektgruppe "Recht auf Nichtwissen" (2016) (403); *Fleischer* (2018), p. 224.

5 ETHICAL ASPECTS

While in Chapter 3 we explained the terms relevant to the analyses presented here, in Chapter 4 we dealt with the legal framework within which genetic and genomic examinations are carried out, and thus also the information about additional findings, the options to be offered concerning the return of said findings, and the return itself. The legal norms provide this framework insofar as any clear violation of them is therefore not legally valid or may even be punishable.

Many legal aspects (goods, rights) are recognized both in the sphere of law and in ethics, which is why conceptualizations and considerations in ethics and law partly sound similar and are analogous to each other. It should be emphasized, however, that there can also be divergences between law and ethics in the interpretation and weighting of rights and goods. Here, ethics sees itself as autonomous and critically notes any differences from law. Wherever the legal framework allows for ethical considerations, the latter are important for concrete weighing of questions and shaping of processes since they can and should offer an ethical orientation and guide free but responsible action.

In this sense, in the following, we provide an explanation of the relevant ethical aspects which are included in a consideration of how the informed consent process, the options to be offered regarding the return of additional findings in minors and, if applicable, the return itself are to be designed. These aspects can be divided into *general aspects* (Chapters 5.1 to 5.3), aspects relating to the *child under investigation* (Chapters 5.4 to 5.9), aspects relating to the *family of the child under investigation* (Chapters 5.10 and 5.11) and aspects relating to *researchers or physicians* (Chapters 5.12 to 5.14) who discover additional findings or who are entrusted with returning additional findings. Finally, we explain how the aforementioned aspects are taken into account when weighing the harms and benefits of the return of additional findings (Chapter 5.15).

5.1 Disease severity

Not every disease with a genetic component is equally damaging for the affected person. This must always be taken into account when deciding how to assess an additional finding and whether or not it should be returned, as the benefit of this return varies depending on the severity of the disease associated with the genetic variant. The severity can be

measured by the extent to which there is a *risk to the child's life*. Furthermore, the potential *burden on the quality of life* is a relevant criterion for disease severity. In the case of children, the *developmental relevance* of the disease must be added to this, i.e., the extent to which the disease damages the child's development in the event of an outbreak. Ultimately, the severity of a child's disease is measured by the negative impact on the child's well-being and self-determination in the present, the immediate future, and later as an adult.

5.2 Uncertainty of genetic knowledge

Additional findings represent genetic knowledge and thus usually contain predictive information about increased (genetically determined) disease probabilities without the disease having already become symptomatic. Additional findings thus always convey *probabilistic knowledge*. Even if a disease-causing variant in a known disease gene has been identified with certainty, this does not mean that the person examined will necessarily become ill: The general probability that this manifestation will occur is called *penetrance* (e.g., 70% for breast cancer in women with a pathogenic variant in BRCA1).

There is also often a degree of uncertainty with regard to the (phenotypic) degree of expression of a disease (expressivity), because a genetic disease can take on more or less pronounced manifestations at its actual onset.

In addition, there are questions of evidence. Knowledge about genetically predisposed disease risks, including their penetrance and expressivity, is backed by scientific evidence with varying strengths. If the evidence for a genetically predisposed disease is low or moderate, evidence deficits may lead to epistemic uncertainty.

Depending on the probability that a detected variant will actually lead to the outbreak of a disease (given the uncertainty factors mentioned above), a "false alarm" may arise from the patient's point of view. In such cases, an affected person is informed about a variant that is associated to a greater or lesser extent with a predisposition to disease but which nevertheless does not lead to disease in the specific individual case.

When evaluating variants, the probability that a given variant is causative of disease is classified into five levels: "pathogenic", "likely pathogenic", "uncertain/variant of unknown significance (VUS)", "likely

benign", and "benign". Only variants in the "pathogenic" and "likely pathogenic" classes in relevant disease genes are recommended for return as additional findings according to the recommendation of the American College of Medical Genetics and Genomics (ACMG) (Miller et al. 2022).

5.3 Probability of treatment success (effectiveness)

Just as there may be uncertainties regarding the effects of an additional genetic finding on the patient's health, the term "medically actionable disease" used in Chapter 3.2.1 is partly misleading in that the treatment of genetic diseases – like any other disease – is always subject to a certain degree of uncertainty regarding its effectiveness. The same applies to the effectiveness of preventive measures. Similar to the (un) certainty of genetic findings, two factors must be strictly distinguished with respect to the effectiveness of prevention or treatment: the degree of evidence that exists about the effectiveness of a prevention or treatment approach and its effectiveness itself. In oncology, for example, there are therapies that are fairly well documented (high level of evidence) to have low effectiveness in certain disease conditions.

The effectiveness of prevention and treatment is fundamental for the assessment of the medical benefit, which is associated with the return of a finding regarding medically actionable diseases. In the case of (predictive) genetic diagnostics, it must be taken into account that, especially in the case of diseases with a late need for medical action, it is often difficult to estimate the effectiveness of future prevention and treatment measures. This estimation must always include the (expected) medical progress in the development of therapies and preventive measures. Thus, new effective approaches could potentially be developed for currently medically hardly actionable or non-actionable diseases, from which young patients in particular may still be able to benefit.

5.4 Capacity of minors to give consent

While young minors are generally considered to have only a limited capacity to make autonomous decisions and thus also to consent to treatment options, this capacity to consent does not arise only when they reach the age of majority but can also develop earlier in very different ways in individual cases (see also Chapter 4.2.3). Plausible and widely accepted criteria for the capacity of minors to give consent are that the minor is able (1) to understand information relevant to the decision in question, (2) to process it in an appropriate manner, (3) to evaluate

it in a comprehensible manner, and (4) to form his or her own will on the basis of 1-3 and to express it (Bundesärztekammer 1997; Opper et al. 2019).[136] The exercise of these abilities (1 to 4) further requires the absence of external and internal constraints, for example, pressure/threats from the family or internal states such as anxiety, depressive moods, etc. The capacity to consent is not established in general, i.e., it is not equally valid for all types of decisions, but always depends on the type of decision to be made. For example, a young person may be capable of giving consent for a vaccination decision but not for a decision to stop chemotherapy.

The capacity to consent is commonly regarded as a sufficient condition for exercising certain autonomy rights (such as the right not to know or to make autonomous decisions about medical treatment). However, there are also doubts as to whether a minor who is capable of consenting can be granted such rights in the same comprehensive manner as is the case for adults (Vinicky et al. 1990; Weir und Peters 1997; Benston 2016; Tunick 2021). In addition, determining capacity to consent is fraught with uncertainty. This uncertainty can lead to concerns on the part of physicians regarding the legal certainty of the treatment carried out on the basis of the decision. This applies, in particular, to serious decisions that minors may make against the will of their parents. A special case here is certainly when mature minors make a decision that, from a doctor's point of view, is against their own health interests. In the context of treatment decisions, it is therefore sometimes argued that mature minors who would harm themselves by their decision are acting unreasonably. In this case, it is argued, the parents must be informed to protect the child from his or her unreasonable decision, and decide by proxy (Schelling und Gaibler 2012), thereby denying the minor his or her capacity to consent retrospectively.

However, such a retrospective denial of capacity to consent is problematic. In our view, which incorporates both ethical and legal perspectives, persons considered capable to consent should be attributed corresponding autonomy rights (specifically for the decision to be made). This consistent approach requires a robust assessment of capacity to consent. Once this has been determined, however, the person in question, regardless of age, must be treated as an adult capable of consenting with respect to his or her autonomy rights, which means that even decisions that appear irrational from a medical perspective must ultimately be

[136] See also the notion of the Gillick competence (named after a formulation of the British judge Lord Scarman: Gillick v West Norfolk and Wisbech AHA [1985] UKHL 7, British and Irish Legal Information Institute. 1985. http://www.bailii.org/uk/cases/UKHL/1985/7.html - last accessed July 6, 2020)

accepted as decisions made by an autonomous person, against the will of the parents if necessary (Valerius 2018). This is because parental decision-making authority is only a legitimate substitute as long as the child is not capable of giving consent him- or herself.

A decision by minor patients who have been assessed as capable of giving consent and which, from the external perspective of the doctors (or parents), is obviously in (serious) contrast to the well-being and interests of the child, cannot simply be taken as a reason or justification for denying the patient's capacity to consent again ex post. However, it can and must be taken as a reason to check through special discussions and questions whether the (aforementioned) aspects of capacity to consent are truly present and sufficiently realized.

5.5 Autonomy of minors

As is already clear from the previous Chapter on capacity to consent, minors have the fundamental right to decide freely and themselves on matters concerning them if they have the necessary and relevant abilities and competences to do so. This right of minors also applies in the field of medicine, and here also in the specific area of genetic and genomic examinations and the associated decisions on return options regarding additional findings. The prerequisite and threshold for granting minors a full right to autonomy in the medical field is the capacity to consent mentioned above. Since this threshold is not usually reached by many (especially younger) children, the basic concept of autonomy plays a rather indirect but nevertheless relevant role at further levels with regard to the rights and concerns of children. On the one hand, the development and practice of autonomy and autonomy skills is an important component of a child's well-being at different stages of his or her life (see Chapter 5.7.3). On the other hand, autonomy as a value and component of a good life, as well as in the form of preconditions for a currently young child to exercise autonomy in the future, also plays an important role in the child's right to an open future (see Chapter 5.8). If one also considers these levels, it becomes clear that the return of additional findings can be relevant to the child's autonomy in several ways.

The return of additional findings may have a benefit for the autonomy of the affected children in the form of predisposition knowledge. In the case of *additional findings regarding medically actionable diseases with an early need for medical action,* this benefit is obvious, as knowledge of a predisposition to a medically actionable disease can inform appro-

priate treatment decisions. In the case of *additional findings regarding medically actionable diseases with a late need for medical action,* the benefit for the child's autonomy is not immediate in the sense of informing treatment decisions to be made promptly. However, this knowledge may become important for autonomous treatment decisions in the future.

Additional findings regarding *medically non-actionable diseases* can also be autonomy-enhancing, insofar as they can serve to promote the development of self-esteem and self-identity (Anderson et al. 2015; Fanos und Johnson 1995). For example, adolescents report that gradually learning about the disease as they grew up helped them cope with risk to themselves or other family members, including their own future offspring (Metcalfe et al. 2011).

In addition, knowledge of a disease predisposition enables informed and autonomous adjustment in one's life planning. For example, using knowledge on genetic predispositions, parents can plan the child's future according to his or her possibilities, prepare him or her for it, and support him or her in making informed and autonomous life-planning decisions on his or her own in the future, based on such knowledge. The same applies to mature minors, who, informed by additional findings, can adjust their life planning accordingly. In addition, knowledge of severe disease predisposition (especially in cases of high penetrance) is helpful for parents to make informed decisions about future care options in the best interest of the child. This may include, for example, parents building financial reserves for their child to provide care for the child at a time when the parents themselves are no longer able to do so.

5.6 The right to participate and have a say

Children have a right to participate in all decisions that affect them in accordance with their level of maturity. This implies that all necessary information is presented to them in a manner appropriate to their age or development, that they are allowed to express their opinion and will, and that this opinion and will are given importance, even if they do not have the full capacity to consent. The right to participate and have a say must therefore be given particular consideration in the informed consent process for children who are no longer quite young but who are not yet mature adolescents either. In medical ethics, when it comes to research on children who are incapable of giving consent, they are largely granted

a right to assent. This gives children the ability to withhold consent, which is equivalent to a veto power. In the context of the question on returning additional findings, it is not easy to say whether children with limited capacity to consent should be granted such a veto right on specific issues. However, there is a tendency to respect their refusal all the more, the more it concerns measures on them, their bodies or their data, from which they have neither direct nor indirect benefit, exclusively benefitting third parties.

5.7 The best interest of the child

It is widely recognized that decisions made on behalf of minors who are incapable of giving consent should always be made in the best interest of the child. The best interest of the child and actively promoting this interest is given great importance in the law and in international conventions such as the UN Convention on the Rights of the Child (UNCRC), Article 3. From an ethical perspective, the orientation towards the best interest of the child is decisive for the responsible treatment of minors who are not capable of self-determination. Thus, from the perspective of child ethics, the role of parents is defined by their orientation towards the best interest of the child, the protection and promotion of which is their task and responsibility. They are committed to the best interest of the child when exercising their powers and rights, e.g., as representatives of their children when in the hospital. From the point of view of medical ethics and professional ethics, the same principle applies to physicians. In contrast to parental responsibility, the responsibility of physicians is, of course, primarily aimed at the health of the child as a fundamental aspect of the child's well-being. The concept of the best interest of the child is complex and raises several theoretical and practical challenges,[137] which will be discussed in more detail below.

5.7.1 Objective determination of the best interest of the child

Although the concept of the best interest of the child remains an undefined term in the German legal system, it has been and continues to be at least partially substantiated by individual norms and in case law. Such substantiation is necessary because a completely undefined concept of the best interests of the child is unmanageable and can have ethically unacceptable consequences. For example, the definition of the concept of the best interest of the child cannot be left to the parents of a child *alone,* since otherwise they could justify all possible ways of dealing with their child in the name of *their* interpretation of the best

[137] The difficulty of grasping the concept of the best interest of the child is discussed by, among others, Wiesemann (2016).

interest of the child. Therefore, following the theories of the good life of John Rawls and Martha Nussbaum and oriented to the idea of universal human rights and the UN Convention on the Rights of the Child, we advocate a "moderately objective-universalist" concept of the best interest of the child. Accordingly, there are objective elements, such as health, education, social relations, subjective well-being, and others, which are to be understood as contents of the child's well-being. How these elements are weighted and implemented as objective interests of children still remains a matter of concrete application and interpretation, in which individual, situational, and contextual aspects must be taken into account. However, the fact that certain elements such as those mentioned are to be recognized in principle as the content of the best interest of the child is not a matter of interpretation but rather results from a substantive-objective partial determination of the best interest of the child.

