# Secondary and Incidental Findings in Genetics: Ethical Issues

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# Abstract

Additional findings are a type of result in genomics that is found secondary to the main result. These can be divided into two categories; secondary findings and incidental findings. While incidental findings are found by accident, secondary findings have to be actively looked for during the analysis of the genetic data. Whether secondary findings should be looked for or not is, however, still heavily debated. In research, searching for secondary findings is usually encouraged as they might advance scientific and medical knowledge, however, most agree researchers have no duty to disclose these results to the study participants. In a clinical setting, genetic tests should also be as targeted as possible for various reasons, including the fact that the scientific knowledge about this subject is not robust enough to justify integrating non-targeted genomic testing into the healthcare system. As such, for the time being, the search for secondary findings should be confined to pilot and evaluation studies to make sure that any potential system is built respecting the ethical principles of proportionality, respect for autonomy, justice, and solidarity. Respect for the tested individuals' right not to know also has to be taken into account by incorporating a robust, well-designed informed consent process.

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# Introduction

Genetic tests have been used for quite some time in research and clinical practice to search for genetic disorders. The methods previously used only sequenced key pieces of DNA depending on the question being asked. However, recently there has been a shift, with genome sequencing and exome sequencing becoming more widely used.[1] These techniques are called high-throughput sequencing, and they have sped up the process while reducing costs. These methods allow the tester to identify more genetic changes than would be possible with select gene sequencing.[2] Secondary findings are these changes or variants that can be anticipated and actively sought with a given procedure that is not related to the reason for which the test was done.[3]

Genomic sequencing usually yields a vast amount of data, which requires curation as very few of the variants found will put individuals at risk for disease. Various methods can be utilised to analyse these results and classify them. During this phase, the choice about whether to look for secondary findings or avoided is made.[4] It is also during this phase that incidental findings are discovered. Incidental findings, as the name implies, are all the findings that are found by accident while searching for the main, primary result.

The field of genomics has progressed at a rapid pace in the last decade. Unfortunately, ethical issues arose alongside it. As the field is still in its infancy, it is still debated whether our

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1 Kevin M. Bowling, Michelle L. Thompson, and Gregory M. Cooper, "How Secondary Findings are Made," in *Secondary Findings in Genomic Research,* ed. Martin Langanke, Pia Erdmann, and Kyle B. Brothers (Massachusetts: Academic Press, 2020), chap. 4, Kindle.

2 Celine Moret, Alex Mauron, Siv Fokstuen, Periklis Makrythanasis, and Samia A. Hurst, "Defining Categories of Actionability for Secondary Findings in Next-Generation Sequencing," *Journal of Medical Ethics* 43, no. 5 (2017): 346-349.

3 Andrew J. Darnell et al, "A Clinical Service to Support the Return of Secondary Genomic Findings in Human Research," *The American Journal of Human Genetics* 98, no. 3 (2016): 435-441.

4 Bowling, Thompson, and Cooper, "How Secondary Findings are Made," chap. 4, Kindle.

understanding of it is enough for it to be used in a clinical setting in a non-targeted manner. While there is significant information and knowledge about certain sections of our genome, this is not the case with all of our genetic material. In fact, some of the additional findings that might be unearthed might not have already been adequately studied. Secondary findings are also referred to as a form of opportunistic genetic screening. It is debated whether clinicians and researchers have a duty to search for these types of findings for various reasons. Though in some literature, the duties of clinicians and researchers are considered to be the same, this is not the case. This distinction is essential as a researcher has different duties towards the participants of a study than a clinician has towards his or her patients. There might be a duty to look for secondary findings in clinical care that is not present in research.[5]

Even if a result is generated in research, it should be noted that before it is given to the research subject by a physician, this should be validated by well-established techniques in clinical care to avoid any false positive results. Another aspect to keep in mind is that secondary findings should not be used as an inducement to participate in a study. People should be free to choose whether to enrol in a research study without having to bear undue influence. In other words, they should be able to make an autonomous choice. Some consider that research subjects being given the choice of receiving secondary findings in research actually amounts to an inducement, particularly when this service is not provided in their health care service or is too expensive for them to access it otherwise.[6]

Policies and guidelines regarding secondary findings have been developed in various countries and internationally. Unfortunately, they do not appear to bring more certainty to

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5 Sebastian Schleidgen, and Kyle B. Brothers, "Informed Consent and Decision-making," in *Secondary Findings in Genomic Research,* ed. Martin Langanke, Pia Erdmann, and Kyle B. Brothers (Massachusetts: Academic Press, 2020), chap. 5, Kindle.

6 Ibid.

clinicians and researchers as their recommendations are very different both nationally and internationally, leaving fundamental ethical and policy issues unresolved. The main issue is whether there is a duty to look for secondary findings. It is also debated as to which results should be sought, if it is indeed a duty, as there are still quite a few uncertainties about the significance of various gene variants.

Although clinicians and researchers might have a duty to look for this type of result, it does not mean that the patient or research subject has to receive them. Various studies have shown that most patients would want to know their results. However, some do not want to know.[7] The right not to know one's genetic information has been criticised as being in contradiction with patients' autonomy, with the doctors' duty to inform patients, and with solidarity with family members. However, legitimate concerns may cause individuals to avoid knowing their genetic makeup, such as avoiding severe psychological consequences.[8]

A right not to know implies that the individual can refuse any of the information gathered. Voluntary and informed consent is the only way the person would have the opportunity to do so. Though it is a fundamental ethical and legal requirement, the traditional model may not be adequate.[9] One of the central tenets of informed consent is to provide the subjects with all necessary information so that they can give their consent to all (or selected) aspects of the study and the study outcomes. However, due to the varied nature of these findings, doing so requires the researcher or clinician to inundate the subject with too much information, which

7 Amy L. McGuire et al., "Ethics and Genomic Incidental Findings," *Science* 340, no. 6136 (2013): 1047-1048.

8 Roberto Andorno, "The Right not to Know: An Autonomy Based Approach," *Journal of Medical Ethics* 30, no. 5 (2004): 435-439.

9 Paul S. Appelbaum et al., "Models of Consent to Return of Incidental Findings in Genomic Research," *Hastings Center Report* 44, no. 4 (2014): 22-32.

might inhibit the subject's ability to make an informed decision.[10] A new format is required to deal with this new type of information. Different forms have been proposed, some more straightforward and user-friendly than others.[11]

[10] Schleidgen, and Brothers, "Informed Consent and Decision-making," chap. 5.
[11] Ibid.

# Chapter 1: Secondary and Incidental Findings in Genetics

## 1.1. Genetics Testing Today

### 1.1.1. Evolution of Genetics

The field of genetics is one of the scientific fields that has evolved most rapidly. The genetic tests that were first developed, such as conventional karyotyping, fluorescence in situ hybridisation (FISH), and array comparative genomic hybridisation (CGH), could detect large changes to the DNA, such as deletions, duplications, and translocations. Also, due to the nature of these tests, their results can be predicted; thus, there was little chance that an incidental finding could be made. Suppose, for example, fluorescence in situ hybridisation (FISH) was used. Due to the nature of this test, the only result that could be given is the result the scientist was looking for, as it could only identify specific chromosomal regions from interphase nuclei.[1]

These methods, however, could not detect the single nucleotide changes that occur in some diseases. New methods were thus necessary. The development of the polymerase chain reaction (PCR) technique revolutionised the field of genetics. It is now used in most genetic laboratories having many clinical applications, making it indispensable in science today. Over the years, the technique has been adapted various times. The most significant adaptation could be the automatisation of DNA sequencing, enabling human genome sequencing and making the Human Genome Project possible. Though the first genome sequencing took many years, it is now possible to sequence the complete human genome in around four hours.[2] Thus, High-Throughput Sequencing (HTS) is more accessible to scientists than ever due to the

[1] Asude Alpman Durmaz et al., "Evolution of Genetic Techniques: Past, Present, and Beyond," *BioMed Research International,* last modified March 22, 2015, https://www.hindawi.com/journals.

[2] "When Do I Use Sanger Sequencing vs NGS?" ThermoFisher Scientific, accessed October 12, 2021. https://www.thermofisher.com/blog/behindthebench/when-do-i-use-sanger-sequencing-vs-ngs-seq-it-out-7.

decreased time and the cost required. Using this technology has enabled researchers to discover causal variants in single-gene disorders, as well as, the complex genomic landscapes of many diseases.[3]

While new technologies can answer more of the scientists' questions, they can also create ethical dilemmas. For example, some conventional karyotyping, FISH, and array-CGH are limited in the type of results they can produce, so the chance of an incidental or secondary finding is practically impossible. On the other hand, NGS produces a large amount of data. Though the scientist conducting the test might be interested in only a tiny portion of the DNA, this technique produces extraneous data that may contain relevant information to the test subject but is not in line with the reason why this test was conducted.[4]

### 1.1.2. High-Throughput Sequencing

Genome sequencing (GS), also referred to as whole-genome sequencing (WGS), is the sequencing of the whole genome, that is, both the coding and the non-coding regions. Exome sequencing (ES), on the other hand, targets only the coding parts of the genome and the DNA adjacent to them. There are various reasons why one might be used over the other, including the lower cost of ES in terms of data storage and analysis. ES produces smaller data sets, reducing the time needed for analysis.

ES, however, requires an additional experimental step. This step involves targeting the exons. An important aspect of this step is the coverage of the exons in question. Coverage refers to the number of times a specific section of the genome is copied. The more times the sequence is copied, the better as it increases the accuracy. Unfortunately, this step may decrease the quality of the data due to poor or inconsistent coverage of exons and reduce the ability to detect structural variation. An advantage of this method is that it can be used to target only the sections of the genome which are known to be pathogenic or that increase the risk of a disease. These “Disease Panels” are used in diagnostic medicine to look for risk factors associated with breast cancers, cardiac arrhythmias and many other diseases. GS, on the

[3] Sam Behjati, and Patrick S. Tarpey, "What is Next Generation Sequencing?" *Archives of Disease in Childhood-Education and Practice* 98, no. 6 (2013): 236-238.