5.7.2 Connection between the child's best interest and children's rights

Important aspects of the child's best interest are incorporated in children's rights. In other words, these rights have the function of ensuring that particularly important and elementary contents of the best interest of the child are respected by everyone (Schickhardt 2017). Conversely, some fundamental rights attributed to children in the UNCRC serve as important baselines of what constitutes the child's best interest "minimally" (Bagattini 2019). Examples would be the right to life (Art. 6), the right to have a relationship with parents (Art. 9), the right to be given due weight to one's will in accordance with the age and maturity (Art. 12), to protection of privacy (Art. 16), to protection from violence and neglect (Art. 19), or to education and schooling (Art. 29).

5.7.3 The temporal dimensions of the child's well-being

When decisions have to be made for a child in the name of his or her best interest, various temporal dimensions have to be taken into account. The best interest of the child should not be understood solely in terms of what is good for the child at the time of the decision nor solely with a view to what will be good in the distant future, when the child will be an adult.[138] As a rough schematic orientation, it can be stated that, especially in the case of decisions that affect young children and may have an impact on the future, the child's present, his or her medium-term future (as an older child or adolescent) and the more distant future (as an adult) must all be taken into account (Schickhardt 2016, S. 181).

[138] Cf. also the classification of the rights and interests of children in Salter (2012).

5.7.4 The role of participation and the child's will in the concrete determination of the child's best interest

The concept of the best interest of the child and recourse to it is needed in situations in which a decision must be made for a child that the child cannot make in a self-determined and responsible manner due to his or her lack of maturity. However, it should be noted that in any situation, when considering the best interests of the child, i.e., what is good for the child in this situation, the child must always be included: his or her voice and will must be taken into account, even if he or she is not deemed to be sufficiently capable of self-determination. The child must be involved and listened to according to his or her maturity (see Chapters 5.4 and 5.5). The child's declaration or expression of will must be taken into account ethically, even if they are only an expression of a limited understanding and a limited or largely absent capacity for self-determination. If the child can plausibly explain why he or she wants or does not want a return of additional findings, then this expression of will should be included in the consideration regarding the return, even if the child is not yet capable of giving consent. To illustrate directly: There is an ethical difference whether a toddler gladly eats spinach, which is considered good because it is healthy for the child, or resists it with all his or her might.

5.7.5 Child welfare in concrete decision-making situations

In concrete decision-making situations in medicine, it is necessary to determine the best interest of the child in order to do what is good for him or her. The concrete determination of the best interest of the child must answer the question of how important aspects, i.e., health, subjective well-being, and good relationships with family members, can best be realized, protected, and promoted in the concrete situation. This involves protecting and promoting the relevant rights of the child (since central aspects of the best interest of the child are also formulated and recognized in the form of rights). Beyond respecting these rights, the individual characteristics including the child's interests and will, as well as situational and contextual aspects, should of course also be taken into account in order to determine what is best for the concrete individual child in the specific situation. In doing so, different aspects of the child's best interest may need to be balanced and weighed against each other, also taking into account the different temporal dimensions of the child's best interest (present/short-term, medium-term, and long-term) where appropriate.

In the question of the return of additional findings in minors, the complexity of the best interest of the child in all its facets must thus be taken into account as much as possible. In addition to interests and rights directed at the *physical well-being*, interests and rights directed at the *psychological and social well-being* of the child must also be considered and weighed against each other. Equally, the directly and exclusive interests of the child must be balanced against the child's interests in his or her relationships with family members. Furthermore, future-oriented interests and rights of the child must be balanced with those relevant for the present.

Two substantive aspects of the best interest of the child require special ethical consideration because of their particular relevance to the question of returning additional findings in minors: the health of the child and the child's interest in the well-being of his or her family.

5.7.5.1 Child health

The child's health is to be understood in any case as an elementary aspect of the child's best interest. Health is of such great importance for the child that it is ethically justified to attribute a right to health to the child. It should be noted that health is a complex concept, especially with regard to children with their own developmental dynamics. Additionally, health is to be understood not only in physiological terms, but in a comprehensive sense: according to the definition of the World Health Organization (WHO), "[h]ealth is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."[139]

5.7.5.2 Interest of the child in the welfare of his family

The concept of the best interest of the child encompasses the interests of the individual child. This also includes social relationships and, of course, especially the child's relationships with her or her parents and siblings. Moreover, it normally is also in the child's best interest that his or her family and all family members are doing well (economically, financially, socially, etc.), since otherwise the child's well-being is likely to be negatively affected.

Thus, the child has an indirect benefit from the return of additional findings if it informs the parents about their own risk of disease or encourages them to conduct their own genetic examinations. This applies in particular to additional findings regarding medically actionable diseases.

[139] WHO: Constitution of the World Health Organization https://www.who.int/about/governance/constitution (last accessed July 6, 2020).

In this way, a serious illness of one of the parents can be prevented or at least treated better. The same applies to possible siblings, who can also benefit from knowledge about a possible inherited predisposition to a disease. Furthermore, genetic knowledge can possibly form the basis for further (informed) family planning by the parents, which is in the interest of the affected child insofar as it makes it easier for the family to better prepare for possible future challenges.

Despite the aforementioned connection between the best interest of the child and the interests of the family, interests of parents or siblings should not simply be understood by definition as parts of the best interest of the child. There may also be tensions between the best interest of the child and certain interests of family members. If this is the case, the first step is to simply identify this tension as such (rather than, for example, understanding all interests of the family as parts of the child's best interest by definition). In a second step, it must then be considered whether and how a balance can or must be struck between the conflicting interests of the child on the one hand and the interests of family members on the other.

5.8 The right to an open future

The right to an open future is a moral right well established in the ethical literature. It refers to the right to be able to exercise relevant options for taking action in the future, which must not be restricted by others at a young age (Feinberg 1992). More precisely, the concept of the "right to an open future" is an umbrella term for the right of the child to know that certain rights, which it can in fact only exercise in adulthood, are secured until then. In addition to other questions concerning the conception of the right to an open future,[140] the question arises as to what degree of openness can be implemented at all, i.e., what options for action can and must be kept "open" in order to do justice to the right to an open future. This question is relevant because many decisions parents make for their children may preclude later courses of action for the child (Garrett et al. 2019; Wilfond et al. 2015). As a guide to what decisions made by parents are compatible with their children's right to an open future, we assume here that one goal of parental actions should be to keep the child's later options for action and decision-making open, to the extent they reasonably can, and to protect or strengthen capacities for a self-directed life.

[140] Part of the debate about the right to an open future concerns whether this is a positive claim right, which obliges parents, for example, to actively enable their child to have as many options for action in the future as possible, or rather a negative defensive right, which obliges parents to restrict as few options for action as possible for their child (Lotz 2006; Millum 2014).

The right to an open future is affected by the return of additional findings in several areas:

(1) *Health* as an important prerequisite for important future options for action and areas of life.

(2) *Knowledge* (and thus also information about one's own genetic disease predispositions) as a basis for dealing with one's own health and disease risks as well-informed and actively as possible within the framework of one's own individual life plans.

(3) Future *informational self-determination* and, related to this, the *right not to know.*

In times of steadily increasing digitization and particularly with a regard to the topic of this position statement, the informational dimension of the right to an open future (future informational self-determination) is particularly relevant, which is why it will be briefly discussed in more detail here. If the right to an open future generally guarantees the child as a future (mature) person the greatest possible leeway in the future shaping of his or her life, then this also applies to the area of privacy and personal data and information. In this area, too, the child should still be able to make as many important decisions as possible for himself or herself in the future, when maturity is reached. To bring this area of the right to an open future into one term, we will speak below of a specific *right of the child to an open informational future*. This right secures both the possibility of being able to decide as freely and independently as possible who has access to what kind of personal data and information about him or her (informational self-determination), and also about what data and information he or she wants to know about himself or herself and also does not want to know (right not to know, see Chapter 5.9).

It is important to realize, especially with regard to the handling of additional findings, that the right to an open future, as well as the specific right to an open informational future, includes but also exceeds the right not to know. This is shown by the fact that the return of an additional finding to the parents does indeed affect the open *informational* future of the child, in that the child will not be able to make this decision of passing on the information himself. Similarly, causing a child to be informed of a genetic predisposition to disease at a particular time affects the child's right not to know. On the other hand, informing the child's par-

ents or the child himself or herself about a particular genetic disease predisposition may also be helpful or beneficial to other aspects of the child's right to an open future. Thus, at the time of maturity, the information may provide the child with a better information basis to effectively plan and shape his or her life and manage his or her health risks.

As far as the application and interpretation of the right to an open future is concerned, current rights and legitimate interests of the child must also always be respected (see Chapter 5.7). This may outweigh the right to an open future, for example, if a decision that affects the right to an open future is necessary to ensure the health and well-being of the child or his or her family at the current time. In such a case, the child's right to health (through the best possible treatment) or the legitimate interest in the well-being of his or her family (see Chapter 5.7.5) may outweigh the right to an open informational future. This applies, in particular, because (the best possible) health or an intact family are prerequisites for the child to be able to exercise other autonomy rights in the future. With regard to the design of the informed consent process, including the envisaged return options for additional findings, the ethical consequence above all calls for exercising caution if the right to an open future is understood as narrowly as a right not to know. Also, the right to an open future can and should not necessarily be understood as an argument against the return of additional findings in childhood.

5.9 The right not to know

In debates about genetic predisposition knowledge in general (e.g., through targeted genetic testing) and in particular in the context of the return of additional findings, the right not to know always plays a major role. This right states (in this context) that a person may decide for himself or herself to receive or not to receive genetic information about himself or herself and thus about his or her (future) state of health, even if refusing to receive this information could have potentially negative consequences for the person himself or herself.

From an philosophical standpoint, there are different approaches to justify the right not to know, e.g. as an expression of autonomy (Andorno 2004) but also as an expression of privacy in the sense of a freedom from interference in one's own life decisions from the outside, or a right to be left alone (Laurie 2014). The existence and especially the scope of a moral right not to know is quite controversial in the ethical-philosophical literature (Dive 2021). Despite these debates, the right not to know

plays an important role in German jurisprudence, as it is recognized in the current German legal system (see Chapter 4.3.6.3). From an ethical perspective, we understand and recognize the right not to know as part of a person's autonomy rights and specifically as part of a person's right to informational self-determination[141] and an open informational future. There are several possible ways in which the right not to know plays a role in the context of this position statement:

(1) As a right of (mature) minors capable of self-determination.
(2) As part of the right to an open informational future for non-self-determining minors who are currently unable to exercise their right not to know themselves.
(3) As part of the *parents*' informational rights concerning their state of health. This right is always indirectly affected when doctors inform the parents of minor patients (without the capacity to consent) that their biological (and therefore genetically related) child has a certain genetic predisposition to a disease (see also Chapter 5.10).
(4) As the right of possible siblings (minor or adult, capable or not capable to consent) of the child concerned, if the return of an additional finding is also relevant for them.

Insofar as we understand the right not to know as an expression of personal autonomy, it can only be granted to persons who are capable of making autonomous decisions. If, however, this ability is not existent, e.g., in the case of young children, no present right not to know can be granted either, since these children are not capable of understanding the implications of a decision for or against the preservation of genetic predisposition knowledge. However, children have a future right not to know as part of their right to an open informational future (see Chapter 5.8). In this case, the parents exercise their children's right to future knowledge or non-knowledge by proxy, i.e., in the best interests of the child, and must decide whether to leave the right intact or to restrict it in favor of other aspects of the child's welfare and rights.

In connection with exercising the child's right not to know by proxy by his or her parents, it should be pointed out that the parents' own right not to know is not part of *role of parental proxy.* In exercising this proxy role, their own right not to know must *not* occupy *any* space (Hens et al. 2011) unless parents also potentially gain indirect knowledge and information about themselves through information or knowledge about their child. That is, parents, by virtue of their normative role and responsibil-

[141] Cf. also Räikkä (1998) and Takala (1999).

ity for the child, have a fundamental duty to take note of all information about their child's health and illnesses, as well as about the child's diagnostics and treatment options, if it is significant and helpful in protecting, restoring, or promoting their child's health. Parents may not, for example, refuse to be informed about the diagnosis of a disease of their child because the knowledge of their child's disease would be a psychological burden for *them.* A special constellation, which makes further ethical analysis and evaluation necessary, only arises if information about a genetic characteristic of the child, e.g., a genetic predisposition to disease, may also imply certain information or probability inferences about genetic characteristics, in particular predispositions to disease, of the parents themselves.

Given this particular ethical constellation to be expected in pediatric genetics, the question arises as to how to deal with such a situation and how to balance the conflicting rights and concerns of the child and the parents. We argue here for a fundamental primacy of the best interest of the child, in particular the child's right to health that should, in principle, be given priority over the parents' right not to know. There are several moral reasons for this primacy:

(a) The role of parents is ethically determined by their responsibility to protect and promote the best interest of the child, especially the elementary aspects that include the child's health. In principle, parents must fulfill this responsibility and perform the corresponding tasks, even if this means sacrificing their interests or limiting their rights.

(b) When it comes to the return of genetic information that may provide a relevant medical benefit to the child, the benefit to the child will usually be expected to outweigh limiting the parents' right not to know that is indirectly associated with this return. This becomes clear, for example, if the return of an additional finding triggers a readily feasible and medically effective prevention of a disease that, if it develops (regardless whether it is discovered or not), can take a severe course and thus endanger the child's quality of life, his or her well-being, and the exercise of his or her life chances and rights, or even his or her life.

(c) Even if the genetic information refers to a genetic trait of the child, with which only a certain probability of the development of a disease

is associated, it is personal information that directly and certainly refers to the child. Usually, it is not possible to say with the same degree of certainty from the same information whether one parent has the same genetic trait. Instead, it can only be concluded that there is a certain probability that the genetic trait is also expressed in one parent.

These considerations and assessments of the right not to know and of possible tensions between the child's right to the best possible health care and the best interest of the child on the one hand and the right not to know of the (future) child and the parents on the other are an argument for *not offering* parents a particular option in the informed consent process: Parents should *not be* given the option of refusing the return of additional findings regarding medically actionable diseases with an early need for medical action that may be potentially important for the child's health (see recommendation B1 in Chapter 6.2.3).

5.10 Relevance of the additional finding for parents and siblings

The fact that genetic variants can be both the result of a so-called *de novo* mutation and inherited from the parents brings with it the possibility that – in the case of inheritance – both the parents of the child under investigation and potential siblings may be affected by the same mutation. We have already pointed out in Chapter 5.7.5.2 that the involvement of family members is also relevant for the best interest of the child. In this Chapter, however, we are concerned exclusively with the interests and rights of family members (in the sense of biological kinship) affected by the return of additional findings. Family members may be affected in different ways, depending on the gene variant discovered:

a) A *dominant hereditary predisposition to disease* that is discovered in the child may have been directly inherited from a parent who is him- or herself affected by the same predisposition. Realistically, the return of such additional findings is relevant for the respective parent, especially in the case of additional findings concerning diseases with a late need for medical action, since an intervention in the parent should possibly be started immediately. In contrast, diseases with an early need for medical action are likely to have already manifested themselves in the parents due to their age, if they are affected by the corresponding gene variant and if it manifests itself in a disease in them at all. Furthermore, siblings may also be affected by a dominant hereditary predisposition to the disease.

b) An *autosomal recessive inherited disease predisposition*, which is detected in the child based on two altered gene copies, occurs when both parents are carriers of this disease. In this case, there is no risk of disease for the parents themselves, but the examined child's siblings have a high probability of developing the same disease or predisposition, and that they will therefore, like the examined child, benefit from the return of an additional finding. The information about both parents being carrier of an autosomal recessive inherited disease predisposition can also be relevant for further reproductive family planning, since future siblings would also be affected by the predisposition

c) A *disease carrier status* that is detected in a child may have been inherited from one or both parents, who either have the predisposition themselves (see a) or are at least carriers (see b). In both cases, there may be consequences for siblings (cf. Chapter 3.4).

When assessing the extent to which the return of the additional finding may be useful for the family, in addition to the relevant criteria previously mentioned (Is the disease treatable? How severe is the disease? When does the disease usually occur for the first time?), the level of probability that the mutation found in the child is a de novo mutation should also be clarified. For this, the family history must be considered. Ideally, the genetic predispositions of parents and child would always be investigated together in a so-called trio sequencing. However, this is associated with high costs, which are currently usually not covered by health insurance companies. Thus, in most cases only a certain probability can be assumed that other family members are affected by an additional finding of the examined minor.

What is the ethical relevance of the involvement of parents and siblings? Since family members may be affected by the additional findings in the manner described above, their rights and interests are also affected by the return of these additional findings:

- **Health:** The return of an additional finding can be useful to parents and (future) siblings in that they are informed about possible predispositions to disease, for which preventive programs and/or treatment options exist. On the other hand, however, there is also the risk that parents and siblings will experience psychological distress as a result of the return (cf. Chapter 5.15.3).

- **Right not to know:** If it turns out that the genetic variant discovered in the child is an inherited mutation, then parents' informational rights – including their right not to know (Chapter 5.9) – must be taken into account when considering whether to return an additional finding.

The possible relevance of additional findings for the family of the minors concerned should always be made emphatically clear in the informed consent process, so that parents or mature minors can include this in their decision regarding the return of additional findings, especially if the return has a health benefit for family members (cf. recommendation C3) or is relevant for further family planning (cf. recommendations D1 and D2).

5.11 Parental decision-making authority

From a child ethics perspective, parenting should be seen as a social-normative role defined by the parents' *responsibility* for the child's well-being and rights (Archard 2010; Schickhardt 2016), which they must protect and promote (within a certain margin of discretion). Parents' power over their children is tied to this purpose. Parents do not have genuine *rights* vis-à-vis their children in the sense that one may freely dispose of something according to one's own interests and preferences (Archard 2010, S. 44; Schickhardt 2016). If their child is undergoing medical treatment, it is therefore the parents' responsibility to safeguard the child's interests and rights and to protect and promote them (to the best of their ability), also through appropriately guided consent or refusal regarding the performance of medical measures on their child. Certain elementary aspects, such as physical and mental health, must be recognized as important components of a general and fundamental understanding of the best interest of the child and the rights of children; they are not simply subject to parental interpretation (see Chapter 5.7.1).

Since medical treatment often involves complex issues that parents are not usually able to navigate independently, they must consider the information they receive from physicians and rely on good medical information and counseling in their search for the best decision for their child. Only when an adequate understanding of the medical situation can be assumed is it plausible to assume that parents know best what is in their child's best interest.

A parental decision regarding medical measures affecting the child (and

thus also the refusal of important information) may be questioned if it seems likely that the parents have not understood important information or contexts or if they are not acting in the child's best interest from a medical point of view. In this case, the treating physicians not only have the right but also the duty to assess the parents' reasons and motives and to enter into further discussions about the best course of action for the child. If parents and physicians are still unable to agree on a course of action that, from a physician's point of view, is in the best interests of the child and if the child is threatened with serious avoidable negative consequences for health and development, physicians can and must initiate proceedings with the help of the youth welfare office, which can replace the specific parental decision if necessary. In the ethical literature, various criteria are discussed under which circumstances parental decisions may or must be overridden.[142] At a minimum, such overriding is justified and even required if it avoids potential harm to the child and, therefore, the serious violation of fundamental needs and interests of the child (Gillam 2015; Diekema 2004; Diekema 2011; Gillam und Sullivan 2011; Hain 2018). It should be noted here that overriding parental decisions may also involve harm to the child, which must be weighed against the harm potentially resulting from the parental decision itself. The answer to the question of whether parental decision-making authority can be overridden in a particular situation must always be guided by the goal of minimizing the expected net harm to the child (Diekema 2004; Gillam 2015; Winters 2018; Vears 2021).

What does this mean for the question on returning additional findings? It is conceivable that parents do not want to receive predictive knowledge about their children and thus also no additional findings. There may be different reasons for such a refusal, e.g., fear of the child being perceived as a "healthy ill" or the right not to know. However, the refusal of additional findings, if they indicate a predisposition to a medically treatable condition, may result in the failure to perform a preventive examination or treatment that is medically necessary or at least reasonable, thereby causing harm to the child (harm A). On the other hand, it must be considered that overriding the parental will can also generate harm, e.g., in the social fabric of the family (harm B). Harm A and harm B must now be weighed against each other.

When returning additional findings regarding medically actionable diseases with an early need for medical action, we assume (especially in the case of severe diseases with high penetrance) that harm A always

[142] A good overview is given by McDougall und Notini (2014).

outweighs harm B, which is why we recommend that such additional findings always be returned (see recommendation B1).

5.12 The medical obligation to the individual welfare of the child

Physicians in general have the professional ethical obligation to always consider the individual "health and well-being [of their] patient [as their] first consideration" (World Medical Association 2017). *Salus aegroti surprema lex* – the health of the sick is the highest law – as a traditional formulation of the medical ethos reads. Even today, a central part of medical professional ethics calls for physicians to "use [their] competence in the best interest of the patient" (Pellegrino 2002). Loyalty and fidelity to their patients are important professional virtues and norms in health care (Beauchamp und Childress 2009). This professional ethical obligation also applies to pediatricians toward their child patients. There is also some reason to believe that this is particularly true for pediatricians, as pediatric patients are generally a vulnerable patient population.

5.13 The cost to physicians and the health care system

Physicians always have to use limited resources, be it financial means for medication, scarce time allotments for shared diagnostic equipment (e.g., MRI) in clinics, or laboratory capacities. A particularly scarce resource is the time that physicians can spend with their patients. Physicians are obliged to use the scarce resources available to them both for the benefit of their current patients and for the benefit of future patients. Time spent on the needs of current patients is thus potentially at the expense of the time available for the care of other (future) patients. In the field of human genetics, the time required for (mandatory and detailed) *information and counseling is* generally particularly high. This is especially true in the field of (genetics in) pediatrics, which already requires a comparatively large amount of time. Pediatricians have to use limited resources in the interest of all patients. Therefore, factors such as effort, feasibility, and practicability of recommendations for returning additional findings in minors play a role, which must be reflected in corresponding recommendations (cf. recommendations E1, E2, F1, and F2).

5.14 Freedom and value of research

Additional findings do not only occur in the treatment context but can also be discovered by researchers or researching physicians, for example, when data from genetic or genomic analyses, which originate from

the treatment context, are used secondarily for research. Especially in the translational context, in which this position paper claims to be applicable, it is quite likely that additional findings will be discovered in the course of research. Similar to the situation for the treating physicians (Chapter 5.13), the return of additional findings also represents a certain additional effort for the researchers involved or the physicians conducting the research, which may conflict with their right to freedom of research and possibly with their obligation to conduct research (e.g., at university hospitals). Furthermore, it is also in the interest of society and future patients that researchers and researching physicians are able to carry out their work as well as possible. When making recommendations on the return of additional findings, the possible additional work for researchers and researching physicians must therefore always be weighed against these conflicting rights and interests. At a certain point, a strong regulation or the burdening of research by considerable additional effort can therefore also be disproportionate and unjustified.

5.15 On the specific assessment of harms and benefits of returning additional findings for affected minors

In the previous sections of this chapter regarding ethics, important ethical aspects have been listed, in particular the moral rights and obligations of the persons involved. These aspects are fundamental to the design of the informed consent process and the related question of what categories of additional findings should be offered for return, and how. It is precisely in this respect that said aspects constitute grounds for the recommendations listed below. Some specific aspects listed, such as children's (lack of or limited) capacity to consent or their right to participate and have a say, obviously relate primarily and almost exclusively to the informed consent process. However, many of the other aforementioned ethical aspects that directly concern the children are also important points of orientation *for the concrete evaluation of the potential benefits and potential risks of the return of a concrete additional finding for an affected child*. Since, in the spirit of a child-centered approach, the concerns of child patients must be paramount when evaluating the benefits of returning an additional finding, below, we summarize the most important ethical aspects listed above, illustrating more concretely how they are affected by the return of an additional finding.

5.15.1 Impact of a return on the child's autonomy

The return of additional findings affects the autonomy of the child insofar as knowledge about one's own disease predispositions enables

future autonomous health decisions, especially in the case of knowledge on predispositions for medically actionable diseases. However, knowledge based on the return of additional findings can also lead to better informed "life plans" and life plan decisions and thus be autonomy enhancing. *(→ life planning benefits)*

5.15.3 Impact of a return on the child's physical health

The return of additional findings regarding medically actionable diseases can be of great benefit to the affected child in that appropriate preventive and/or treatment measures can be initiated. In addition, the knowledge of a genetic predisposition (regarding medically actionable as well as medically non-actionable diseases) can avoid unnecessary and burdensome diagnostics in the future. The potential benefits of genetic predisposition knowledge depend on what type of disease predisposition is involved (treatable or not, penetrance, expressivity, burden of treatment if treatable, and likelihood of success of same). Likewise, burdens and effectiveness of any screening that may be triggered by the return of an additional finding must be considered. *(→ medical benefit)*

5.15.3 Impact of a return on the child's mental health

Knowledge about the possible burden of predictive knowledge (from targeted genetic tests as well as from additional findings) is relatively limited (see infobox 1). It can be stated that negative psychological effects of the return of the results from *genetic tests are* generally rather low in the existing studies. In individuals in whom a relevant burden could be determined directly after the return of results, this burden was generally only a temporary phenomenon. Both adults and children showed little lasting psychological impairment or burden from genetic test results in the studies mentioned, although in the case of children, a non-significant increase in depressive symptoms was found in some studies, some of which could be measured over a period of up to 12 months. There are few studies that address the question of whether knowledge of disease carrier status is a burden for minors. However, these indicate that a burden is rather unlikely. While the above findings refer to children and adults in the context of targeted genetic testing, only a few small, predominantly qualitative studies of *adults* exist to date with respect to the *impact of additional findings*. In these studies, similar psychological effects (or lack thereof) were observed as in studies on the psychological effects of targeted genetic testing. In some cases, positive effects from the return were even reported. Nevertheless, because the evidence is only rudimentary, it is difficult to say whether these results are, first,

valid and generalizable to adults and, second, transferable to children. This relatively weak evidence regarding the psychological burden of the return of additional findings (which may differ from the burden of genetic predisposition knowledge from targeted genetic tests)[143] suggests, especially due to the individuality of each patient, that caution should be exercised when estimating possible damage from the return of additional findings; in other words, the possibility of psychological distress should not be excluded.

Empirical studies on the possible burden of genetic knowledge

Impact of predictive knowledge on adults

Crozier et al. (2015) in a meta-study of psychological effects of presymptomatic predictive mutation testing for Huntington's disease in at-risk individuals, report no significant differences over the long term (i.e., after an initial increase in feelings of hopelessness) between those who tested positive and those who tested negative for the disease. This result is particularly noteworthy because Huntington's disease is a non-treatable disorder whose onset is highly predictable with genetic testing (high penetrance). Heshka et al. (2008) examined the psychological impact of genetic predisposition knowledge in presymptomatic adults with a multifactorial genetic disorder in adulthood in their family history in a systematic review. A large proportion of the studies reviewed by Heshka et al. involved different types of cancer risk. While an initial burden could often be detected after positive findings were reported, this was usually measurable for only a few weeks or months. As a caveat, however, it should be noted that both Crozier et al. and Heshka et al. consider the possibility of self-selection bias likely, which could bias the outcome of the studies toward a more positive perception of the impact of genetic knowledge. Furthermore, Crozier et al. (2015) suggest that the psychological instruments used may not have been sensitive enough to reliably measure subclinical forms of distress.

Effects of predictive knowledge on children

Wakefield et al. (2016) examined the effects of predictive knowledge on children tested for various genetic predispositions in a systematic review. In most of the studies examined, there was generally no significant increase in anxiety, depression, or distress after a positive result (neither in relation to children with a negative result nor in comparison of

[143] There are certain reasons to assume a difference between the return of results of targeted genetic testing and the return of additional findings. While a targeted genetic test is usually performed on the basis of a concrete suspicion (e.g., due to unexplained symptoms or due to the occurrence of the disease in the family), patients who receive additional findings are already in a disease situation (which indicated the genetic diagnosis in the first place) and additionally receive a finding about possible future diseases. Furthermore, targeted genetic testing is also less likely to unexpectedly affect family members, as these tests are often performed based on a family history, so the disease is usually already known in the family (Dondorp et al. 2021).

before and after the result was reported). However, five studies found a nonsignificant increase in depressive symptoms in children (some up to 12 months after diagnosis (Codori et al. 2003)). There was also evidence that the development of these depressive symptoms was favored when parents were affected by the disease in question.