[4] Asude Alpman Durmaz et al., "Evolution of Genetic Techniques: Past, Present, and Beyond."

other hand, has a more uniform coverage, resulting in the better capture of coding exons, helped by the fact that there is no additional step to target the capture. It also decodes all the genetic material, including gene regulatory regions.

Conversely, it produces a large amount of data, which requires more time and staffing to decode and costs more to produce and store. However, the disparity between the costs is decreasing, and the ability to interpret gene regulatory regions is increasing, making GS more useful. GS is consequently becoming ever more prevalent over ES.[5]

### 1.1.3. Procedure used for ES and GS

The first step is isolating the DNA from the sample provided. After isolation, the DNA needs to be broken down into small fragments. The most common method used is sonication,[6] which shears the DNA into smaller, more manageable pieces, and adapter sequences[7] are added. The adapter sequences are added as these will later aid the fragments in attaching to a glass slide. Certain protocols then use PCR to amplify the sample provided, making more copies of the sample. This creates what is known as the ES or GS sequencing libraries. If ES is in progress, complementary oligonucleotide probes are added, which hybridise to select the needed sections of DNA.[8]

These are then placed on a flowcell, which is a specialised glass slide that has grooves on its surface. The sequencing library is generated on this slide. The adapter sequences previously added will attach to the glass slide together with the rest of the DNA to be sequenced. PCR amplifies these fragments to create clusters of identical copies of each fragment in a channel. Once this is completed, a sequencing machine is used to sequence all the fragments attached to the flowcell in question.[9]

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5 Britt-Sabina Petersen et al., "Opportunities and Challenges of Whole-Genome and -Exome Sequencing," *BioMed Central Genetics* 18, no. 1 (2017): 1-13.

6 Sonication uses sound waves to break down the cell to extract the DNA. It is also used to break down the DNA into smaller pieces.

7 An adaptor sequence is a portion of DNA specifically syntesised to perform a task. In this case, one end will bind to the DNA pieces while the other end will attach to molecules on a glass slide, acting as a bridge.

8 Kevin M. Bowling, Michelle L. Thompson, and Gregory M. Cooper, "How Secondary Findings are Made," in *Secondary Findings in Genomic Research,* ed. Martin Langanke, Pia Erdmann, and Kyle B. Brothers (Massachusetts: Academic Press, 2020), chap. 4, Kindle.

9 Ibid.

During the sequencing process, new DNA strands are created to attach to the strands already attached to the flowcell, similar to PCR. The nucleotides used, however, are different because they are labelled with fluorescent dye. Each of the four different types of nucleotides is attached to a dye of a different colour. Sequencing occurs in cycles. During each cycle, a nucleotide attaches to the end of each strand of DNA. Around three hundred cycles are needed to analyse the genome, each cycle producing one new data point for each of the hundreds of millions of reads. An image is taken after each cycle to see the new colour, which is attached. The images are analysed by software, which interprets each colour as a nucleotide and simultaneously calculates quality data, ultimately showing the DNA sequence of each strand on a "fastq" file for later analysis.[10]

### 1.1.4. Sequence Analysis

Though the sequencing is completed, these are still bits of DNA without any order or context. The pieces are aligned to the reference genome, and any variations are identified. The fastq file containing the new sequence must be compared to a reference genome to put the pieces in order within the genome. Two types of quality scores are then produced. One is used to determine whether the genetic variant sequenced are of sufficient quality using quality control metrics to determine the sequencing data's effectiveness and accuracy.[11]

The other quality score produced is about the uniformity of coverage, which indicates confidence in the variant call. The more times a portion is sequenced, the higher the read quality, as any mistake that occurs might be caught and corrected during analysis. A high sample coverage, however, is not enough for a sample might have a high coverage overall, but this coverage could be only concentrated on a small part of the sample. This area would be highly covered, while others will have abysmal coverage. The more uniform the coverage, the higher the chance that all of the genome is of higher quality with fewer mistakes made during the analysis.[12]

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[10] A "fastq" file is a text file that stores all the data from each cluster processed. Using different tools, the fragments can br re-ordered to form a complete genome. This format is also ideal for downstream analysis.

[11] Bowling, Thompson, and Cooper, "How Secondary Findings are made," chap. 4.

[12] Ibid.

Coverage of different regions will vary from sample to sample. There are also some areas of the genome which are notorious for their consistently low coverage. These regions may contain genes known to be clinically relevant, causing interference with identifying secondary or incidental findings.[13] Indeed, before a variant result can be issued the number of reads that had taken place at that position has to be taken into account so as to verify its accuracy. The coverage also has to be taken into account before a negative result is issued so as to make sure that nothing is missed. Further, the coverage of the genes of particular interest, i.e., the genes to be examined and why the test is being conducted, should be high enough that no variation is missed due to poor coverage.

The next step is variant calling. The sequence is compared to the reference genome during this step,[14] and any variations are flagged. As humans inherit their genetic code from both parents, there are two copies of each chromosome, except in the sex chromosomes in men. Thus it is crucial to know whether any variation is found on both copies of the gene or only one. There might also be sequencing errors that occur, which will read as a variant. All of this makes it difficult to accurately make the call that a variant is actually present. The type of variant present also affects the accuracy. It is, for example, easier to find a single-nucleotide variant than an insertion or deletion variant. There are various methods that can be used that help mitigate this, increasing the accuracy of the sequencing as a whole.[15]

All the variants found will then need to be annotated. During this step, each variant found would be associated with biological information to clarify which genes are affected by the variation and to understand potential disease consequences.[16] After annotations have been added, quality control is performed using statistics. This process would highlight an error in the sequencing process that has happened thus far if a particular sample does not meet one or more of the quality points.

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13 Rashesh V. Sanghvi et al., "Characterizing Reduced Coverage Regions through Comparison of Exome and Genome Sequencing Data across 10 Centers," *Genetics in Medicine* 20, no. 8 (2018): 855-866.

14 Aaron McKenna et al., "The Genome Analysis Toolkit: a MapReduce Framework for Analyzing Next-generation DNA Sequencing Data," *Genome Research* 20, no. 9 (2010): 1297-1303.

15 Bowling, Thompson, and Cooper, "How Secondary Findings are made," chap. 4.

16 Melissa J. Landrum et al., "ClinVar: Improving Access to Variant Interpretations and Supporting Evidence," *Nucleic Acids Research* 46, no. D1 (2018): D1062-D1067.

### 1.1.5. Variant Filtering

All variants found in the previous step would now be filtered according to the annotation attached to them and their pattern of inheritance so as to reduce the number of variants that require further examination. This is an essential step as each ES will usually yield tens of thousands of variants while each GS will yield millions of variants, few of which increase the risk of a genetic disease. The variants are therefore filtered by comparing them to a database containing the common gene variations, taking into account their frequency in different populations.[17] For rare diseases, common variants are removed automatically from a list of variants, such as synonymous variants. Some of the annotations that are used for variant filtration include the effect on gene protein product, and information contained within clinical disease databases.[18]

During variant filtration any additional findings may be looked for or avoided. Various lists exist of pathogenic genetic variations. These gene lists and the annotations previously made can be used as a filter to identify additional findings. On the other hand, a gene list can also be compiled that when applied will remove these genes from those that are analysed, thus avoid specific additional findings. Due to multiple factors, including the fact that some of the same genes might be useful to the primary findings, this method is rarely used. Even if this method is used, there is no guarantee that all additional findings are avoided as a finding not on this list may still be generated.[19]

It is important to note that GS and ES are still mainly used for research, not for clinical use. In a clinical setting, panels are usually used which have less genes and more coverage. By using these panels, only the sections of the DNA the clinician is interested in are amplified, which increases the accuracy and specificity of the test. When GS and ES are used in research, the results are valid for the purposes of the research being done. The same result cannot be used in a clinical setting. The method used has to either be validated for clinical purposes, or the test has to be conducted again using clinically validated methods. The result cannot be told

[17] Monkol Lek et al., "Analysis of Protein-Coding Genetic Variation in 60,706 Humans," *Nature* 536, no. 7616 (2016): 285-291.

[18] Bowling, Thompson, and Cooper, "How Secondary Findings are made," chap. 4.

[19] Ibid.

to the patient before this step is complete so as to avoid as much as possible the presence of false positive and false negative results.[20]

## 1.2. Terminology used

There are various terminologies used to refer to the findings not associated with the primary investigations. One of these is unexpected findings. This term could be helpful as it is a familiar word, making it beneficial when communicating these types of results to the tested individual. At the same time, it lacks the precision required to discuss the problems raised by genomics results effectively. One of the problems with this term is that the difference between expected and unexpected is not always clear. Those conducting the tests will already know that they may uncover a result not sought by the primary investigation.[21]

Another more practical way to speak of results would be to do so in relation to the purpose of the study. Thus any finding not relevant to the primary investigation is an additional finding. This term is preferred by many as it is easily understood.[22] Not all additional findings, however, are the same. The most important differentiation between the two types of additional findings, which are secondary and incidental findings, is how they are found. Incidental results, as can be deduced from the name, are found by accident and could not have been avoided during the testing for the primary results. For example, incidental findings are found as a part of the quality control procedure. Some laboratories match the given sex of the individuals being tested with the genetic sex of the sample, as a quality control step to make sure that the samples have not been accidentally switched or that data has not been incorrectly transposed. The genome of the individual is thus being tested away from the site of the primary investigation. This is unavoidable. The examination of these genes may lead to abnormalities with the sex chromosomes being found, such as revealing sex chromosome

[20] Yuriy Shevchenko, and Sherri Bale, "Clinical versus Research Sequencing," *Cold Spring Harbor Perspectives in Medicine* 6, no. 11 (2016): a025809.

[21] Kyle B. Brothers, Martin Langanke and Pia Erdmann, "Introduction," in *Secondary Findings in Genomic Research*, ed. Martin Langanke, Pia Erdmann and Kyle B. Brothers (Massachusetts: Academic Press, 2020), chap. 1, Kindle.

[22] Nina Tan et al., "Is “Incidental Finding” the Best Term?: A Study of Patients’ Preferences," *Genetics in Medicine* 19, no. 2 (2017): 176-181.

aneuploidies (medical conditions like Turner syndrome are a result of a difference in the number of X and Y chromosomes).[23]

As previously mentioned, however, many of the findings generated by GS and ES are not genuinely unavoidable. As the variants in the genome can be selected for or against during the filtration process, these findings are not incidental but are secondary findings. As the term implies, a secondary finding is a result which has nothing to do with the primary cause for testing. Secondary findings are thus results which are found intentionally while analysing the genetic code. In this sense, "additional findings" is a collective term that includes both incidental and secondary findings.[24]

### 1.2.1. Genomic Risk of Disease

Using GS or ES, the risk of developing various diseases, such as heart disease, dementia and cancer, can be calculated. This, however, is usually not as easy to do as it first appears. It is pretty complex to work out the exact risk inherent in the DNA of an individual, as there are various factors in play. Also, due to the complexity involved, researchers and clinicians are still working out the utility of their discoveries.

One of the challenges faced is the fact that most of the functions of the body rely not just on one gene or a few genes but on thousands of genes. Thus, in complex diseases mutations have to occur at various points in the genome, each mutation increasing the risk by small degrees. Also, not all mutations are created equal. A gene can incur different types of mutations in different people. Although the same gene is mutated, the amount of risk varies.[25]

While this polygenic underpinning is ideal, as the risk of most diseases relies on multiple genetic variants, it makes it harder to accurately measure the risk involved. It is important to also mention that the risk of developing a disease is not reliant solely on genetic factors. Environmental factors, such as smoking, diet or stress, also play an essential role.[26] It is thus

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23 Langanke et al., "Concept, History and State of Debate," chap. 1.

24 Ibid.

25 Cathryn Lewis and Oliver Pain, "Genetics Helps Estimate the Risk of Disease – But How Much Does It Really Tell Us?" last modified January 26, 2022, https://theconversation.com.

26 Ibid.

vital when communicating these types of results to the individual that they are made aware that even though they might have an increased risk of developing a disease or disorder, this does not necessarily mean that they will develop it.

## 1.3. History of the debate

### 1.3.1. The First and Second Phases

The debate about secondary findings began in the early 2000s concentrating on the normative and practical challenges related to handling additional findings, all of which were at the time referred to as incidental findings, in research. This discussion progressed and developed in phases as time passed. During the first phase, the main focus was on the handling of incidental findings in neuroimaging studies and how they should be disclosed to the research subjects. Practical and normative questions were being raised about this topic in literature. The start of the discussion is mainly attributed to the publication of three papers in high-impact journals.[27]

The debate progressed in 2008 to the second phase, where the debate evolved to include more general topics. Though papers focusing mainly on neuroimaging continued to be published,[28] others focused on other topics including the normative problems associated with the use of imaging techniques in medical research.[29] Two papers, in particular, sparked the debate,[30] one of which included recommendations for responsibly managing incidental

[27] Judy Illes et al., "Ethical and Practical Considerations in Managing Incidental Findings in Functional Magnetic Resonance Imaging," *Brain and Cognition* 50, no. 3 (2002): 358-365; Judith Illes et al., "Ethical Consideration of Incidental Findings on Adult Brain MRI in Research," *Neurology* 62, no. 6 (2004): 888-890; Judy Illes et al., "Incidental Findings in Brain Imaging Research," *Science* 311, no. 5762 (2006): 783-784.

[28] Nigel Hoggard et al., "The High Incidence and Bioethics of Findings on Magnetic Resonance Brain Imaging of Normal Volunteers for Neuroscience Research," *Journal of Medical Ethics* 35, no. 3 (2009): 194-199; Andrew Chow, and Katharine J. Drummond, "Ethical Considerations for Normal Control Subjects in MRI Research," *Journal of Clinical Neuroscience* 17, no. 9 (2010): 1111-1113; Ronald J. H. Borra, and A. Gregory Sorensen, "Incidental Findings in Brain MRI Research: What Do We Owe Our Subjects?" *Journal of the American College of Radiology* 8, no. 12 (2011): 848-852.

[29] Hassan Siddiki et al., "Incidental Findings in CT Colonography: Literature Review and Survey of Current Research Practice," *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 320-331; C. I. Woodward, and A. P. Toms, "Incidental Findings in “Normal” Volunteers," *Clinical Radiology* 64, no. 10 (2009): 951-953.

[30] Susan M. Wolf, "The Challenge of Incidental Findings," *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 216-218; Susan M. Wolf et al., "Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations." *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 219-248.

findings generated through imaging research.[31] Another development of note within this period is the publication of a series of papers dealing with normative and practical aspects associated with the use of whole-body MRI in population-based research.[32]

### 1.3.2. The Third Phase

During this phase, there was a massive shift in the discourse from research imaging to non-imaging contexts, mainly genetics and genomics. Papers began discussing incidental findings in genetics and genomics, using the same terminology used while discussing imaging.[33] Papers on this subject increased over time with contributions from various disciplines and national contexts,[34] culminating in the publication of various guides on how to responsibly disclosure additional findings in genetics and genomics research.[35]

At the tail end of this phase, the discourse began to diverge between imaging and genetics in terminology as well as methodology. In imaging contexts, the main focus was on incidental findings in population-based imaging research.[36] On the other hand, it was becoming increasingly clear that actual, incidental findings in genetics do not happen very often,[37]

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31 Wolf et al., "Managing incidental findings," 219-248.

32 S. H. X. Morin et al., "Incidental Findings in Healthy Control Research Subjects using Whole-Body MRI," *European Journal of Radiology* 72, no. 3 (2009): 529-533.

33 Bartha Maria Knoppers et al., "The Emergence of an Ethical Duty to Disclose Genetic Research Results: International Perspectives," *European Journal of Human Genetics* 14, no. 11 (2006): 1170-1178; Vardit Ravitsky, and Benjamin S. Wilfond, "Disclosing Individual Genetic Results to Research Participants," *The American Journal of Bioethics* 6, no. 6 (2006): 8-17.

34 Mildred K. Cho, "Understanding Incidental Findings in the Context of Genetics and Genomics," *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 280-285; Jonathan S. Berg, Muin J. Khoury, and James P. Evans, "Deploying Whole Genome Sequencing In Clinical Practice and Public Health: Meeting the Challenge One Bin at a Time," *Genetics in Medicine* 13, no. 6 (2011): 499-504; Annelien L. Bredenoord, N. Charlotte Onland-Moret, and Johannes J. M. Van Delden, "Feedback of Individual Genetic Results to Research Participants: In Favor of A Qualified Disclosure Policy," *Human Mutation* 32, no. 8 (2011): 861-867; Holly K. Tabor et al., "Genomics Really Gets Personal: How Exome and Whole Genome Sequencing Challenge the Ethical Framework of Human Genetics Research," *American Journal of Medical Genetics* Part A 155, no. 12 (2011): 2916-2924.

35 Wylie Burke et al., "Recommendations for Returning Genomic Incidental Findings? We Need to Talk!" *Genetics in Medicine* 15, no. 11 (2013): 854-859; Robert C. Green et al., "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing," *Genetics in Medicine* 15, no. 7 (2013): 565-574; Guido de Wert et al., "Opportunistic Genomic Screening. Recommendations of the European Society of Human Genetics," *European Journal of Human Genetics* 29, no. 3 (2021): 365-377.

36 Carsten Oliver Schmidt et al., "Psychosocial Consequences and Severity of Disclosed Incidental Findings from Whole-Body MRI in a General Population Study," *European Radiology* 23, no. 5 (2013): 1343-1351.

37 Sebastian Schuol et al., "So Rare We Need to Hunt for Them: Reframing the Ethical Debate on Incidental Findings," *Genome medicine* 7, no. 1 (2015): 1-7.

mainly confined to accidental findings during quality control procedures, as mentioned above. Most of the additional findings are found quite intentionally; thus, continuing to call them incidental findings was confusing and incorrect. New terminology was needed therefore to differentiate actual, incidental findings from the other types of results that can be generated during genetic and genomic studies. New terms like “unsolicited findings,” “secondary findings,” or “additional findings” started being used.

### 1.3.3. Lessons learned from population-based imaging

As previously stated, incidental findings in imaging studies and secondary findings in genetics and genomics share several key features, one of which is that they both may be medically relevant and are unexpected by the tested subject. Thus, legal and ethical debates discussing one can also be broadly applicable to the other.[38]

Although the methods and processes used by the two disciplines are very different from one another, they have the same issues when it comes to quality. The issue of quality arises from two parts of the methods used, the quality of the methodology and equipment used to conduct the study, as well as the quality of the interpretation of the data collected so that it makes medical sense. Thus, the quality of the tests done may be affected if innovative, nonstandard, or unvalidated tests or methods are used during a research study. The data generated is of unknown quality and thus cannot be directly used for medical purposes. These results cannot be considered medically relevant until they are corroborated with results from traditional tests that are standardised and validated for diagnostic and treatment purposes. Failure to do so may result in information being given to the subjects that is misleading and of poor quality.