*Implications of predictive knowledge in the context of additional findings for adult*s

On the question of the specific effects of genetic predisposition knowledge generated in the context of additional findings, no large reviews exist to date but rather only a few, predominantly qualitative, studies with limited explanatory power. Lewis et al. (2016) reported in interviews (N=29) that healthy study participants who received feedback of genetic predisposition knowledge responded predominantly neutrally to positively to the feedback, and that those who initially felt negative effects of the knowledge became neutral to positive again toward this knowledge after a few weeks. In a small study (N=35 of whom only 7 received an additional finding), Sanderson et al. (2017) report that healthy study participants generally responded positively to neutrally to the return of additional findings, but that there were isolated cases in which the return initially caused concern. Wynn et al. (2018) examined differences in anxiety and depression between individuals who received health-related additional findings (i.e., return of additional findings regarding predisposition to serious illness) (N=40) and two other groups: individuals who had no or low personal disease risk (N=67) and individuals who were not sequenced (N=85). No difference in mean scores of anxiety and depressiveness was demonstrated across the three groups, although the authors observed a trend among those who had received health-related additional findings to use specific coping strategies. In addition, subjects with health-related additional findings reported feeling empowered by knowledge gained from the additional findings. Nambot et al. (2021) conducted interviews with cancer patients (N=10) who had additional findings returned as part of a disease-specific genetic diagnosis. The patients reported that they had not experienced any negative psychological effects one month after the return. In an interview study with patients who had either a predisposition to an oncological disease (N=10) or a predisposition to a heart disease (N=10) Schoot et al. (2021) reported that most participants were initially shocked by the return of the additional finding, but that this feeling gave way over time to an appreciation for the knowledge, especially with regard to planning possible preventive measures.

Special case: disease carrier status

It has been shown that knowledge of a disease carrier status for severe diseases can lead to psychological distress, e.g., in the form of guilt, in adults who already have children suffering from the very disease for which they themselves are carriers (Lewis et al. 2011). Relatively little is known about the impact of knowledge of disease carrier status in children, as disease carrier status is usually not tested until adulthood. However, the few long-term observations of children specifically tested for carrier status suggest that psychological distress to children is unlikely (Jarvinen et al. 2000b; Jarvinen et al. 2000a).

Infobox 1: Empirical studies on possible burdens of genetic knowledge

5.15.4 Impact of a return on the child's interest in the well-being of his or her family

Family members can also have a medical benefit from the return of additional findings. This represents a benefit for the child him- or herself, who has an interest in a family that is as healthy as possible *(→social benefit).* At the same time, however, the psychological burden of genetic knowledge on the parents could be a burden for the family and thus also for the child.

5.15.5 Impact of a return on the child's right to an open future

The child's right to an open future is affected by the return of additional findings on the one hand with regard to his or her right to an *open informational future,* since the return generates knowledge in a certain way (stored in an electronic patient record), which is the subject of future informational self-determination. This knowledge may be used in a way that is abusive to the detriment of the child or result in disadvantages in the area of insurance. For example, under the GenDG (Section 18), insurers may not require a genetic or genomic examination when taking out a life insurance policy, nor may they require the results of genetic or genomic tests that have already been performed to be communicated. However, this only applies up to an agreed insurance benefit of a €300,000 single benefit or a €30,000 annual annuity. The existence of information about any disease predispositions that must be disclosed above these amounts could, for example, lead to higher premiums or even to the person in question not being insured. Furthermore, the right to an open informational future is also affected by the return of additional findings in the sense that the return violates the (future) *right not to know,* since the child can no longer decide *against* knowing later, i.e., in adulthood.

On the other hand, knowledge of genetic predispositions is also an important factor for *open life paths* (see Chapter 5.15.1), insofar as the (future) health of the child can be significantly influenced depending on the type of predisposition reported. Health, in turn, is a prerequisite for being able to take certain life paths at all. Furthermore, knowledge of genetic predispositions forms the basis for informed decisions about possible life paths and can provide information about the options available.

6 RECOMMENDATIONS

In this chapter, we provide recommendations on how the informed consent process should be structured with regard to the handling of additional findings in minors. The recommendations thus refer to what should be discussed and clarified with the minors concerned and their parents prior to genetic or genomic testing, i.e., before additional findings may occur. Based on the criteria discussed in the previous chapters, we provide in the following Chapter 6.1 some *general recommendations* on how to respond appropriately to the challenges associated with additional findings. In addition, we address *special cases* and explain how we believe they should be handled. In the next step (Chapters 6.2 to 6.6), we make *specific recommendations on how to deal with the different categories of possible additional findings,* i.e., how to provide information about the different categories and what options for return should be made available for parents or mature minors to choose from. Four of the five different categories of possible additional findings result from the criteria "type and relevance of the additional finding" (see Chapter 3.2) and "onset of disease and time for medical action" (see Chapter 3.3). The fifth category refers to additional findings regarding a disease carrier status (see Chapter 3.4).
Thus, the overall categories for classifying the additional findings are as follows:

- Additional findings regarding **medically actionable diseases** with an **early** need for medical action
- Additional findings regarding **medically actionable diseases** with a **late** need for medical action
- Additional findings regarding a **disease carrier status**
- Additional findings regarding medically **non-actionable diseases** with **early** onset
- Additional findings regarding medically **non-actionable diseases** with **late** onset

All recommendations are based on the aspects explained in the previous chapters that are relevant to the handling of additional findings in minors. In addition, a (general) benefit-harm assessment is carried out within the scope of the specific recommendations on the feedback of different categories of additional findings. For this purpose, the aspects explained in Chapter 5.15 are used and examined further: (1) which **benefit** arises for the child from a return of additional findings, be it (i)

the possible *medical benefit* or (ii) the *life planning benefit* (the medical benefit and the life planning benefit serve to *create or realize open life paths, respectively*). Furthermore, (iii) the *social benefit* is examined, which results for the child if the parents or (future) siblings benefit significantly from the return of additional findings. Contrasting this benefit, (2) the potential **harm** of the return of additional findings is also considered. This harm can potentially (although rather unlikely) arise (a) from *psychological distress* due to predictive knowledge. In addition, there is always (b) a possible impairment of the *right to an open informational future* and (c) a violation of the *right not to know*.

Weighing the potential benefits and harms, recommendations are made for each category of additional findings with respect to their return to the *parents of younger children* as well as to *mature minors.*

Important notes:

1. *The recommendations given here describe what the EURAT Group considers to be the correct procedure for the informed consent process with regard to additional findings. The aim is to anticipate potential conflicts and thus, if possible, to avoid them. The procedure recommended here also serves to minimize the risks identified in the legal analysis. Conversely, this means our recommendations do not claim to instruct practitioners on what to do with additional findings that have already occurred. The procedure to be followed in the event of a specific occurrence of an additional finding is always bound by what was agreed in the informed consent process.*
2. *The recommendations made here necessarily deal with rather general abstract categories that are applied to the persons concerned and/or their parents in the informed consent process. In the specific case in which an additional finding occurs, it is the responsibility of the treating physician to classify it in one of the categories and to assess the concrete benefit of a return of the additional finding.*

6.1 General recommendations for the return of additional findings

6.1.1 Uncertainty of the additional findings

As already explained in Chapter 5.2, genetic findings are always subject to a certain degree of uncertainty, insofar as they only indicate the probability that a corresponding disease will develeop. In order to keep the burden on patients and their parents as low as possible and to minimize

the risk of a “false alarm”, the following basic recommendation can be made:

Recommendation A1

Only additional findings that are clinically validated and have high penetrance should be returned.

6.1.2 Communication challenges

Due to the uncertainty of genetic findings, both the information on possible additional findings and the possible return of the same entail certain challenges in communication. For example, it may be difficult for individuals without experience with genetic predisposition knowledge and without prior medical knowledge to adequately grasp the consequences of a return of additional findings and thus to make a decision that corresponds to their own values. In the concrete return situation itself, one should also keep in mind that information about disease predispositions can be emotionally overwhelming, especially when one considers that many people find it difficult to deal with probabilistic knowledge.

Thus, the following recommendations result:

Recommendation A2

Both the information on the possibility of additional findings and how to deal with them, as well as the return of these additional findings, must always be provided by trained professionals who can adequately address the questions of parents and their children. Beyond the clinical context, i.e., when providing information and returning additional findings in the research context, the requirements of the German Genetic Diagnostics Act should also be taken into account.

Recommendation A3

In addition to the regular informed consent process, easily understandable explanatory material should be made available that answers the relevant questions in layman’s terms and in a compact form.

A proposal for the explanatory material addressed in recommendation A3 can be found at the end of this position paper in the form of an infor-

mation brochure for parents (Chapter 8.1) or mature minors (Chapter 8.2). Furthermore, we make a proposal for the actual patient information text regarding the handling of additional findings (Chapter 9).

6.1.4 Special case: Mature minors

When discussing mature minors, this term refers to minors who have been determined to have the capacity to consent to the decision regarding the return of additional findings (for capacity to consent, see sections 4.2.3 and 5.4). They are therefore formally free to make this decision on their own, i.e., without the consent of their parents. Nevertheless, in order to avoid conflicts within the family in particular, it is advisable to strive for joint decision-making with the parents, even in the case of mature minors.

Thus, the following recommendation results:

Recommendation A4

As part of the informed consent process for mature minors, parents should be involved in decision making regarding the return of additional findings whenever possible.

6.1.4 Special case: Findings relevant to treatment

In the course of genetic or genomic analyses, findings may arise that do not meet our definition of additional findings listed in Chapter 3.1 insofar as they are relevant to the treatment of the disease for which the child (or adolescent) is currently being treated. Findings that are relevant to current treatment are explicitly excluded from our definition of additional findings. A possible real-world example of such a treatment-relevant finding is a pathogenic variant in the *TP53* gene in a child with a brain tumor. Individuals with a TP53-associated tumor predisposition syndrome, known as Li-Fraumeni syndrome, should not receive therapeutic radiation whenever possible because of the increased risk for the occurrence of secondary malignancies in the radiation field. Findings of this type are directly relevant to current therapy and their return (at least to treating physicians) is urgently required. In the entire informed consent process, there must be no doubt that all findings that may be relevant to the diagnosis or treatment of the child's current illness will be reported back to the treatment team and integrated into the diagnosis and treatment of the sick child. Accordingly, parents must not be offered options in the consent process that allow them to refuse the return of findings that are relevant to the treatment of the child's current condition.

Thus, the following recommendation results:

Recommendation A5

Findings that are of potential relevance to the current treatment must always be returned (to the medical staff initiating the examination). The parents must be clearly informed that they are not offered the option of deciding whether to receive such findings (i.e., they are not given the option of rejecting such findings), but that such findings will be reported to the treatment team as standard and included in treatment.

6.2 Additional findings regarding medically actionable diseases with an early need for medical action

6.2.1 Possible benefit from a return

The return of additional findings regarding medically actionable diseases with an early need for medical action can initiate appropriate preventive examinations or treatments at an early age. This may prevent a disease or at least mitigate its consequences. In addition, the return of an additional finding can, possibly, facilitate the diagnosis of a disease, if, for example, non-specific symptoms already occur (*medical benefit*). Particularly in very young children, the return of additional findings can have *life planning benefits*, as the parents can prepare themselves and their child for an expected disease. Medical benefits and life planning benefits serve to *create or realize open life paths*. In addition, knowledge of disease predisposition can enable conclusions to be drawn about possible predispositions of relatives and thus a medical benefit for them, thereby indirectly benefiting the child (*social benefit*). The magnitude of the benefit of the return of additional findings regarding medically actionable diseases with an early need for medical action varies with the corresponding disease predisposition, e.g., as measured by penetrance and disease severity: The more severe and likely a possible disease that can be prevented or at least treated, and the more effective the respective treatment, the greater the benefit.

6.2.2 Possible damage due to a return

The return of additional findings regarding medically actionable diseases with an early need for medical action impairs the *right to an open informational future* and violates the *right not to know*. Possible damage in the sense of *psychological distress* is possible, although rather unlikely. Furthermore, burdens may arise from any preventive medical examina-

tions, which, depending on the nature of the predisposition to the disease, may be burdensome in different ways.

6.2.3 Weighing the benefits and harms

The benefits of a return of additional findings, here, outweigh the potential harms, especially for severe diseases with high penetrance. This assessment may be different for disease predispositions with low penetrance and disease severity and, at the same time, a high distress, e.g., due to preventive examinations. It is within the physician's discretion to determine whether the return of a particular additional finding is in the best interest of the child, as recommended by us. Parents should not be offered an option in the informed consent process whereby they can refuse to receive additional findings regarding medically actionable diseases with an early need for medical action. Accordingly, it must be explained to the parents in the informed consent process that additional findings in this category will be returned if a medical benefit for the child is likely.

Thus, the following recommendation results:

Recommendation B1

As a rule, additional findings regarding medically actionable diseases with an early need for medical action should be returned. Parents should not be offered an option in the informed consent process whereby they can refuse to receive this category of additional findings. Accordingly, parents must be informed that additional findings regarding medically actionable diseases with an early need for medical action will be returned if a medical benefit for the child is likely.

6.2.4 Special case: Mature minors

If adolescent patients are determined to have decision-making capacity, they can exercise their rights themselves. This means they also have the right to decide whether or not they want to be informed of additional findings regarding medically actionable diseases with an early need for medical action (in the event of their occurrence). If mature minors refuse this return, then this decision must be accepted in principle, even if it may appear hardly comprehensible from a medical point of view. In the discussion, the physician should nevertheless point out once again what the potential benefit of the additional findings mentioned can be for the patient (and his or her family) and what potential benefits are excluded by refusing their return. Furthermore, even in the case of mature minors,

joint decision-making with the involvement of the parents is probably the normal case and should always be aimed for in order to avoid intra-family conflicts as far as possible (see recommendation A3 above).

Thus, the following recommendation results:

Recommendation B2

In the informed consent process, mature minors should have the option to refuse the return of additional findings regarding actionable diseases with an early need for medical action. However, in the event of a refusal, the potential benefits of such return to the patient and family members should be strongly emphasized.