The main aim of returning additional findings is to minimise potential harm to the tested individual. Giving them unvalidated results may have the inverse effect and should thus be avoided. This is due to the fact that poor-quality results have a high incidence of false negatives and false positives. Without proper validation the sensitivity, specificity, and

[38] Langanke et al., "Concept, History and State of Debate," chap. 1.

reliability of innovative tests and methods are not reliable, even if at first glance they produce results of a better quality than those that can be achieved using existing validated methods.[39]

Unfortunately, in some cases, corroboration with validated test results is very difficult to achieve, especially if the type of result produced is not usually generated in a clinical setting due to the absence of specialised equipment or personnel expertise. Another obstacle faced is that the scientists do not have access to the clinical resources or expertise necessary, either, for example, due to constraints in funding or the geographical location the study is taking place. In both these cases, the additional results could not and should not be disclosed to the patient as the benefits that may be experienced do not outweigh the potential harms.[40]

The quality of the data depends on many factors including on the skill of the person interpreting the data, be it a laboratory scientist, radiologist, or physician-scientist. On the surface, interpreting the data appears relatively easy. This is, however, far more complex than it initially appears. The data has to be interpreted in a way where it is not only correct and reliable but also valuable in some context. As part of the interpretation process, therefore, the investigators should also consider other aspects, not only the quality of the result in itself. They should also take into account whether the result is actionable, not redundant, and of pathological relevance.[41]

The actionability of a result is highly important as this affects how useful the result could potentially be for the tested individual. If a result is termed as actionable, this means that it could be useful for clinical diagnostics, screening, prevention measures, or treatment interventions.[42] Actionability is thus usually associated with the malfunction of a particular gene and the medical condition that is associated with it. It is sometimes forgotten that there are other aspects that can influence actionability, such as societal factors. Thus a scientific result must not be seen only from the scientific point of view as there are a myriad of other factors involved that will vary from one tested subject to another.[43] Some of the factors that will influence the actionabilty are the persons' family history, their access to social support

39 Ibid.
40 Ibid.
41 Ibid.
42 Berg, Khoury, and Evans, "Deploying whole genome sequencing in clinical practice and public health," 499-504.
43 Langanke et al., "Concept, History and State of Debate," chap. 1.

and health care, their primary condition for which the test was originally done, as well as any previous experience they might have had with genetic testing and counselling.[44]

One of the main differences to keep in mind between a research setting and a clinical one, is the fact that in a clinical setting, the clinician has access to the patient history which gives all the relevant background information. Thus, the clinician can use this information to produce context specific results. On the other hand, most researchers are not privy to the clinical history of their research subjects. This lack of data will decrease the quality of the secondary results produced by the research team. The lack of clinical history is more acutely felt when the methods used for research analysis are not the same as those used for clinical practice, and thus cannot be directly compared. It is, thus, of utmost importance that any result produced in research, is verified in a clinical setting before it is issued to the research participant. The quality of a result is thus a critical issue in examining the ethical implications of incidental and secondary results.[45]

Another key difference between research and clinical practice is how a result is handled once it is known. In a clinical setting, there would be protocols in place that allow the different professions that are a part of the patient's team to meet and discuss the patient's result at length, making sure that all aspects are considered before a result is given to the patient. This is usually called a Clinical Multidisciplinary Team. In research, each member of the Scientific Research Team has their own tasks to accomplish. Their main aim is the research being done and would not have the time or funding to give such a service to the research subject.

### 1.3.4. Fourth Phase

The current and fourth phase of discourse focuses on the issues that are specific to secondary findings. While ES and GS have been performed for some time in research, the field has recently started being used in a clinical setting. As ES and GS are not yet validated for clinical applications, any result found using these methods has to then be validated using other more conventional methods. As stated in the Belmont Report, there must be a strict division

[44] Marlies Saelaert, Heidi Mertes, Elfride De Baere, and Ignaas Devisch, "Incidental or Secondary Findings: An Integrative and Patient-inclusive Approach to the current Debate," *European Journal of Human Genetics* 26, no. 10 (2018): 1424-1431.

[45] Langanke et al., "Concept, History and State of Debate," chap. 1.

between research and clinical care. The use of genomics has, unfortunately, blurred this boundary.[46] As such, one of the issues is whether medical research using genomics should be considered research or clinical care. This distinction is essential as a researcher has different duties towards the participants of a study than a clinician has towards his or her patients. There might be a duty to look for secondary findings in clinical care that is not present in research. A research team cannot be held to the same standard and responsibility as a clinical team. A research team may lack the necessary funding and staffing, such as not having a genetic counsellor to give results to the research subject, that are available in a clinical setting.

Another issue faced by clinicians and researchers is that the patients or participants themselves have certain rights that are not congruent with the purported duty to look for secondary findings. By exercising their right not to know, the patient can decide not to be informed of any of the secondary findings. It is still debated, however, if this right exists where secondary findings are concerned or not, especially as these results can have far-reaching implications, including for the patients' biological family.[47]

Another aspect of genomic testing that differs from other forms of testing is that it changes the relationship between clinicians and patients. As has already been mentioned, the interpretation of genomic data, particularly for secondary findings, is very complicated. It is often the case that clinicians are not comfortable relaying the results to patients, either due to lack of treatment or prevention available, because of the unreasonable expectations the patients might have or because the clinicians themselves are not well versed about this type of testing. This problem is also found in research to a greater degree as most researchers are mainly trained in their scientific field, do not have the same experience as a medical doctor and do not have the same type of relationship with their subjects. Any result found should, thus, be validated by a medical doctor and communicated to the participant via this medical professional. Thus, a standardised method has to be in place, which helps the clinicians to communicate and be able to explain all that the patient needs to know.[48]

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[46] Sandi Dheensa, Gabrielle Samuel, Anneke M. Lucassen, and Bobbie Farsides, "Towards a National Genomics Medicine Service: the Challenges facing Clinical-Research hybrid Practices and the Case of the 100 000 Genomes Project," *Journal of Medical Ethics* 44, no. 6 (2018): 397-403.

[47] Marie Gaille, and Ruth Horn, "The ethics of Genomic Medicine: Redefining Values and Norms in the UK and France," *European Journal of Human Genetics* 29, no. 5 (2021): 780-788.

[48] Ibid.

# Chapter 2: The Duty to Look for Secondary Findings

Secondary findings, as described in the previous chapter, are not found by accident but involve an active search, mainly using opportunistic genetic screening (OGS). OGS differs from the usual population-based screening programs in that not all of the population is being screened in a systematic fashion. The only screened individuals are those who are already being tested for another reason. In this instance, only those already undergoing ES or GS for another reason would be eligible for this type of screening. The individuals who would undergo this type of screening would not have to be subjected to additional medical tests or procedures.[1] As previously described (in section 1.1.4), secondary findings are found in the analysis phase of the sequencing process. It is not, however, clear-cut whether this should be conducted in practice or not, with various institutions publishing their own recommendations of whether this should be done. Moreover, if this is put into practice as is done in certain countries, which genes should be targeted for testing would also become debatable.

The most influential of these are the recommendations issued by the American College of Medical Genetics and Genomics (ACMG)[2] and the European Society of Human Genetics (ESHG).[3] Other entities, such as the French Society of Preventative and Personalised Medicine (SFMPP),[4] and the Heidelberg-based interdisciplinary Ethical and Legal Aspects of Next Generation Sequencing (EURAT) Group.[5] The SFMPP recommends that when secondary findings are present, they should be classified into three groups, based on their actionability,

1 Guido de Wert et al., "Opportunistic Genomic Screening. Recommendations of the European Society of Human Genetics," *European Journal of Human Genetics* 29, no. 3 (2021): 365-377.

2 Sarah S. Kalia et al., "Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing, 2016 Update (ACMG SF V2. 0): A Policy Statement of the American College of Medical Genetics and Genomics," *Genetics in Medicine* 19, no. 2 (2017): 249-255.

3 de Wert et al., "Opportunistic Genomic Screening," 365-377.

4 Pascal Pujol et al, "Guidelines for Reporting Secondary Findings of Genome Sequencing in Cancer Genes: the SFMPP Recommendations," *European Journal of Human Genetics* 26, no. 12 (2018): 1732-1742.

5 Project EURAT, "Cornerstones for an ethically and legally informed practice of Whole Genome Sequencing: Code of Conduct and Patient Consent Models," last modified May, 2016, https://www.uni-heidelberg.de/md/totalsequenzierung.

their potential risk, and the level of evidence found in published papers. Whether the results are given to the patients depends on which category the results found are placed in.[6]

The EURAT Group recommendations apply only to a research setting. They state that researchers have no obligation to deliberately search for findings that are beyond the scope of the primary result. They also state that any finding must be clinically validated before it is communicated to the participant by a physician. The physician should be the one to choose how the results are validated and, depending on these results, should be the one to decide whether to inform the subject or not.[7]

## 2.1. Proportionality

Since the search for secondary findings is done on the data of individuals who had no prior medical history based reason for the investigations done, the issue of proportionality applies to research as well as to clinical investigations. Opportunistic screening of any genetic data may result in beneficial information to the tested individuals; however, the opposite is also possible. The benefits and harms must be balanced before any OGS framework is put in place, as the whole exercise must ultimately be of undoubted benefit to the tested individuals. Another aspect that should be taken into account is that this is a form of genetic screening.

Any result issued by any type of genetic investigation will affect not just the individual being tested but also their genetic relatives. Thus, the proportionality balance must be positive not only for the tested individuals but also for their genetic relatives, taking into account third-party effects.[8] While a result might be beneficial for the tested individual, this might not be so for their relatives. They might experience psychological harm and anxiety by knowing that they might have a genetic risk for a specific disease, especially if they did not want to know about it in the first place. It might also be the case that while the tested individual has the resources to undergo additional testing, their relatives do not, leaving them with only the uncertainty without being able to get a definitive diagnosis about themselves.

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6 Pujol et al, "Guidelines for Reporting Secondary Findings," 1732-1742.

7 Project EURAT, “Cornerstones for an ethically and legally informed practice of Whole Genome Sequencing.”

8 Ibid.

### 2.1.1. Possible Benefits

There are various benefits that can be reaped by knowing secondary findings, including important information about one's reproductive health. The main, most important benefit, however, will always be medical in nature. Before an additional result is given to the tested individual, it must pass through various check points, one of which is deciding whether the result found is actionable or not. Only those results which are actionable are usually given to the tested individual. This inherently means that the tested individuals will only receive results that can be useful for a clinical diagnosis, screening, prevention measures, or treatment interventions. Such a result could potentially be useful to prevent serious genetic disorders.[9] As these tests are done on people who are currently asymptomatic for these disorders, this could have a large effect on the prevention of disease or treatment of the individual. The diseases that are most commonly tested for are hereditary cardiac and cancer disorders.

As with any genetic result, additional findings would impact not only the person who was tested but also their biological relatives, as they might have inherited the same variant. A recent study has shown that when healthy individuals are tested using the ACMG list, 2.6% of those tested have gene variants which increases the risk for a severe dominant disease.[10] If this is extrapolated to represent the whole population, this shows that there might be considerable benefits to conducting OGS, though this depends on multiple factors. The positive predictive value of the secondary findings targeted in the OGS panel must be high, the effectiveness of any preventative measure to be used has to be scientifically proven, and access to these preventative measures, as well as genetic counselling, should be guaranteed. In a research setting, it is impossible to guarantee that the research subject would have access to preventative measures and genetic counselling, as they fall outside their remit. It can, therefore, be inferred that for a result to have a possible benefit, it must be issued in a clinical setting.

The medical benefits also include the possibility of a more favourable risk-to-benefit ratio for medical interventions or treatments that the individual might undergo in the future, including

[9] Roel H. P. Wouters et al., "Is It Our Duty to Hunt for Pathogenic Mutations?" *Trends in Molecular Medicine* 24, no. 1 (2018): 3-6.

[10] Lonneke Haer-Wigman et al., "1 in 38 Individuals at Risk of a Dominant Medically Actionable Disease," *European Journal of Human Genetics* 27, no. 2 (2019): 325-330.

screening for genetic variants causing severe adverse effects to anaesthetics or for pharmacogenomics variants. The pharmacogenetics variants are considered of increasing importance, especially those variants "related to commonly prescribed medications as well as medications associated with serious adverse events for which there is greater urgency surrounding actionability."[11] Another possible benefit may be of reproductive value. Any person screened or their relatives may obtain positive results that can help them make informed reproductive choices, such as avoiding the conception of a child with a severe genetic disorder.

As more research is done on the genome, it is probable that the list of benefits will increase as more variants will be found that meet the criteria for pathogenicity and actionability. Currently, only single genetic variants are included. In the future, genome-wide polygenic risk scores might also be added if evidence shows that they have a clinical utility, such as reducing the risk of developing common disorders like diabetes type 2 and coronary heart disease.[12] The reproductive benefits may also increase if the carrier status of an individual for a potentially large number of serious recessive disorders is tested.

### 2.1.2. Possible Risks

Though the possible benefits are medical in nature, the possible risks can be psychological, social as well as medical. There are various scenarios in which these can occur.

Psychological and medical harm can occur, especially if results are given to the patient that are based on inadequate scientific and medical knowledge. Moreover, if the variant tested has low pathogenicity (its ability to cause damage), penetrance (how many of the population who have the variant also have the disease) and expressivity (how severe any malady caused is), it is of no use to the tested individual. It might also be the case that a result is found whose pathogenicity, penetrance and expressivity are not known. These alleles might be prevalent in affected families, but their penetrance in the wider population is either uncertain or lower.[13] Ongoing research is of vital importance in this issue of penetrance as well as

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11 Kalia et al., "Recommendations for Reporting of Secondary Findings," 249-255.

12 Amit V. Khera et al., "Genome-wide Polygenic Scores for Common Diseases Identify Individuals with Risk Equivalent to Monogenic Mutations," *Nature Genetics* 50, no. 9 (2018): 1219-1224.

13 Burke et al., "Recommendations for returning genomic incidental findings?" 854-859; Neil A. Holtzman, "ACMG Recommendations on Incidental Findings Are Flawed Scientifically and Ethically," *Genetics in Medicine* 15, no. 9 (2013): 750-751.

expressivity, as the penetrance of specific genes has been shown to have been overestimated.[14] This is mainly due to the fact that when a defect in a gene is first identified, the families of those affected will be extensively tested. The incidence is naturally higher in these families as opposed to the general population. The penetrance of a variant, however, is sometimes calculated based mainly on the first studies of which these families form a large part, leading to higher penetrance figures than is actually the case when seen from a population perspective.[15] Some variants have also been misclassified as pathogenic. One reason could be due to the research subjects being from a diverse ethnic population, with researchers not giving the inherent variations in the genome of differing populations due consideration.[16]

This overestimation of the risks involved may result in unnecessary anxiety for the tested individuals, and they might have to be subjected to the psychological distress of long-term surveillance. There is not sufficient empirical data, however, to support this claim. Some studies have found that people are more psychologically resilient than professionals expect, with long-term anxiety or depression rarely seen.[17] That being said, there are instances when such a diagnosis would clearly cause psychological harm, such as when one is told that they carry the genetic variants which cause Huntington's disease.[18]

Also, due to their perceived abnormal results, they might be subjected to a myriad of unnecessary, sometimes invasive, procedures for diagnostic or preventative measures, which in themselves may cause harm.[19] This is not to say that the penetrance and pathogenicity of the variant in a given population might not still be high enough to warrant investigation during

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14 Arnon Adler et al., "An International, Multicentered, Evidence-Based Reappraisal of Genes Reported to Cause Congenital Long QT Syndrome," *Circulation* 141, no. 6 (2020): 418-428; Roddy Walsh et al., "Reassessment of Mendelian Gene Pathogenicity Using 7,855 Cardiomyopathy Cases and 60,706 Reference Samples," *Genetics in Medicine* 19, no. 2 (2017): 192-203.

15 Heather Turner, and Leigh Jackson, "Evidence for Penetrance in Patients without a Family History of Disease: A Systematic Review," *European Journal of Human Genetics* 28, no. 5 (2020): 539-550.

16 Arjun K. Manrai et al., "Genetic Misdiagnoses and the Potential for Health Disparities," *New England Journal of Medicine* 375, no. 7 (2016): 655-665.

17 April Malia Hirschberg, Gayun Chan-Smutko, and William F. Pirl, "Psychiatric Implications of Cancer Genetic Testing," *Cancer* 121, no. 3 (2015): 341-360.

18 Tarja-Brita Robins Wahlin, "To Know or Not to Know: A Review of Behaviour and Suicidal Ideation in Preclinical Huntington's disease," *Patient Education and Counseling* 65, no. 3 (2007): 279-287.

19 Jaeger P. Ackerman et al., "The Promise and Peril of Precision Medicine: Phenotyping Still Matters Most," *Mayo Clinic Proceedings* 91, no. 11 (2016): 1606-1616.

OGS. The lower risks found would merely have to be paired with preventative plans, which reflect its overall risk.

A genetic result could also have the opposite effect, causing an underestimation of the risks involved by offering a false reassurance. After undergoing a Breast Cancer Panel and getting a negative result, individuals might be falsely reassured that they are not at risk of developing breast cancer. This might lead the individuals to decide that as they are not at risk, they do not have to undergo any other screening procedure and not participate in any breast screening programs.

All of the variants of the genes screened should be known to be actionable. An actionable variant is defined as a "pathogenic variant for which preventive and/or treatment measures are available to significantly improve health outcomes associated with the condition,"[20] meaning that the tested individuals are not told of any genetic risk of developing a severe disorder to which there is no prevention, treatment or cure. The actionability of the variant should be given due consideration, as limited actionability can still cause more harm than good.[21]

The societal risks that might be faced by those who have undergone OGS include the fact that they might be treated as a 'patient-in-waiting' in the future,[22] especially if they have received results that show a high risk of severe genetic disease. These individuals might also face adverse effects in the form of higher insurance costs,[23] and being barred from certain types of jobs. One such example is that 1% of asymptomatic individuals have a variant related to sudden cardiac death.[24] These individuals may be prohibited in the future from certain professions like aircraft pilots or bus drivers. There is currently minimal evidence of these

[20] Jonathan S. Berg et al., "A Semiquantitative Metric for Evaluating Clinical Actionability of Incidental or Secondary Findings from Genome-Scale Sequencing," *Genetics in Medicine* 18, no. 5 (2016): 467-475.

[21] Bertrand Isidor et al., "Searching for Secondary Findings: Considering Actionability and Preserving the Right Not to Know," *European Journal of Human Genetics* 27, no. 10 (2019): 1481-1484.

[22] Stefan Timmermans, and Mara Buchbinder, "Patients-in-waiting: Living between Sickness and Health in the Genomics Era," *Journal of Health and Social Behavior* 51, no. 4 (2010): 408-423.

[23] Saira Mohammed et al., "Genetic Insurance Discrimination in Sudden Arrhythmia Death Syndromes: Empirical Evidence from a Cross-Sectional Survey in North America," *Circulation: Cardiovascular Genetics* 10, no. 1 (2017): e001442.

[24] Amit V. Khera et al., "Rare Genetic Variants Associated with Sudden Cardiac Death in Adults," *Journal of the American College of Cardiology* 74, no. 21 (2019): 2623-2634.

types of societal repercussions,[25] especially if the disease is preventable or treatable.[26] These societal risks, however, should be seen in context with the relevant laws and regulations in place in different countries.

## 2.2. Secondary Findings in Research

Koplin et al argue that clinicians, as well as researchers, have a duty to disclose pathogenic, actionable incidental findings, based on the duty of easy rescue.[27] They claim that this duty is more tenuous when dealing with biobank participants and research using data already collected in other studies (secondary uses of data).[28] The duty of easy rescue has many interpretations. The one used here is that the costs to the rescuer need to be proportionally much smaller than the benefits to the beneficiary and that the costs are borne by the rescuer need to be reasonably bearable.[29]

Using the duty of easy rescue, Koplin et al argue that researchers are morally required to help others when the harm that could potentially be averted is excellent while the costs that they will incur are small. They argue that if the rescue-based moral duty to disclose these findings exists, then so does the rescue-based moral duty to look for them. This is the case if the potential benefits to the subjects are significant enough that the costs to the researchers are small in comparison to them.[30] Some even argue that researchers should hunt for secondary findings and should use the ACMG list (even though this is aimed at clinical uses).[31] This practice remains uncommon thus far, particularly outside of the United States.