6.3 Additional findings regarding medically actionable diseases with a late need for medical action

6.3.1 Possible benefit from a return

The return of additional findings regarding medically actionable diseases with a late need for medical action has no *medical benefit for the child* at the time of return or in the childhood (or adolescence) phase. However, knowledge of a future (in adulthood) medically actionable disease represents a potential future benefit, insofar as appropriate action can be taken at the given time to treat the disease. However, this requires knowledge of the predisposition be made available to the child in the future. Furthermore, knowledge about a possible future disease has a *life planning benefit*. The future medical benefit and the life planning benefit serve to *create or realize open life paths*, although at a later point in time than is the case with additional findings regarding medically actionable diseases with an early need for medical action. Knowledge of the predisposition to the disease can also enable conclusions to be drawn about possible predispositions of family members and thus already indirectly benefit the child if a possibly severe disease of the parents or possibly adult siblings is avoided or treated (*social benefit*). The magnitude of the potential benefit varies with the corresponding disease predisposition measured by penetrance and disease severity but also with the degree of medical actionability.

6.3.2 Possible damage due to a return

The return of additional findings regarding medically actionable diseases with a late need for medical action impairs the *right to an open infor-*

mational future, which may present problems in the future (for example, when taking out life insurance). In addition, the *right not to know* is violated. Possible damage in the sense of *psychological distress* is possible, although rather unlikely. Furthermore, burdens may arise from any preventive medical examinations, which, depending on the nature of the predisposition to the disease, may be stressful in different ways.

6.3.3 Weighing the benefits and harms

The return of additional findings regarding medically actionable diseases with a late need for medical action represents a violation of the rights of the child, which at the present time cannot be contrasted with any medical benefit for the child. However, there is a future medical benefit that would be missed if the relevant information were lost. The weighing of these potential benefits and harms should be left to the child's parents or the mature minor as part of the informed consent process. The risk that medically relevant knowledge may be lost if parents (or responsible minors) decide not to provide feedback should be pointed out in detail there. In the case of mature minors, an attempt should be made to involve parents as far as possible in the information and decision-making process, (see recommendation A3).

Thus, the following recommendations result:

Recommendation C1

Parents or mature minors should be offered the return of additional findings regarding medically actionable diseases with a late need for medical action as part of the informed consent process. Three options should be available: (1) no return; (2) notice of the existence of an additional finding that is not yet relevant for action, with an indication of when medical action is required (i.e., in the case of younger children, when the parents should inform the then adult child that a relevant additional finding exists); (3) return of the additional finding and genetic counseling.

Recommendation C2

As part of the informed consent process for parents of younger minors, the potential benefit of additional findings regarding medical actionable diseases with a late need for medical action for the future adult child

should be emphasized to stress the importance of their return.[144]

Recommendation C3

As part of the informed consent process (for both parents and mature minors), the potential benefit of additional findings regarding medically actionable diseases with a late need for medical action to other family members should always be emphasized to stress the importance of their return.

6.4 Additional findings regarding a disease carrier status

6.4.1 Possible benefit from a return

The return of an additional finding regarding a disease carrier status does not benefit the health of the affected child (*medical benefit*). However, knowledge of the disease carrier status may become relevant for family planning in the future (in adulthood) (*life planning benefit*) and, thus, helps in his or her *realization of open life paths*. With regard to the child's current family members, it should be noted that male siblings in particular, depending on the type of disease carrier status, may not only also be carriers but may sometimes (in the case of x-linked inheritance, see Chapter 3.4) be directly affected by the disease. Thus, the return can generate a *social benefit* in several respects: with regard to the possible medical benefit for siblings, with regard to the life planning of already existing siblings and with regard to the further family planning of the parents. Depending on the type of predisposition (type of inheritance, treatability, penetrance, and severity of the possible disease), the benefit for the child as well as for the family may vary.

6.4.2 Possible damage due to a return

Knowledge of a disease carrier status is not likely to cause *psychological distress,* as it is not associated with any disease, although this assessment may be different in individual cases. However, the return impairs the right to an *open informational future* and violates the *right not to know.*

[144] In the medium term, it would be desirable to strive for a technical solution for the return of additional findings regarding medically actionable diseases with a late need for medical action, for example the entry of information on the additional finding in the electronic patient record, which, for example, indicates at a defined point in time that genetic information exists about which the now adult child can inform him- or herself and which may possibly be relevant to health. Care must be taken to ensure that no information is provided that could indicate whether or not additional findings are actually available, in order to protect the right not to know as much as possible.

6.4.3 Weighing the benefits and harms

The harm caused by the return of additional findings regarding a disease carrier status is likely to be minimal, and the benefit for the child will only arise in the future, if at all, in the context of family planning. However, if family members are affected, there could be an indirect (social) benefit to the child. As part of the informed consent process, parents should be made aware of the various possible benefits (to the family and thus indirectly to the child). Parents should be given the opportunity to receive any additional findings regarding disease carrier status that may be relevant for themselves or for siblings but not those that are unlikely to be relevant for family members.

Thus, the following recommendation results:

Recommendation D1

As part of the informed consent process, parents should only be offered to receive additional findings regarding a disease carrier status of their child if the return may be useful for themselves or the child's siblings.

6.4.4 Special case: Mature minors

As mentioned, the return of additional findings regarding a disease carrier status is not expected to be a relevant burden and at the same time complies with the information rights of the minor who is capable of giving consent. For this reason, mature minors should be given the opportunity to opt for this return as part of the informed consent process. In this context, reference should also be made to the possible involvement of family members as described in Chapter 3.4. With regard to the decision-making process, parents should be involved as much as possible, precisely because information about the disease carrier status is also relevant for them (see recommendation A3).

Thus, the following recommendation results:

Recommendation D2

As part of the informed consent process, mature minors should be offered the opportunity to receive additional findings relating to their disease carrier status. In this context, the possible benefit of the return for other family members, especially siblings (brothers), who may themselves be affected by the respective disease (not only by the disease carrier status), should also be pointed out.

6.5 Additional findings regarding medically non-actionable diseases with early onset

6.5.1 Possible benefit from a return

The return of additional findings regarding (according to the current state of science) medically non-actionable diseases with early onset has no direct *medical benefit for* the affected child. However, depending on the type of disease, knowledge of a genetic predisposition may help children with unspecific symptoms to avoid unnecessary and burdensome diagnostics. In addition, the knowledge can enable life planning adapted to the (possible) disease (*life planning benefit*), especially if it can be assumed that the disease is so severe in childhood that the child will *not* develop into an independent adult and the parents have to provide accordingly for the child's future. Thus, the life planning benefit also helps in the *realization of open life paths*. In addition, the knowledge may also be relevant to life and family planning for other family members (*social benefit*).

6.5.2 Possible damage due to a return

The return of additional findings regarding medically non-actionable diseases with early onset impairs the *right to an open informational future* and violates the *right not to know.* Damage in the sense of *psychological distress* is possible and, especially in view of the untreatable nature of the disease associated with the additional findings, more likely than in the case of additional findings regarding medically actionable diseases. However, the probability and extent of psychological distress are difficult to assess and may vary considerably from one individual to another, depending on the severity of the disease.

6.5.3 Weighing the benefits and harms

Depending on the nature and severity of the disease associated with an additional finding, its return may be of great importance for the life planning of the minor and parents, even if it violates some of the minor's rights. This means parents or mature minors should be given the opportunity to receive additional findings. However, it should be ensured that only additional findings are offered for return where a benefit for life planning is probable (an additional finding regarding a high risk of a serious disease), in order to guarantee a sensible ratio of counseling effort to benefit from the return. The need to limit the return of additional findings to those with life planning relevance must be clearly communicated. Furthermore, in the case of mature minors, an attempt should be made to involve the parents as far as possible in the clarification and decision-making process (see recommendation A3).

Thus, the following recommendations result:

Recommendation E1

Parents of immature minors should be offered, as part of the informed consent process, the opportunity to receive additional findings regarding medically non-actionable diseases with early onset and great relevance for life planning (additional findings regarding a high risk of serious disease).

Recommendation E2

Analogous to recommendation E1, mature minors should be offered the opportunity to receive additional findings regarding medically non-actionable diseases with early onset and high relevance for life planning (additional findings regarding a high risk of serious disease) as part of the informed consent process.

6.6 Additional findings regarding medically non-actionable diseases with late onset

6.6.1 Possible benefit from a return

The return of additional findings on medically non-actionable diseases with late onset has no direct *medical benefit* for the child. The *life planning benefit depends* (apart from the aforementioned factors penetrance and disease severity) on how late the disease onset is. For example, an Alzheimer's risk allele probably has no relevance to life planning in early adulthood, but other predispositions such as Friedreich's ataxia – a neurodegenerative disease that usually occurs before the age of 25 – do. The potential life planning benefit serves the *realization of open life paths*. A *social benefit* for the child arises at most in the future, for example, when it is a question of organizing early care for parents who are also affected by the disease risk (e.g., of Alzheimer's disease). However, it can be assumed anyway that children will have to take care of their parents sooner or later. The additional knowledge about certain predispositions for medically non-actionable diseases with a late onset is thus generally of little importance in terms of social benefit.

6.6.2 Possible damage due to a return

The return of additional findings on medically non-actionable diseases with late onset impairs the *right to an open informational future*, and

this impairment may lead to problems in the future (for example, in the context of life insurance). In addition, the *right not to know* is violated. Damage in the sense of *psychological distress* is possible and, especially in view of the untreatable nature of the disease associated with the additional finding, may be more likely than in the case of additional findings relating to medically actionable diseases. However, the likelihood and extent of psychological distress is difficult to assess and may vary considerably from one individual to another, depending on the severity of the disease.

6.6.3 Weighing the benefits and harms

The infringement on the rights of the child (depending on the type and severity of the disease) is countered by the potential life planning benefit, which, however, in all likelihood only occurs in adulthood. The return of the additional finding to the parents is not justifiable at the present time, since knowledge of a predisposition to a medically non-actionable disease with late onset only becomes relevant to the child when he or she can autonomously (without parental influence) determine how to exercise his or her informational rights. At the same time, the knowledge has no medical benefit that would justify the parents' co-determination for the protection of the child, as we concede in the case of additional findings regarding medically actionable diseases with a late need for medical action (recommendation C1). Accordingly, in the informed consent process, parents should not be offered the option of receiving additional findings regarding medically non-actionable diseases with late onset. Instead, they should be told that these types of additional findings will not be returned. However, children in adulthood should be given the opportunity to decide whether or not they want to receive additional findings regarding medically non-actionable diseases with late onset. Therefore, when they are adults, they should be informed by their parents that a genetic or genomic analysis has been performed and they should have the opportunity to obtain information on *possible* additional findings regarding non-treatable late-onset diseases if they so desire. Information on whether such additional findings exist at all should not be provided in advance.

This results in the following recommendations

Recommendation F1

As part of the informed consent process, parents should not be offered the option of receiving any additional findings regarding medically non-actionable diseases with late onset. They should be informed about this circumstance in advance.

Recommendation F2

To allow the child to decide for him- or herself in adulthood if he or she wishes to receive additional findings regarding medically non-actionable diseases with late onset, parents should be advised to inform their child, when he or she is an adult, **that a genetic or genomic analysis has been performed.**

6.6.4 Special case: Mature minors

Mature minors have a right to know about their own predisposition to disease, especially when it comes to knowledge relevant to life planning. Therefore, as part of the informed consent process, mature minors should be offered the option of receiving additional findings regarding medically non-actionable diseases with late onset. Similar to the return of additional findings regarding medically non-actionable diseases with *early* onset, the effort for the return itself including the informed consent process and possible genetic counseling has to be considered. This effort suggests a limitation to the return of additional findings regarding predispositions with a *relevance for life planning*. The restriction to these additional findings relevant for life planning must be clearly communicated to the mature minors. Furthermore, the possibility that the additional findings may also be relevant to other family members should be clearly communicated. In addition, an attempt should also be made here to involve the parents as much as possible in the informed consent and decision-making process (see recommendation A3).

Thus, the following recommendation results:

Recommendation F3

As part of the informed consent process, mature minors should be offered the opportunity to receive additional findings regarding medically non-actionable diseases with late onset and a high probability of occurrence and presumably considerable impact of quality of life, as these have a high relevance for individual life planning.

7 CASE STUDIES

To illustrate the application of the recommendations from Chapter 6, we apply them in to two case studies below:

Case study 1

A newborn boy with a heart defect was examined. Genomic analysis could not detect a cause for the heart defect but did discover a pathogenic variant in the *OTC* gene as an additional finding. This variant is associated with ornithine transcarbamylase deficiency. If left untreated, there is a risk of life-threatening crises due to hyperammonemia, especially in catabolic situations. This can be prevented by diet if the diagnosis is known, and should a derailment occur, acute therapy can be started immediately and without loss of time (e.g., due to delayed diagnosis).

This case falls into the category *additional finding regarding a medical actionable disease with an early need for medical action* (Chapter 6.2).

Failure to return the additional finding could lead to serious and possibly life-threatening damage for the child due to hyperammonemia, i.e., the return of the additional finding would have great *medical benefit*, since any acute derailments can be responded to quickly and adequately if the diagnosis is known. Furthermore, the return brings a great *life planning benefit*, since, for example, catabolic situations can be prevented by low-protein diets. The medical benefit and the life planning benefit for the child serve to *create or realize open life paths.* In principle, this benefit also exists for siblings who could be affected by the same mutation (*social benefit*).

The immense benefit for the child is offset by damage in the form of a violation of the *right to an open informational future* and the *right not to know.* Likewise, further damage, e.g., in the form of *psychological distress* or in the insurance sector, is very unlikely, but not entirely excluded.

The aforementioned damages are of little importance in relation to the benefits resulting from a return of the additional finding. Instead, infringement of future rights can be neglected insofar as a future is uncertain without certain (preventive) measures that are triggered by return of the additional finding in the first place.

Case study 2

In genetic testing by single exome analysis of a 6-year-old boy with cognitive developmental disorder and microcephaly and epilepsy, no cause was found. However, a pathogenic variant was found in the MLH1 gene. This variant is associated with Lynch syndrome, a tumor predisposition of adulthood (colorectal cancer and other tumors) for which there is effective early detection. The variant is not relevant to the boy in childhood. For the parents, however, this information would be directly relevant to their health, since it is likely that one parent carries this predisposition, thus having a high tumor probability himself and being aware of early detection.

This case falls into the category *additional finding regarding a medically actionable disease with a late need for medical action* (Chapter 6.3).