They, however, fail to take into account various factors when issuing this claim. Some of these include the fact that the research methods used are usually not clinically validated. It would in fact be reckless for the researchers to issue these results, potentially harming the research subject. The research team would have to have the results validated before they can be issued

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25 Yann Joly, Ida Ngueng Feze, and Jacques Simard, "Genetic Discrimination and Life Insurance: A Systematic Review of the Evidence," *BioMed Central Medicine* 11, no. 1 (2013): 1-15.

26 Yann Joly et al., "The Ethical Framing of Personalized Medicine," *Current Opinion in Allergy and Clinical Immunology* 14, no. 5 (2014): 404-408.

27 Julian J. Koplin, Julian Savulescu, and Danya F. Vears, "Why Genomics Researchers are sometimes morally required to Hunt for Secondary Findings," *BioMed Central Medical Ethics* 21, no. 1 (2020): 1-11.

28 Ibid.

29 Ibid.

30 Ibid.

31 Kalia et al., "Recommendations for Reporting of Secondary Findings," 249-255.

to the research subjects, and offer their subjects the prerequisite genetic counselling so that their subjects can make sense of the result that they are given. The research team would also need to take out additional liability insurance which may make research costs prohibitive. These factors apply to both incidental and secondary findings. In view of these factors, it is erroneous to claim that the costs borne by the research team is much smaller than the benefits reaped by the research subjects.[32]

Another argument used in favour of secondary findings is that they are a part of the researchers' ancillary care obligations, which are moral duties researchers are bound to. To fulfil this duty, they have to provide their research subjects with information and treatment for reasons other than for scientific discovery, thus helping their participants with diseases that are not caused or affected by the study.[33] The findings are to be disclosed as the researchers have a moral duty to do so as a kind of compensation for the relaxation of participants' privacy rights. This argument fails to take into consideration the fact that the result may not be a benefit but might cause harm instead. Due to this result, the individual might not be able to take out and insurance policy or get a loan.

Researchers should, thus, not bear the responsibility to meet the participants' health needs as this lies with the health care system. The diseases which result from the increased risks found in the genome are dealt with in the health system, and thus looking for the genetic indications should be the responsibility of the health system. Searching for these findings only in research subjects would be a very low-yield form of health screening while also being inequitable, as only those participating in a research study would have the opportunity to have these types of results. Research projects should focus on the primary objectives of the study, one of which is the generation of generalisable medical knowledge.[34]

Thus, currently, the duty to search for secondary findings is not applicable in research as the duty of easy rescue is not met. The same applies to the principle of proportionality, as the benefits to the beneficiary do not currently outweigh the costs of research. As time passes,

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[32] Franklin G. Miller, Michelle M. Mello, and Steven Joffe, "Incidental Findings in Human Subjects Research: What Do Investigators Owe Research Participants?" *The Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 271-279.

[33] Henry S. Richardson, "Ancillary-Care Obligations," last modified August 11, 2021, https://academic.oup.com.

[34] Ibid.

however, the methods used for genomic testing and analysis will improve, decreasing the time and costs associated with them. The research into the various genes, finding out more genetic variants that are pathogenic and actionable, will also progress. This might alter the cost-to-benefit ratio that currently exists. It might be more beneficial in the future than costly to do these types of analyses. As such, the issue has to be revisited periodically to check whether the balance has shifted or not.[35]

This is not to say that researchers should avoid incidental findings or not look for secondary findings as this might hinder the generation of new knowledge. It is only through this type of research that our understanding of secondary findings, and our knowledge of the genome in general, can increase. Researchers do not, however, have a duty to look for secondary findings to aid their research subjects. Various methods can be put in place to avoid any ethical dilemmas that may arise with the generation of actionable incidental and secondary findings. One of these is to de-identify all samples as soon as they are taken with the consent of the research subject.

## 2.3. International Clinical Recommendations

### 2.3.1. ACMG Recommendations

The American College of Medical Genetics and Genomics (ACMG) is in favour of opportunistic screening and has issued a list of highly penetrant, actionable variants in preselected genes that should be tested in a clinical setting. The first list was published in 2013,[36] which was then updated in 2016.[37] The ACMG has since then issued another policy statement[38] regarding this list, stating that it will now be updated on a yearly basis to keep up with the scientific and medical developments in the field.

This list should be considered the minimum list of actionable secondary findings, meaning that investigators should search for any genetic variants occurring in the genes listed and add

35 Ibid.

36 Green et al. "ACMG recommendations for reporting of incidental findings," 565-574.

37 Kalia et al. "Recommendations for reporting of secondary findings," 249-255.

38 David T. Miller et al., "ACMG SF v3. 0 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)," *Genetics in Medicine* 23, no. 8 (2021): 1381-1390.

to it if they are so inclined. The genes recommended for testing can broadly be divided into two, those that indicate a predisposition to specific forms of cancer and those indicating a predisposition to cardiac diseases, as these are the areas where pre-symptomatic medical interventions may be the most critical. All the genes listed should be tested regardless of the person's age, though the best interests of the child should still be prioritised in regard to disclosing the risk for adult-onset conditions.

The ACMG is in favour of an 'opt out' system where all patients are tested unless they explicitly refuse.[39] This is due to the fact that they assert that this system has considerable benefits with minimal risks, making it unethical not to offer OGS.[40] In fact, these recommendations may be considered the standard of care that should be given to a patient.[41]

### 2.3.2. ESHG Recommendations

The European Society of Human Genetics (ESHG) recommends that any genomic analysis in health care should be as targeted as possible for the time being.[42] Any form of OGS offered should be considered as a form of a pilot project, which is combined with rigorous evaluation studies. This may aid in reducing the uncertainties that this practice currently faces and help determine the proportionality of this analysis in a healthcare system, especially one that is publicly funded, as is the case in most of Europe. Even if a system is implemented in the future, it would not be a one size fits all solution. There are various ways European countries differ from one another, including the amount of funding that they assign to their health care, and the ethnic diversity of their populations, with different ethnic groups requiring different lists of relevant, actionable genetic variants.[43]

Before recommending this practice in a clinical setting, the ESHG requires that it meets the widely endorsed criteria for genetic screening, ethical principles of proportionality, respect for autonomy and justice. Moreover, since it is not necessary for diagnosis and is merely

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39 Ibid.

40 American College of Medical Genetics Board of Directors, "ACMG Practice Guidelines: Incidental Findings in Clinical Genomics: A Clarification," *Genetics in Medicine* 15, no. 8 (2013): 664-6.

41 McGuire et al., "Point-counterpoint. Ethics and Genomic Incidental Findings," 1047-1048.

42 C. G. Van El et al., "ESHG Public and Professional Policy Committee. Whole-genome sequencing in Health Care. Recommendations of the European Society of Human Genetics," *European Journal of Human Genetics* 21, no. Suppl 1 (2013): S1-5; De Wert et al., "Opportunistic genomic screening," 365-377.

43 De Wert et al., "Opportunistic genomic screening," 365-377.

preventative, this analysis must be clearly beneficial to the patient and not cause any harm. Though thus far, there has been no evidence of psychological harm done to patients, more research is needed. More research is also necessary when OGS is conducted on minors for variants that effect late-onset actionable conditions.[44]

## 2.4. Clinical Obligations to the Patients

These two international institutions have issued recommendations which are diametrically opposed to one another. There are various arguments in the literature supporting one side over the other.

### 2.4.1. Screening vs Individual Care

OGS can be viewed as a form of screening or as a part of individual care. The focus and emphasises of the ACMG lies mainly on the latter.[45] The ACMG recommendations essentially argue that doctors and laboratory scientists have a professional obligation to look for these types of results as they have a duty to conduct a thorough evaluation of any test that they conduct. This is an ethical standard that governs all clinical testing, thus including clinical genetic testing. For example, in routine day-to-day clinical procedures, doctors should take a patient's history to find out the genetic risk of any disease.[46] Using genetics is considered by some to be merely an extension of this. Genetics provides the same type of information, albeit more accurate and in detail, that the clinicians already look for. All clinicians thus have the same opportunity and obligation to identify and report secondary findings as it is a matter of providing exemplary clinical care to the patient. This perceived obligation would make them hesitant about not providing their patients access to their own genetic results, especially as it might contain lifesaving information.[47]

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44 Ibid.

45 Miller et al., "ACMG SF v3. 0 list for reporting of secondary findings," 1381-1390.

46 McGuire et al., "Point-counterpoint. Ethics and genomic incidental findings," 1047-1048.

47 Catherine Gliwa, and Benjamin E. Berkman, "Do Researchers Have an Obligation to Actively Look for Genetic Incidental Findings?" *The American Journal of Bioethics* 13, no. 2 (2013): 32-42.

The screening aspect of it, however, should not be ignored. Usually, a normative framework applies to screening that was developed by the WHO,[48] and other international institutions.[49] The main difference between this framework and the one used for OGS is that this framework targeted screening towards public health, organising screening programs that are targeted towards the entire population, not just in an opportunistic clinical context.

Certain aspects of the framework, however, should still apply as the main point of screening is that testing is being done on individuals that have no clinical indications of the disease that they are being tested for. In contrast to indication-based testing, Cochrane and Holland contend that screening's non-indicated nature results in a more unstable benefits-to-risks balance:

> "If a patient asks a medical practitioner for help, the doctor does the best he can. He is not responsible for defects in medical knowledge. If, however, the practitioner initiates screening procedures he is in a very different situation. He should in our view, have conclusive evidence that screening can alter the natural history of disease in a significant proportion of those screened."[50]

For a screening program to be viable, there needs to be solid evidence that those being tested would benefit from this exercise,[51] meeting the proportionality prerequisite for offering screening using the "evidentiary model."[52] Due to the fact that there are still many questions, uncertainties, unknowns and concerns about OGS, the ESHG states that it is too early to start screening patients, let alone make it the standard of care, as is recommended in by the ACMG.[53]

### 2.4.2. Standards for Testing

As clinical GS and ES become widespread, some argue that a list of variant genes is vital as this standardises testing across various laboratories, thus setting a standard for best laboratory practices. This can only be to the patients' benefit, as all laboratories would be

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48 James Maxwell Glover Wilson, Gunnar Jungner, and World Health Organization, "Principles and practice of screening for disease," (1968).

49 Anne Andermann et al., "Revisiting Wilson and Jungner in the Genomic Age: A Review of Screening Criteria over the Past 40 Years," *Bulletin of the World Health Organization* 86 (2008): 317-319.

50 A. L. Cochrane, and W. W. Holland, "Validation of Screening Procedures," *British Medical Bulletin* 27, no. 1 (1971): 3-8.

51 De Wert et al., "Opportunistic genomic screening," 365-377.

52 Benjamin S. Wilfond, and Kathleen Nolan, "National Policy Development for the Clinical Application of Genetic Diagnostic Technologies: Lessons from Cystic Fibrosis," *Journal of the American Medical Association* 270, no. 24 (1993): 2948-2954.

53 De Wert et al., "Opportunistic genomic screening," 365-377.

limited to only issuing results that are of high clinical utility. Before the ACMG recommendations were issued, everyone had different criteria that they followed, causing some patients to receive findings of undetermined significance or those of limited or dubious clinical utility. The recommendations thus reduced over-reporting and unjustified variation in reporting practices.[54] The ACMG recommendations, however, fail to mention the fact that secondary findings have to be reviewed periodically by the diagnostic team for any reclassifications of the variants reported, as over time, there might be changes to the classification of the pathogenicity of the variants.

On the other hand, the ESHG recommendations also standardise the process, as no secondary findings will currently be looked for. Any other incidental finding would be treated on a case-by-case basis, depending on its clinical significance.[55]

### 2.4.3. Justice

When compared to the traditional forms of screening, OGS will incur fewer costs overall. This is due to the fact that it is an add-on to a medical test that is already being done for medical reasons as opposed to the establishment of a screening program aimed at the entire population. Though the costs are less, they might still be a burden on some health care systems, mainly if they are publicly funded. The costs include but are not limited to the additional manual bioinformatics analysis that must take place and the confirmation of the variants, along with the clinical assessment that has to be done, as well as the additional procedures that the individuals tested have to undergo for prevention or treatment. The costs will further increase if cascade testing is done on the genetic relatives of the individuals who possess the variant.[56]

The fact that OGS leads to downstream costs is not particularly concerning as these might prevent the development of a disease which would incur much higher costs if it actually develops. This is only applicable if the variant found truly has an impact on the health of these individuals so that the costs of unnecessary interventions are avoided. “Over-diagnosis” is of particular concern as it will negatively impact the patient as well as the health care system as

[54] McGuire et al., "Point-counterpoint. Ethics and genomic incidental findings," 1047-1048.
[55] De Wert et al., "Opportunistic genomic screening,” 365-377.
[56] Ibid.

a whole, using up resources which would have otherwise been used for indication-based care pathways.[57]

In light of these additional costs, there might be other methods that give similar results for a lesser cost. One of these is cascade testing. Instead of opportunistic screening for all who undergo GS and ES, the screening is only done on individuals whose relatives already have a clinical indication of a genetic disease. If there are clearly pathogenic, highly penetrant and actionable variants that are associated with the disease in question, such as BRCA1- and BRCA2-related hereditary breast and ovarian cancer, then the relatives are tested for these genetic indications of increased risk. The United States Centers for Disease Control and Prevention Office of Genomics and Precision Public Health has defined such gene variants as "Tier 1" due to scientific evidence showing that knowing about their presence would have a significant potential for a positive impact on the individual and on public health, thus recommending that they are found."[58] Unfortunately, cascade testing is not currently prevalent.[59] Whether cascade testing, OGS or a combination of both should be used varies in terms of distributive justice from country to country, as one might have already implemented a cascade-based system while others have not.

If the only prevention possible for the reduction of the risk associated with a gene variant is a change in lifestyle, it has been argued that it would be better for the population if, instead of investing in OGS, the health system invests in other collective measures, such as general health education and protecting the health of the population by protecting the environment.[60] These measures would have a far more significant benefit if proven effective, especially in under-resourced communities. In more affluent communities, however, distributive justice allows for these methods to be combined with OGS.

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57 Franziska Severin et al., "Points to Consider for Prioritizing Clinical Genetic Testing Services: A European Consensus Process Oriented at Accountability for Reasonableness," *European Journal of Human Genetics* 23, no. 6 (2015): 729-735.

58 "Tier 1 Genomics Applications and their Importance to Public Health," Centers for Disease Control and Prevention, last modified March 6, 2014, https://www.cdc.gov/genomics/implementation.

59 P. Pujol et al., "Lack of Referral for Genetic Counseling and Testing in BRCA1/2 and Lynch Syndromes: A Nationwide Study Based on 240,134 Consultations And 134,652 Genetic Tests," *Breast Cancer Research and Treatment* 141, no. 1 (2013): 135-144.

60 Kathleen McGlone West, Erika Blacksher, and Wylie Burke, "Genomics, Health Disparities, and Missed Opportunities for the Nation's Research Agenda," *Journal of the American Medical Association* 317, no. 18 (2017): 1831-1832.

Another factor that affects the use of OGS in under-resourced communities is the fact that most of the reference variant databases have a strong bias towards European-derived variant frequencies, mainly because the majority of those first tested were of European descent. If these databases are used on ethnically diverse populations, certain individuals may be harmed as there is insufficient evidence on whether certain variants should be classified as pathogenic or not.[61]

This form of screening also raises issues with formal justice. Formal justice is essentially the concept that each individual should be treated the same. If in one scenario, for example, someone is given treatment for a disease, in a similar scenario, the same outcome should occur. The issue raised is the fact that this screening would be offered only to an individual who is undergoing genetic testing for a medically indicated reason. OGS tests for other genetic information are outside of the scope of the primary objective. These individuals thus have the same perceived amount of risk of having a genetic variant as is found in the general population,[62] though they are being treated differently from the rest of the population.

Offering OGS to these individuals only could cause unequal access to health care that should be avoided. One of the two solutions, in this case, would be to offer this type of genetic screening to everyone. This would increase the costs exponentially as the costs of setting up the infrastructure for programmatic screening have to be taken into account together with the running costs of such a program.[63]

The only other solution would be to deny access to all, though this would clearly not be in anyone's best interest. This issue with formal justice could be mitigated by the fact that the possibility of needing genetic testing in the first place is equally distributed within a population. A segment of the population, however, namely those with higher education and income, is often over-represented,[64] which could be seen as increasing the current inequalities in access to health care.[65]

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61 Amy R. Bentley, Shawneequa Callier, and Charles N. Rotimi, "Diversity and Inclusion in Genomic Research: Why the Uneven Progress?" *Journal of Community Genetics* 8, no. 4 (2017): 255-266.

62 De Wert et al., "Opportunistic genomic screening," 365-377.

63 Ibid.

64 J. A. M. Van der Giessen et al., "Referral to Cancer Genetic Counseling: Do Migrant Status and Patients' Educational Background Matter?" *Journal of Community Genetics* 8, no. 4 (2017): 303-310.

65 Julian Tudor Hart, "The Inverse Care Law," *The Lancet* 297, no. 7696 (1971): 405-412.

The considerations to justice vary across different health care settings. For example, if the treatment or prevention methods for an actionable variant found are so costly that many people could not possibly afford it, the screening done would be more beneficial for those who can afford it than for others.[66]

## 2.5. National Recommendations

The ACMG[67] and ECHG[68] recommendations were discussed and contrasted as they are the most mentioned in the literature, and their contents are diametrically opposed. This does not mean, however, that other countries and institutions have not also issued their guidelines and recommendations.

### 2.5.1. United States of America

In the United States of America, even though the ACMG guidelines are followed in most clinical laboratories[69] and some research laboratories, this does not mean that their use is enforced. The guidelines are used in various laboratories in the USA for various reasons, including the fact that they were published at a time when there was very little published material on how these findings should be handled. Thus they filled a much-needed gap in clinical care.[70]

Though most laboratories follow the guidelines, there is still no clear consensus on what exactly constitutes an actionable gene, with the ACMG list being periodically updated to keep up with the latest information.[71] Also, other American entities, such as Geisinger Health System's MyCode Community Health Initiative, offer a different list of secondary findings, including seventy-seven (as opposed to the fifty-nine mentioned by the ACMG) actionable genes.[72] In research, certain studies have offered up to one hundred and sixty-eight medically

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66 Bernarda Zamora et al., "Comparing Access to Orphan Medicinal Products in Europe," *Orphanet Journal of Rare Diseases* 14, no. 1 (2019): 1-12.

67 Miller et al., "ACMG SF v3. 0 list for reporting of secondary findings," 1381-1390.

68 de Wert et al., "Opportunistic genomic screening," 365-377.

69 Sara A. Fowler, Carol J. Saunders, and Mark A. Hoffman, "Variation among Consent Forms for Clinical Whole Exome Sequencing," *Journal of Genetic Counseling* 27, no. 1 (2018): 104-114.

70 Michael Morrison et al., "Implications of Secondary Findings for Clinical Contexts," in *Secondary Findings in Genomic Research,* ed. Martin Langanke, Pia Erdmann, and Kyle B. Brothers (Massachusetts: Academic Press, 2020), chap. 8, Kindle.

71 Miller et al., "ACMG SF v3. 0 list for reporting of secondary findings," 1381-1390.

72 Geisinger, "MyCode Genetic Conditions," accessed on October 29, 2022, www.geisinger.org.

actionable genes to their participants.[73] This further highlights that it is still unclear what constitutes a medically actionable secondary finding, what criteria should be used to determine which genes are medically actionable, and how these criteria should be applied.

### 2.5.2. The United Kingdom

A national genomic sequencing program was launched in 2013 in the UK called the 100,000 Genomes Project.[74] This project aims to collect and sequence 100,000 genomes using the National Health Service (NHS) from individuals suffering from rare genetic diseases and individuals who have cancer. This aims to simplify the diagnosis of rare conditions and to aid in the development of patient-specific medications for those who have cancer.[75] As such, this project is at the boundary between research and clinical care.