The return of the additional finding would not result in any medical benefit for the child at the current time, as the tumor predisposition only becomes relevant in adulthood. However, the knowledge may bring a *future medical benefit* and a *life planning benefit*, e.g., through regular colorectal cancer screening, etc. The medical benefits and life planning benefits serve to *create or realize open life paths.* The probable involvement of parents suggests a significant *social benefit*: for them, the aforementioned screening examinations are already indicated now and can, if necessary, significantly increase the treatability of any tumors.

The return of the additional finding would violate the *right to an open informational future* or the *right not to know.* Damage caused by the return in the sense of *psychological distress* is possible, although not very probable, especially because effective preventive examinations for the discovered predispositions exist.

The great social benefit that a return of the additional finding could bring for the child (by presumable helping the parents and, if applicable, siblings) speaks at first glance in favor of returning it, but in addition to the restrictions and violations of the child's rights, it also affects the informational rights of parents (and said siblings). A possible benefit for siblings, similarly to the boy concerned himself, will only arise in the future (depending on the age of the sibling).

8 INFORMATION BROCHURE ON ADDITIONAL FINDINGS

In the following, we present an information brochure that provides parents (Chapter 8.1) and mature minors (Chapter 8.2) with what we consider to be relevant information on possible additional findings in a form that is understandable to laypersons. This information brochure is **not to be** understood as a substitute for a detailed informed consent process, but it can supplement it.

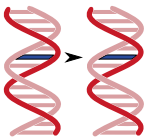
Both versions of the information brochure as well as the text modules for information and consent documents presented in Chapter 9 can be downloaded from www.eurat.info

8.1 Information brochure for parents

What are genetic variants?

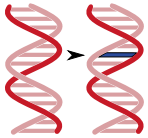
All externally visible (e.g., hair color) but also invisible characteristics that are passed on via genes are referred to as genetic traits. They are passed on over generations. In the process, changes, new combinations, or deviations in the genes (so-called genetic variants) continuously arise naturally, making each person unique. As we know today, a very small fraction of these variants plays a role in the development of certain (genetically determined) diseases. This small fraction of variants is of particular importance for the person being examined if courses of medical action (e.g., for improved treatment of diseases) can be derived from them. In scientific studies, these variants are also important for researchers because they can contribute to understanding the diagnosis and treatment of diseases. Knowledge about the health significance of different variants is constantly growing. This is leading to improvements in diagnostics and therapies, even though the health significance of many of these variants is currently still unclear due to the large number of possible genetic variants. With medical progress, these will increasingly be uncovered in the future.

Where do genetic variants come from?



Genetic variants are either **inherited** or **emerge**.

Inherited genetic variants are passed on from parents to their children. They are already present at the time of birth and continue to exist in a stable manner. If the genetic variants are those for which an association with a disease has already been proven, they can cause symptoms either from birth or later in life. Since inherited genetic variants are passed on from generation to generation, they often allow conclusions to be drawn that blood relatives may also be affected by the variant.



Genetic variants were not inherited in all cases. They may also **emerge** anew from one generation to the next, which is referred to as *"de novo mutation".*

Why are genetic variants searched for in the course of diagnostics?

In **genetic diagnostics**, genetic variants that could be the cause of an already existing disease are searched for. Depending on the findings, **therapy recommendations or preventive options** can be derived from this. Sometimes genetic variants are also searched for in healthy individuals (predictive diagnostics), for example if a family history provides evidence of a genetic disease. Knowledge of such variants is important, for example, in the case of a hereditary predisposition to tumors, so that tumors can be **detected and treated at an early stage**.

What are additional findings?

In genetic tests aimed at identifying the genetic cause of a disease and, if necessary, deriving recommendations for its treatment, variants can be discovered that are not related to the original question. These so-called additional findings in genetic diagnostics are thus findings that are discovered in the course of diagnostics, for which no active search was made but which are nevertheless associated with other, possibly inherited and heritable characteristics and diseases.

How sure can I be that a discovered predisposition will lead to disease?

An additional finding indicates that the **probability of developing** a certain disease is **increased to a greater or lesser extent.** How strong this increase is, depends on the type of additional finding. We will only inform you of additional findings that have a high probability of actually leading to a disease.

What are the types of additional findings?

Additional findings may indicate **predispositions to diseases** for which **preventive programs and/or treatment options** exist, as well as diseases for which (according to current medical knowledge) **no preventive programs and/or treatment options** exist at this time.

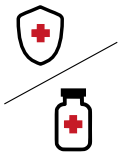
Both types of predispositions can lead to disease either in **childhood** or in **adulthood.**

There are also additional findings that are not medically significant for the person examined because they do not lead to a disease. However, the knowledge of this so-called **disease carrier status** can be significant for their **offspring** and, under certain circumstances, for **parents** and **siblings**.

What does it mean if no preventive programs and/or treatment options exist <u>at this time?</u>

New findings are constantly being made in medical research and the spectrum of diagnosis and treatment is being expanded. Thus, there is a possibility that a currently untreatable disease will be treatable in a few years. However, it is often not possible at the present time to estimate how likely this is to be the case.

What does it mean that a disease is "treatable"?



A disease is considered treatable if **medical measures** are known that allow this disease to be **prevented** or **therapeutically counteracted.**

What is a disease carrier status?

A so-called disease carrier status describes a genetic variant that usually does **not cause any disease in the affected person.** However, the variant can be inherited, which may have consequences for the **offspring**. The probability of disease in the offspring depends on the **mode of inheritance.** For example, in many inheritance modes, the offspring will only become ill (with a probability of 25%) if the partner also happens to carry a disease-causing variant in the same gene (i.e., is also a disease carrier). In other modes of inheritance, a disease carrier status in a female (independent of the partner) is sufficient for the male offspring in particular to develop the disease with a relatively high probability.

Is there an active search for additional findings?

No, additional findings are not actively sought. There is also no obligation to collect them.

What additional findings will I be notified of?

In principle, only additional findings are reported that are **highly likely** to lead to **a disease**. The following cases must be distinguished:

Additional findings for diseases for which **preventive programs and/or treatment options** exist that can be carried out in **childhood are always returned** to you.

In the case of additional findings for diseases for which **preventive programs and/or treatment options do not exist until adulthood**, you can decide whether to

(1) receive the additional findings and appropriate genetic counseling.

(2) receive information that there is an additional finding that will become medically relevant in your child's adulthood, without further counseling.

(3) receive no return at all.

Additional findings for diseases for which there are **no preventive programs and/or treatment options** at this time, and which may occur in **childhood**, will be shared with you **upon request** if they are conditions that may be relevant to your or your child's **life plans**.

Additional findings for diseases for which there are **no preventive programs and/or treatment options** at this time, and which may occur in **adulthood, will not** be returned to you.

Findings on the **disease carrier status** will be returned to you **upon request** if there is a high probability that you or any siblings can benefit from the return.

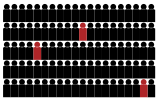
Can I refuse the information about additional findings?

You can refuse information on additional findings related to diseases for which there are **preventive programs and/or treatment options in adulthood**, as well as on additional findings for diseases for which there are **no preventive programs and/or treatment options.** You can also refuse to receive information on the **disease carrier status**.

You **cannot refuse** additional findings on diseases that are highly likely to occur in your child and for which **preventive programs and/or treatment options already exist in childhood.** You also cannot refuse knowledge of findings that are **relevant to your child's current treatment**.

How common are additional findings?

Additional findings are detected in approximately **3 out of 100 individuals** who have undergone comprehensive genetic diagnosis.



What are the benefits and potential burdens of receiving additional findings?

The return of additional findings is only given on the assumption that it is **medically useful** for your child. Nevertheless, the return may also result in **burdens** or **risks** for your child (and possibly also you), such as worry and concern; the need for additional examinations for clarifica-

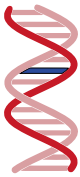
tion; insurance aspects; reconsideration of family planning. In addition, a situation may arise in which you have to decide whether to **inform relatives about an identified hereditary predisposition** (which could also affect these relatives themselves) without knowing whether they want to be informed at all. Your doctor can advise you on how to communicate with your relatives.

What significance can additional findings have for the family?

Genetic predispositions can **emerge spontaneously** (de novo mutation) or be **inherited**. Thus, it is possible that additional genetic findings in your child may also have a significance for **you as parents** or for **siblings**. Consequently, either you yourself may be suffering from **the same genetic predisposition** and be at risk of developing the corresponding disease. Or both parents are **disease carriers**, i.e., you yourself do not have an increased risk of the disease but have passed the disease on to your child. In both cases, siblings can potentially also be affected by the same predisposition. It is not possible to say with certainty whether you as parents, and therefore possibly also your child's siblings, are affected by the same predisposition as your child on the basis of the genetic analyses of your child alone. This would require an analysis of your own genetic material (and possibly the genetic material of the child's siblings).

8.2 Information brochure for mature minors

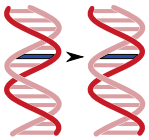
What are genetic variants?



All externally visible (e.g., hair color) but also invisible characteristics that are passed on via genes are referred to as genetic traits. They are passed on over generations. In the process, changes, new combinations, or deviations in the genes (so-called genetic variants) continuously arise naturally, making each person unique. As we know today, a very small fraction of these variants plays a role in the development of certain (genetically determined) diseases. This small fraction of variants is of particular importance for the person being examined if courses of medical action (e.g., for improved treatment of diseases) can be derived from them. In scientific studies, these variants are also important for researchers because they can contribute to understanding the diagnosis and treatment of diseases. Knowledge about the health significance of different variants is constantly growing. This is leading to improvements in diagnostics and therapies, even though the health significance of many of these variants is currently still unclear due to the large number of possible genetic variants. With medical progress, these will increasingly be uncovered in the future.

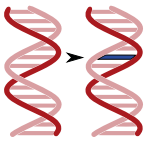
Where do genetic variants come from?

Genetic variants are either **inherited** or **emerge.**



Inherited genetic variants are passed on from parents to their children. They are already present at the time of birth and continue to exist in a stable manner. If the genetic variants are those for which an association with a disease has already been proven, they can cause symptoms either from birth or later in life. Since inherited genetic variants are passed on from generation to generation, they often allow conclusions to be drawn that blood relatives may also be affected by the variant.

Genetic variants were not inherited in all cases. They may also **emerge** anew from one generation to the next, which is referred to as *"de novo mutation"*.



Why are genetic variants searched for in the course of diagnostics?

In **genetic diagnostics**, genetic variants that could be the cause of an already existing disease are searched for. Depending on the findings, **therapy recommendations or preventive options** can be derived from this. Sometimes genetic variants are also searched for in healthy individuals (predictive diagnostics), for example if a family history provides evidence of a genetic disease. Knowledge of such variants is important, for example, in the case of a hereditary predisposition to tumors, so that tumors can be **detected and treated at an early stage**.

What are additional findings?

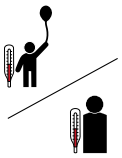
In genetic tests aimed at identifying the genetic cause of a disease and, if necessary, deriving recommendations for its treatment, variants can be discovered that are not related to the original question. These so-called additional findings in genetic diagnostics are thus findings that are discovered in the course of diagnostics, for which no active search was made, but which are nevertheless associated with other, possibly inherited and heritable characteristics and diseases.

How sure can I be that a discovered predisposition will lead to disease?

An additional finding indicates that the **probability of developing** a certain disease is **increased to a greater or lesser extent**. How strong this increase is, depends on the type of additional finding. We will only inform you of additional findings that have a high probability of actually leading to a disease.

What are the types of additional findings?

Additional findings may indicate **predispositions to diseases** for which **preventive programs and/or treatment options** exist, as well as diseases for which (according to current medical knowledge) **no preventive programs and/or treatment options** exist at this time.



Both types of predispositions can lead to disease either in **childhood** or in **adulthood**.

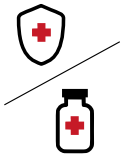
There are also additional findings that are not medically significant for the person examined because they do not lead to a disease. However, the knowledge of this so-called **disease carrier status** can be significant for their **offspring** and, under certain circumstances, for **parents** and **siblings**.

What does it mean if no preventive programs and/or treatment options exist <u>at this time</u>?

New findings are constantly being made in medical research and the spectrum of diagnosis and treatment is being expanded. Thus, there is a possibility that a currently untreatable disease will be treatable in a few years. However, it is often not possible at the present time to estimate how likely this is to be the case.

What does it mean that a disease is "treatable"?

A disease is considered treatable if **medical measures** are known that allow this disease to be **prevented** or **therapeutically counteracted**.



What is a disease carrier status?

A so-called disease carrier status describes a genetic variant that usually does **not cause any disease in the affected person**. However, the variant can be inherited, which may have consequences for the **offspring**. The probability of disease in the offspring depends on the **mode of inheritance**. For example, in many inheritance modes, the offspring will only become ill (with a probability of 25%) if the partner also happens to carry a disease-causing variant in the same gene (i.e., is also a disease carrier). In other modes of inheritance, a disease carrier status in a female (independent of the partner) is sufficient for the male offspring in particular to develop the disease with a relatively high probability.

Is there an active search for additional findings?

No, additional findings are not actively sought. There is also no obligation to collect them.

What additional findings will I be notified of?

In principle, only additional findings are reported that are **highly likely to lead to a disease**. The following cases must be distinguished:

You can decide whether you want to receive additional findings on diseases for which **preventive programs and/or treatment options** exist that can be carried out **before the age of 18**.

In the case of additional findings for diseases for which **preventive programs and/or treatment options** do not exist until **after the age of 18**, you can decide whether to

(1) receive the additional findings and appropriate genetic counseling.

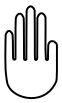
(2) receive information that there is an additional finding that will become medically relevant in adulthood, without further counseling.

(3) receive no return at all.

Additional findings for conditions for which there are **no preventive programs and/or treatment options** at this time will be provided to you upon request if they are conditions that may be relevant to your **future life planning**.

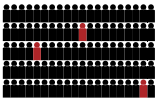
Findings on the **disease carrier status** will be provided to you **upon request**.

Can I refuse the information about additional findings?



You can refuse to receive additional findings. This refusal is possible separately for each of the mentioned categories of additional findings.

How common are additional findings?



Additional findings are detected in approximately **3 out of 100 individuals** who have undergone comprehensive genetic diagnosis.

What are the benefits and potential burdens of receiving additional findings?

The return of additional findings is only given on the assumption that it is **medically useful** for you. Nevertheless, the return may also result in **burdens** or **risks**, such as worry and concern; the need for additional examinations for clarification; insurance aspects; reconsideration of family planning. In addition, a situation may arise in which you have to decide whether to **inform relatives about an identified hereditary predisposition** (which could also affect these relatives themselves) without knowing whether they want to be informed at all. Your doctor can advise you on how to communicate with your relatives.

What significance can additional findings have for the family?

Genetic predispositions can **emerge spontaneously** (de novo mutation) or be **inherited**. It is therefore possible that your additional genetic findings may also have a significance for **your parents** or **siblings**. They may either be **suffering from the same genetic predisposition** themselves and, thus, be at risk of developing the corresponding disease. Or both your parents may be **disease carriers**, i.e., they themselves do not have an increased risk of the disease but have passed the disease on to you. In both cases, your siblings can potentially also be affected by the same predisposition. It is not possible to say with certainty whether your parents, and therefore possibly also your siblings, are affected by the same predisposition as you on the basis of your genetic analyses alone. This would require an analysis of the genetic material of your parents and, if applicable, siblings.

9 MATERIALS FOR THE INFORMED CONSENT PROCESS

9.1 Information passage on additional findings (parents)

It is possible that we discover findings that are not related to your child's disease but to other, possibly inherited and/or hereditary characteristics. These are so-called **additional findings** that indicate a more or less strong predisposition to other diseases.

For some predispositions there are **preventive programs and/or treatment options**, but for others there are not. Some predispositions can already lead to a disease in **childhood**, some only in **adulthood**. If there are preventive programs and/or treatment options for the respective disease, these can also be carried out in part during childhood. If there are no preventive programs and/or treatment options for the respective disease, knowledge about the predisposition to the disease can be relevant for your child's **life planning**. An additional finding can also reveal a so-called **disease carrier status**. This is not medical relevant for your child him- or herself but may be relevant for its offspring and siblings or for you as parents. In the case of the other categories of additional findings listed above, there is also the possibility that not only your child but also yourself or your child's siblings may be affected by the possible disease. We will not actively search for additional findings, and there is no obligation to collect them.

Types of additional findings:

Additional findings regarding diseases for which **preventive programs and/or treatment options** already exist in **childhood or adolescence.**

Additional findings regarding diseases for which **preventive programs and/or treatment options** exist in **adulthood**.

Additional findings regarding diseases that occur in **childhood or adolescence** and for which **neither preventive programs nor treatment options** exist.

Additional findings regarding diseases that do **not occur until adulthood** and for which **neither preventive programs nor treatment options** exist.

Additional findings regarding a **disease carrier status**.

How do we deal with additional findings?

- We will **always inform** you of additional findings concerning diseases that are **very likely** to occur and for which, according to the current state of medical knowledge, there are **successful preventive programs and/or treatment options already in childhood.**
- Additional findings that are **relevant** to the **treatment** of your child's **current condition** will **always be shared with** you.
- **If you wish**, we will also provide you with additional findings on diseases that are **very likely to occur** and for which, according to the

current state of medical knowledge, there are **successful preventive programs and/or treatment options in adulthood** (e.g., familial breast and ovarian cancer).

- **If you so wish**, we will provide you with additional findings on the **disease carrier status** if such knowledge is useful for **yourself or other family members**.
- Furthermore, **if you wish**, we will provide you with additional findings on diseases that are **very likely to occur in childhood** but for which there are **no successful preventive programs and/or treatment options** according to the current state of medical knowledge, provided that these additional findings are relevant to **your child's life planning.**

We do not evaluate and communicate:

- Genetic alterations that, according to the current state of science, are **not** associated with an **increased likelihood of disease**.
- Genetic alterations that are associated with a **disease** that is **not life-threatening** but have a **low probability** of causing that disease.
- Genetic alterations that have a **high probability** of leading to **disease in adulthood** but for which there are **no successful preventive programs and/or treatment options** based on current medical knowledge.
- Genetic alterations that are **highly likely** to be related to **childhood disease** for which there is **no successful screening or treatment** and which are **not relevant to future life planning**.

9.2 Information passage on additional findings (mature minors).

It is possible that we discover findings that are not related to your disease but to other, possibly inherited and/or hereditary characteristics. These are so-called **additional findings** that indicate a more or less strong predisposition to other diseases.

For some predispositions there are **preventive programs and/or treatment options** but not for others. Some predispositions can already lead to a disease **before the age of 18**, some only **after the age of 18**. If there are preventive programs and/or treatment options for the respective disease, these can also be carried out in part during childhood or adolescence. If there are no preventive programs and/

Types of additional findings:

Additional findings regarding diseases for which **preventive programs and/or treatment options** already exist **before the age of 18.**

Additional findings regarding diseases for which **preventive programs and/or treatment options** exist only **after the age of 18.**

Additional findings regarding diseases that occur **before the age of 18** and for which **neither preventive programs nor treatment options** exist.

Additional findings regarding diseases that do **not occur until the age of 18** and for which **neither preventive programs nor treatment options** exist.

Additional findings regarding a **disease carrier status**.

or treatment options for the respective disease, knowledge about the predisposition to the disease can be relevant for your **life planning**. An additional finding can also reveal a so-called **disease carrier status**. This is not medically relevant for you but may be relevant for your offspring and for your siblings or parents. In the case of the other categories of additional findings listed above, there is also the possibility that not only you, but also your siblings or parents may be affected by the possible disease. We will not actively search for additional findings, and there is no obligation to collect them.

How do we deal with additional findings?

- **If you wish**, we will provide you with additional findings on diseases that are **most likely** to occur and for which there are **successful preventive programs and/or treatment options.**
- **If you so wish**, we will also provide you with additional findings on the **disease carrier status**.
- Furthermore, **if you wish**, we will provide you with additional findings on diseases that are **very likely to** occur and for which there are no **successful preventive programs and/or treatment options** according to the current state of medical knowledge, provided that these findings are **relevant** to your **life planning**.

We do not evaluate and communicate:

- Genetic alterations that, according to the current state of science, are **not** associated with an **increased likelihood of disease**.
- Genetic alterations that are associated with a **disease** that is **not life-threatening** but have a **low probability** of causing that disease.
- Genetic alterations that are **highly** likely to be related to a disease **for which there is no successful screening or treatment** and which are **not relevant** to future **life planning**.

9.3 Passage on additional findings in the consent form (parents)

I agree

that I would like to be informed of medically relevant findings about my child that are not related to his or her current illness and for which there are targeted *preventive programs and/or treatment options in adulthood.*

☐ yes

☐ I do not want to know details about the finding at this time but would like to be informed if there is a finding that will be relevant to my child at a later date.

☐ no. I disagree, I do not want to be informed about such findings.

Additional findings regarding diseases for which **preventive programs and/or treatment options** exist in **adulthood**.

I agree

that I would like to be informed of medically relevant findings about my child that are not related to his or her current illness and which, according to the current state of scientific knowledge, are insignificant for my child him- or herself but which indicate hereditary diseases that may possibly be passed on to offspring or which may possibly be relevant for siblings or myself.

☐ yes

☐ no. I disagree, I do not want to be informed about such findings.

Additional findings on a **disease carrier status**.

I agree

that I would like to be informed of medically relevant findings about my child that are not related to his or her current illness, that are *important for my child's or our family's life planning,* and that are highly likely to lead to an illness still in childhood for which there are no *preventive programs and/or treatment options* according to the current state of knowledge.

Additional findings regarding diseases that occur in **childhood or adolescence** and for which **neither preventive programs nor treatment options** exist.

☐ yes

☐ no. I disagree, I do not want to be informed about such findings.

9.4 Passage to additional findings in the consent form (mature minors).

I agree

that I would like to be informed of medically relevant findings that are not related to my current illness and for which there are *targeted preventive programs and/or treatment options* that can be carried out *before the age of 18.*

☐ yes

☐ no. I disagree, I do not want to be informed about such findings.

Additional findings regarding diseases for which **preventive programs and/or treatment options** already exist **before the age of 18**.

I agree

that I would like to be informed of medically relevant findings that are not related to my current illness and for which there are targeted *preventive programs and/or treatment options* that can only be carried out *after I have reached the age of 18.*

☐ yes

☐ I do not want to know details of the finding at this time but would like to be informed if there is a finding that will be relevant to me at a later date.

☐ no. I disagree, I do not want to be informed about such findings.

Additional findings regarding diseases for which **preventive programs and/or treatment options** exist **only after the age of 18.**

I agree

that I would like to be informed of medically relevant findings that are not related to my current illness and for which, according to current knowledge, there are *no preventive programs and/or treatment options* but which may be important for my *life planning or that of my close relatives.*

Additional findings regarding diseases that occur **before or after the age of 18** and for which **neither preventive programs nor treatment options** exist.

☐ yes, if the disease is very likely to occur before the age of 18.

☐ yes, if the disease is highly likely to occur after the age of 18.

☐ no. I disagree, I do not want to be informed about such findings.

I agree

that I would like to be informed of medically relevant findings which are not related to my current illness and which, according to the current state of science, are *insignificant for myself* but which indicate hereditary diseases which may possibly be passed on to *descendants* or which may possibly be relevant for my *siblings* or parents.

Additional findings regarding a **disease carrier status**.

☐ yes

☐ no. I disagree, I do not want to be informed about such findings.

10 LITERATURE

Abdul-Karim R, Berkman BE, Wendler D, Rid A, Khan J, Badgett T, Hull SC (2013) Disclosure of incidental findings from next-generation sequencing in pediatric genomic research. Pediatrics 131(3):564-571.

ACMG (2015) ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. *Genet Med* 17(1):68-69.

Amelung K (1992) Über die Einwilligungsfähigkeit (Teil I). *ZStW* 104(3):525-558.

American Academy of Pediatrics (2013) Ethical and policy issues in genetic testing and screening of children. *Pediatrics* 131(3):620-622.

Anderson JA, Hayeems RZ, Shuman C, Szego MJ, Monfared N, Bowdin S, . . . Meyn MS (2015) Predictive genetic testing for adult-onset disorders in minors: a critical analysis of the arguments for and against the 2013 ACMG guidelines. *Clin Genet* 87(4):301-310.

Andorno R (2004) The right not to know: an autonomy based approach. *J Med Ethics* 30(5):435-439.

Archard D (2010) *The family: A liberal defence*. Palgrave Macmillan, Basingstoke, Hampshire.

Avard D, Sénécal K, Madadi P, Sinnett D (2011) Pediatric research and the return of individual research results. *J Law Med Ethics* 39(4):593-604.

Bagattini A (2019) *Kindeswohl*. In: Drerup J, Schweiger G (Hrsg) Handbuch Philosophie der Kindheit. Springer, Heidelberg, S 128-136.

Beauchamp TL, Childress JF (2009) *Principles of Biomedical Ethics*. Oxford University Press, Oxford.

Benston S (2016) Not of minor consequence: Medical decision-making autonomy and the mature minor doctrine. *Ind Health L Rev* 13(1):1-16.

BMBF-Projektgruppe "Recht auf Nichtwissen" (2016) Empfehlungen zum anwendungspraktischen Umgang mit dem "Recht auf Nichtwissen" – Ergebnisse einer rechtsethischen Grundlagenanalyse auf erfahrungswissenschaftlicher Basis in den Anwendungsfeldern von Humangenetik und Psychiatrie. *MedR* 34:399-405.

Borry P, Evers-Kiebooms G, Cornel MC, Clarke A, Dierickx K (2009) Genetic testing in asymptomatic minors: recommendations of the European Society of Human Genetics. *Eur J Hum Genet* 17(6):720-721.

Botkin JR, Belmont JW, Berg JS, Berkman BE, Bombard Y, Holm IA, . . . McInerney JD (2015) Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents. *Am J Hum Genet* 97(1):6-21.

Boycott K, Hartley T, Adam S, Bernier F, Chong K, Fernandez BA, . . . Canadian College of Medical G (2015) The clinical application of genome-wide sequencing for monogenic diseases in Canada: Position Statement of the Canadian College of Medical Geneticists. *J Med Genet* 52(7):431-437.

Bundesärztekammer (1997) Stellungnahme der 'Zentralen Ethikkommission'bei der Bundesarztekammer zum Schutz nichteinwilligungsfahiger Personen in der medizinischen Forschung. *Dtsch Arztebl* 94:C759-760.

Codori AM, Zawacki KL, Petersen GM, Miglioretti DL, Bacon JA, Trimbath JD, . . . Giardiello FM (2003) Genetic testing for hereditary colorectal cancer in children: long-term psychological effects. *Am J Med Genet* 116A(2):117-128.

Coester M (1983) *Das Kindeswohl als Rechtsbegriff: die richterliche Entscheidung über die elterliche Sorge beim Zerfall der Familiengemeinschaft*, Bd 114. Arbeiten zur Rechtsvergleichung. Metzner, Frankfurt am Main.

Crozier S, Robertson N, Dale M (2015) The psychological impact of predictive genetic testing for Huntington's disease: a systematic review of the literature. *J Genet Couns* 24(1):29-39.

Damm R (2012) Prädiktive Gendiagnostik im Familienverband und Haftungsrecht. *MedR* 30(11):705-710.

Damm R (2014) Prädiktive Gendiagnostik, Familienverband und Haftungsrecht. *MedR* 32(3):139-147.

de Wert G, Dondorp W, Clarke A, Dequeker EMC, Cordier C, Deans Z, . . . European Society of Human G (2021) Opportunistic genomic screening. Recommendations of the European Society of Human Genetics. *Eur J Hum Genet* 29(3):365-377.

Diekema D (2004) Parental refusals of medical treatment: the harm principle as threshold for state intervention. *Theor Med Bioeth* 25(4):243-264.

Diekema DS (2011) Revisiting the best interest standard: uses and misuses. *J Clin Ethics* 22(2):128-133.

Dive L (2021) From a Right to a Preference: Rethinking the Right to Genomic Ignorance. *J Med Philos* 46(5):605-629.

Dondorp W, Bolt I, Tibben A, De Wert G, Van Summeren M (2021) 'We Should View Him as an Individual': The Role of the Child's Future

Autonomy in Shared Decision-Making About Unsolicited Findings in Pediatric Exome Sequencing. *Health Care Anal* 29(3):249-261.
Duttge G (2010) Das Recht auf Nichtwissen in der Medizin. *DuD* 34(1):34-38.
eMerge Clinical Annotation Working Group (2020) Frequency of genomic secondary findings among 21,915 eMERGE network participants. *Genet Med* 22(9):1470-1477.
EURAT (2015) *Eckpunkte für eine Heidelberger Praxis der Ganzgenomsequenzierung*. Forum Marsilius Kolleg, Heidelberg.
EURAT (2019) *Zur Herausgabe genomischer Rohdaten an Patient_innen und Studienteilnehmende*. Forum Marsilius Kolleg, Heidelberg.
Fanos JH, Johnson JP (1995) Perception of Carrier Status by Cystic Fibrosis Siblings. *Am J Hum Genet* 57:431-438.
Feinberg J (1992) *The child's right to an open future*. In: Feinberg J (Hrsg) Freedom and Fulfilment: Philosophical Essays. Princeton University Press, Princeton, New Jersey, S 76-91.
Fenger H (2010) Das neue Gendiagnostikgesetz (GenDG). *GesR* 9(2):57-60.
Fleischer H (2018) *Rechtliche Aspekte der Systemmedizin: der Umgang mit Gesundheitsdaten und-informationen in der Big Data-basierten Medizin unter besonderer Berücksichtigung des Gendiagnostikgesetzes*. LIT Verlag, Münster.
Garrett JR, Lantos JD, Biesecker LG, Childerhose JE, Chung WK, Holm IA, . . . Clinical Sequencing Exploratory Research Consortium Pediatrics Working G (2019) Rethinking the "open future" argument against predictive genetic testing of children. *Genet Med* 21(10):2190-2198.
Gendiagnostik-Kommission (2011) Richtlinie der Gendiagnostik-Kommission (GEKO) zu genetischen Untersuchungen bei nicht-einwilligungsfähigen Personen nach § 14 in Verbindung mit § 23 Abs. 2 Nr. 1c GenDG. *Bundesgesundheitsbla* 54:1257-1261.
Gesellschaft für Humangenetik (2013a) Stellungnahme der Deutschen Gesellschaft für Humangenetik zu genetischen Zusatzbefunden in Diagnostik und Forschung. *Med Genet* 25(2):284-286.
Gesellschaft für Humangenetik (2013b) Stellungnahme der Deutschen Gesellschaft für Humangenetik zur Genetischen Diagnostik bei Kindern und Jugendlichen. *Med Genet* 25(3):395-397.
Gillam L (2015) The zone of parental discretion: An ethical tool for dealing with disagreement between parents and doctors about medical treatment for a child. *Clin Ethics* 11(1):1-8.
Gillam L, Sullivan J (2011) Ethics at the end of life: who should make

decisions about treatment limitation for young children with life-threatening or life-limiting conditions? *J Paediatr Child Health* 47(9):594-598.

Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, . . . Genomics (2013) ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med* 15(7):565-574.

Hain RDW (2018) Voices of moral authority: parents, doctors and what will actually help. *J Med Ethics* 44(7):458-461.

Hart D (2016) Haftungsrecht und Standardbildung in der modernen Medizin: e: med und Probleme der Definition des Standards: Eine Skizze. *MedR* 34:669-675.

Hart MR, Biesecker BB, Blout CL, Christensen KD, Amendola LM, Bergstrom KL, . . . Hindorff LA (2019) Secondary findings from clinical genomic sequencing: prevalence, patient perspectives, family history assessment, and health-care costs from a multisite study. *Genet Med* 21(5):1100-1110.

Hens K, Nys H, Cassiman JJ, Dierickx K (2011) The return of individual research findings in paediatric genetic research. *J Med Ethics* 37(3):179-183.

Heshka JT, Palleschi C, Howley H, Wilson B, Wells PS (2008) A systematic review of perceived risks, psychological and behavioral impacts of genetic testing. *Genet Med* 10(1):19-32.

Holm IA, Savage SK, Green RC, Juengst E, McGuire A, Kornetsky S, . . . Taylor P (2014) Guidelines for return of research results from pediatric genomic studies: deliberations of the Boston Children's Hospital Gene Partnership Informed Cohort Oversight Board. *Genet Med* 16(7):547-552.

Jarvinen O, Hietala M, Aalto AM, Arvio M, Uutela A, Aula P, Kaariainen H (2000a) A retrospective study of long-term psychosocial consequences and satisfaction after carrier testing in childhood in an autosomal recessive disease: aspartylglucosaminuria. *Clin Genet* 58(6):447-454.

Jarvinen O, Lehesjoki A-E, Lindlof M, Uutela A, Kaariainen H (2000b) Carrier testing of children for two X-linked diseases: a retrospective study of comprehension of the test results and social and psychological significance of the testing. *Pediatrics* 106(6):1460-1465.

Kern BR (2003) *Unerlaubte Diagnostik - Das Recht auf Nichtwissen*. In: Dierks C, Wienke A, Eberbach W, Schmidtke J, Lippert H (Hrsg) Genetische Untersuchungen und Persönlichkeitsrecht. MedR Schriftenreihe Medizinrecht. Springer, Berlin, Heidelberg, S 55-69.

Kern BR (2012) Arzthaftung für Mitteilung einer gravierenden Erbkrankheit (Chorea Huntington). *GesR*:352-353.

Knoppers BM, Avard D, Senecal K, Zawati MH, Members PGIPP (2014) Return of whole-genome sequencing results in paediatric research: a statement of the P3G international paediatrics platform. *Eur J Hum Genet* 22(1):3-5.

Laurie G (2014) Recognizing the right not to know: conceptual, professional, and legal implications. *J Law Med Ethics* 42(1):53-63.

Lewis C, Skirton H, Jones R (2011) Can we make assumptions about the psychosocial impact of living as a carrier, based on studies assessing the effects of carrier testing? *J Genet Couns* 20(1):80-97

Lewis KL, Hooker GW, Connors PD, Hyams TC, Wright MF, Caldwell S, . . . Biesecker BB (2016) Participant use and communication of findings from exome sequencing: a mixed-methods study. *Genet Med* 18(6):577-583.

Linoh KP, Rosenau H (2020) Gilt das GenDG auch für die Forschung? *MedR* 38:1-9.

Lionel AC, Costain G, Monfared N, Walker S, Reuter MS, Hosseini SM, . . . Marshall CR (2018) Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. *Genet Med* 20(4):435-443.

Lotz M (2006) Feinberg, Mills, and the Child's Right to an Open Future. *J Soc Philos* 37(4):537-551.

McCullough LB, Brothers KB, Chung WK, Joffe S, Koenig BA, Wilfond B, Yu J-H (2015) Professionally responsible disclosure of genomic sequencing results in pediatric practice. *Pediatrics* 136(4):e974-e982.

McDougall RJ, Notini L (2014) Overriding parents' medical decisions for their children: a systematic review of normative literature. *J Med Ethics* 40(7):448-452.

Metcalfe A, Plumridge G, Coad J, Shanks A, Gill P (2011) Parents' and children's communication about genetic risk: a qualitative study, learning from families' experiences. *Eur J Hum Genet* 19(6):640-646.

Meyer K (2016) *Genetische Untersuchungen zu medizinischen Zwecken und zu Forschungszwecken an nicht einwilligungsfähigen Personen*, Bd 42. Schriften zum Gesundheitsrecht. Duncker & Humblot, Berlin.

Miller DT, Lee K, Abul-Husn NS, Amendola LM, Brothers K, Chung WK, . . . Acmg Secondary Findings Working Group (2022) ACMG SF v3.1 list for reporting of secondary findings in clinical exome and

genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 24(7):1407-1414.

Miller DT, Lee K, Gordon AS, Amendola LM, Adelman K, Bale SJ, . . . Herman GE (2021) Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 23(8):1391-1398.

Millum J (2014) The foundation of the child's right to an open future. *J Soc Philos* 45(4):522-538.

Nambot S, Sawka C, Bertolone G, Cosset E, Goussot V, Derangere V, . . . Faivre L (2021) Incidental findings in a series of 2500 gene panel tests for a genetic predisposition to cancer: Results and impact on patients. *Eur J Med Genet* 64(5):104196.

OLG Koblenz (2012) Prädiktive Gendiagnostik im Familienverband und Haftungsrecht. *Medizinrecht* 11(30):742-744.

OLG Koblenz (2014) Prädiktive Gendiagnostik, Familienverband und Haftungsrecht. *Medizinrecht* 3(32):168-174.

Opper J, Fangerau H, Braune F, Gassner UM (2019) *Prädiktive und präsymptomatische Diagnostik spätmanifestierender Erkrankungen: Empfehlungen zur Testung einwilligungsfähiger Minderjähriger*, Bd 40. Nomos Verlag, Baden Baden.

Pellegrino ED (2002) Professionalism, Profession and the Virtues of the Good Physician. *Mt Sinai J Med* 69(6):378-384.

Räikkä J (1998) Freedom and a right (not) to know. *Bioethics* 12(1):49-63.

Salter EK (2012) Deciding for a child: a comprehensive analysis of the best interest standard. *Theor Med Bioeth* 33(3):179-198.

Sanderson SC, Linderman MD, Suckiel SA, Zinberg R, Wasserstein M, Kasarskis A, . . . Schadt EE (2017) Psychological and behavioural impact of returning personal results from whole-genome sequencing: the HealthSeq project. *Eur J Hum Genet* 25(3):280-292.

Schelling P, Gaibler T (2012) Aufklärungspflicht und Einwilligungsfähigkeit: Regeln für diffizile Konstellationen. *Dtsch Arztebl* 109(10):A-476 / B-410 / C-406.

Schickhardt C (2016) *Kinderethik: der moralische Status und die Rechte der Kinder*. 2 Aufl. Brill mentis, Paderborn.

Schickhardt C (2017) *Der Begriff des Kindeswohls in der Moral*. In: Drerup J, Schickhardt C (Hrsg) Kinderethik. Aktuelle Perspektiven - klassische Problemvorgaben Brill mentis, Paderborn, S 63-87.

Schoot VV, Viellevoije SJ, Tammer F, Brunner HG, Arens Y, Yntema HG,

Oerlemans AJM (2021) The impact of unsolicited findings in clinical exome sequencing, a qualitative interview study. *Eur J Hum Genet* 29(6):930-939.

Schuol S, Schickhardt C, Wiemann S, Bartram CR, Tanner K, Eils R, . . . von Kalle C (2015) So rare we need to hunt for them: reframing the ethical debate on incidental findings. *Genome Med* 7(1):1-7.

Senecal K, Rahimzadeh V, Knoppers BM, Fernandez CV, Avard D, Sinnett D (2015) Statement of principles on the return of research results and incidental findings in paediatric research: a multi-site consultative process. *Genome* 58(12):541-548.

Sosnitza O, Op den Camp A (2011) Auswirkungen des Gendiagnostikgesetzes auf klinische Prüfungen. *MedR* 29(7):401-404.

Takala T (1999) The right to genetic ignorance confirmed. *Bioethics* 13(3–4):288-293.

Taupitz J (1998) *Das Recht auf Nichtwissen*. In: Hanau P, Lorenz E, Matthes H-C, Wiese G (Hrsg) Festschrift für Günther Wiese zum 70. Geburtstag. Luchterhand, Neuwied, S 583-602.

Thevenon J, Duffourd Y, Masurel-Paulet A, Lefebvre M, Feillet F, El Chehadeh-Djebbar S, . . . Chouchane M (2016) Diagnostic odyssey in severe neurodevelopmental disorders: toward clinical whole-exome sequencing as a first-line diagnostic test. *Clin Genet* 89(6):700-707.

Tunick M (2021) State Authority, Parental Authority, and the Rights of Mature Minors. *J Ethics*:1-23.

Valerius B (2018) Die Einwilligungsfähigkeit Minderjähriger. *Recht der Jugend und des Bildungswesens* 66(3):243-256.

Van Hout CV, Tachmazidou I, Backman JD, Hoffman JD, Liu D, Pandey AK, . . . Banerjee N (2020) Exome sequencing and characterization of 49,960 individuals in the UK Biobank. *Nature* 586(7831):749-756.

Vears DF (2021) Should we respect parents' views about which results to return from genomic sequencing? *Hum Genet* 141(5):1059-1068.

Vears DF, Ayres S, Boyle J, Mansour J, Newson AJ, Education E, Social Issues Committee of the Human Genetics Society of A (2020) Human Genetics Society of Australasia Position Statement: Predictive and Presymptomatic Genetic Testing in Adults and Children. *Twin Res Hum Genet* 23(3):184-189.

Vinicky JK, Smith ML, Connors Jr RB, Kozachuk WE (1990) The Jehovah's Witness and blood: new perspectives on an old dilemma. *J Clin Ethics* 1(1).

Vossenkuhl C (2013) *Der Schutz genetischer Daten: Unter besonderer*

Berücksichtigung des Gendiagnostikgesetzes. Springer, Berlin, Heidelberg.

Wakefield CE, Hanlon LV, Tucker KM, Patenaude AF, Signorelli C, McLoone JK, Cohn RJ (2016) The psychological impact of genetic information on children: a systematic review. *Genet Med* 18(8):755-762.

Weir RF, Peters C (1997) Affirming the decisions adolescents make about life and death. *Hastings Cent Rep* 27(6):29-40.

Wiesemann C (2016) Kindeswohl: ein Problemaufriss aus der Perspektive der Medizinethik. *Z Med Eth* 62(3):235-244.

Wilfond BS, Fernandez CV, Green RC (2015) Disclosing Secondary Findings from Pediatric Sequencing to Families: Considering the Benefit to Families. *J Law Med Ethics* 43(3):552-558.

Winters JP (2018) When Parents Refuse: Resolving Entrenched Disagreements Between Parents and Clinicians in Situations of Uncertainty and Complexity. *Am J Bioeth* 18(8):20-31.

Wynn J, Martinez J, Bulafka J, Duong J, Zhang Y, Chiuzan C, . . . Chung WK (2018) Impact of Receiving Secondary Results from Genomic Research: A 12-Month Longitudinal Study. *J Genet Couns* 27(3):709-722.

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