This UK project mentions secondary findings "additional findings", and the tested individuals have the option to know their secondary findings, which are available on an opt-in basis. The list of medically actionable genes differs from the ACMG recommendations and is shorter, including fewer genes for testing. Like the ACMG list, this list is not static and is subject to change. While the tested individual has the right to choose whether to know the results, it is an all-or-nothing situation. They cannot choose which genes or groups of genes they want the results of. Also, they will receive the results of the genes listed at the time of testing, not those on the list at the time of consent, which means that they might consent to know (in the future) the result of genetic conditions they are unaware of. The secondary finding results are also not issued with the primary clinical result but are issued separately at a later date so as not to confuse the tested individuals.[76]

This project is the only one of its kind in the UK. Secondary findings are not mentioned or looked for in any other scenario. Even the procedure for dealing with incidental findings is not standardised, varying from one laboratory to another. As there is no standardisation, it leaves clinicians in doubt about their duty of care to their patients regarding genomic sequencing and whether it is their duty to look for secondary findings. Some entities based in the UK, such

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[73] Jonathan S. Berg et al., "A Semiquantitative Metric for Evaluating Clinical Actionability of Incidental or Secondary Findings from Genome-Scale Sequencing," *Genetics in Medicine* 18, no. 5 (2016): 467-475.

[74] Genomics England, “100,000 Genomes Project,” last accessed October 28, 2022, https://www.genomicsengland.co.uk.

[75] Ibid.

[76] Morrison et al., "Implications of Secondary Findings for Clinical Contexts," chap. 8.

as the Public Health Genomics Foundation, agree with the ESHG recommendations and favour a targeted approach in sequencing.[77] Thus, while the UK has started the process for secondary findings, they still have a way to go before a nationwide service is offered.

### 2.5.3. Germany

Whole genome sequencing and whole exome sequencing are not offered as a part of the German public health system, with their use mostly relegated to clinical research or medical fields closely related to research, such as paediatric genetics or in oncology centres studying the aetiology of certain tumours. However, even though genomic testing in a clinical context is not widespread, Germany is one of the few countries that has passed legislation about the topic. The German Gene Diagnosis Act was passed on April 24, 2009, and entered into force on February 1, 2010.[78] While this act does not directly mention secondary findings, it mentions unexpected findings, which it defines as genetic findings outside the scope of the primary result. This can refer to both incidental findings as well as secondary findings. The law states that during the informed consent process, the individual has to be informed about the possibility of additional findings. They can choose whether they want to receive these types of findings. This law only applies to clinical practice and does not cover research.[79]

As this law does not apply to research, various German entities have published guidelines on handling this. One of these is the German Society of Human Genetics, which issued two sets of guidelines, one for research and one for clinical applications.[80] While the clinical part of the recommendations is similar to the law in force, the research aspect is quite different. In a research scenario, the researchers do not have an obligation to make a diagnosis, nor do they have the duty to inform the tested individual of an additional finding. If the researcher and research subject agree that secondary findings are to be returned during the consent process, then a time period has to be specified in which these results have to be returned.[81]

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77 PHG Foundation, “Managing incidental and pertinent findings from WGS in the 100,000 Genomes Project,” last modified April, 2013, www.phgfoundation.org.

78 German Reference Centre of Ethics in the Life Sciences, “Legal Aspects,” accessed 21 October, 2022, https://www.drze.de.

79 Ibid.

80 Klaus Zerres et al., "Statement of the German Society for Human Genetics on genetic Additional Findings in Diagnosis and Research," *Medizinische Genetik* 25, no. 2 (2013): 284-286.

81 Morrison et al., "Implications of Secondary Findings for Clinical Contexts," chap. 8.

# Chapter 3: The Right Not to Know and Informed Consent

## 3.1. The right not to know

When discussing secondary findings, one of the main points of discussion is whether researchers and clinicians should look for these findings and whether they have a duty to look for them. Even if they look for these results, however, it is still debated whether tested subjects should have a say in whether they receive their results, as is traditionally the case, or if the unique properties of genetic information preclude the tested individuals from having the right to refuse to know.

The right not to know is well established, as stated by various institutions. For example, the European Convention on Human Rights and Biomedicine, states in Article 10.2 that "[e]veryone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be so informed shall be observed."[1] The UNESCO Declaration on the Human Genome and Human Rights, Article 5c, also claims that "[t]he right of each individual to decide whether or not to be informed of the results of the genetic examination and the resulting consequences should be respected."[2]

Though the right to know and the right not to know are well established, they are not in themselves as important when compared to other, more essential rights, such as the right to privacy and the right not to be discriminated against. While the right to know and the right not to know are important, when other competing rights are also in play, it is impossible to argue that these rights should always be prioritised over another.[3] Priority should be given to

1 Council of Europe, *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine,* 1997.

2 UNESCO, *Universal Declaration on the Human Genome and Human Rights*, 1997.

3 Rosalind McDougall, "Rethinking the 'Right not to Know'," *Monash Bioethics Review* 23, no. 1 (2004): 22-36.

these rights where possible, though this does not mean that they must be placed first in every scenario.[4]

### 3.1.1. Arguments for a right not to know

One of the main arguments for a right not to know is that doing so avoids harm, mainly psychological harm.[5] This can be clearly seen when children are genetically tested, as telling them or their guardians about the findings can cause damage to the child's self-esteem, as well as lead to discrimination against the child in education and employment.[6] Another type of harm that might occur is the diminishment of liberty and future flourishment that anyone might experience. By knowing the information, a person might hold back from doing certain activities. The fear induced by this information might not allow the individual to live to one's full potential.

The other main argument is based on individuals' right to autonomy. By choosing whether to receive the information, they are exercising their autonomy.[7] Forcing someone to receive the results against their will diminishes autonomy, leading to paternalism, as the professional is making the decision instead of the patient.[8] This argument holds more weight when the result in question is not actionable, as in the case with Huntington's disease.[9] While it is possible to get a definitive answer form the genome about whether one will develop the disease, there is no cure for it. Most of the individuals who might have inherited it from their parents chose not to know whether they have the genetic variant or not.[10] Insisting that they should know the result might have a negative effect on their lives, knowing that they will develop an incurable disease in the future but having no way to delay or stop it from happening.

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4 Ronald Dworkin and Jeremy Waldron, *Theories of Rights* (Oxford: Oxford University Press, 1984), 153-67.

5 Roberto Andorno, "The Right not to Know: An Autonomy Based Approach," *Journal of Medical Ethics* 30, no. 5 (2004): 435-439.

6 Rony E. Duncan, and Martin B. Delatycki, "Predictive Genetic Testing in Young People for Adult-Onset Conditions: Where is the Empirical Evidence?" *Clinical Genetics* 69, no. 1 (2006): 8-16.

7 Andorno, "The right not to know," 435-439.

8 Pascal Borry, Mahsa Shabani, and Heidi Carmen Howard, "Is there a Right Time to Know?: The Right not to Know and Genetic Testing in Children," *Journal of Law, Medicine & Ethics* 42, no. 1 (2014): 19-27.

9 Tarja-Brita Robins Wahlin, "To Know or Not to Know: A Review of Behaviour and Suicidal Ideation in Preclinical Huntington's disease," *Patient Education and Counseling* 65, no. 3 (2007): 279-287.

10 Roslyn J. Tassicker, et al., "Problems Assessing Uptake of Huntington Disease Predictive Testing and a Proposed Solution," *European Journal of Human Genetics* 17, no. 1 (2009): 66-70.

Another critical factor to consider is the right to privacy. It is every individual's right to be able to control the information that exists about one's self and who possesses it. This holds especially true before the testing is done. If the person refuses to know about secondary findings, then they should not be looked for. By not analysing the data generated, no one will know what information might have come to light, preserving the right to privacy. The right to privacy, however, might not be as applicable when secondary results have already been produced and information exists about one's self, that one chooses not to know about.[11] Though the tested individual does not know the results, the researchers or clinicians do.

### 3.1.2. Arguments against the Right not to Know

One of the main arguments against the right not to know is also based in autonomy. However, as Harris and Keywood argue, if people avoid knowing information about themselves, they are not exercising their right to an autonomous choice as they do not have the required information to truly make an informed autonomous choice.[12]

A similar argument is that knowledge is a good in itself, and as such, everyone should be given this knowledge. Having a right not to know contradicts this. Proponents of this argument refer to a Kantian perspective where remaining in ignorance is an irrational attitude.[13] Not informing an individual about any of their results would hamper their autonomy and increase paternalism.

While the right to remain in ignorance holds water in most cases, this is not the case where genetic information is concerned. The aspect of genetic information that renders it utterly different from any other type of medical information is the fact that it concerns not only the tested individual but also their biological family. Any information generated about an individual could inherently apply to other members of the family, and as such, there might be an obligation to know and pass on the relevant information. This argument is based on solidarity[14] and avoiding harm to others. This, of course, does not take into consideration that

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11 Bjørn Hofmann, "Incidental Findings of Uncertain Significance: To Know or not to Know - That is not the Question." *BMC Medical Ethics* 17, no. 1 (2016): 1-9.

12 John Harris, and Kirsty Keywood, "Ignorance, Information and Autonomy," *Theoretical Medicine and Bioethics* 22, no. 5 (2001): 415-436.

13 Matti Häyry, and Tuija Takala, "Genetic Information, Rights, and Autonomy," *Theoretical Medicine and Bioethics* 22, no. 5 (2001): 403-414.

14 Bartha Maria Knoppers, and Ruth Chadwick, "Human Genetic Research: Emerging Trends in Ethics," *Nature Reviews Genetics* 6, no. 1 (2005): 75-79.

the rest of the family might also choose not to know in the same situation, as is the case with Huntington's disease.[15]

As this argument is based on the fact that accepting the information might prevent harm to others, it cannot be refuted merely on the basis that it is the person's autonomous choice whether to accept the information or not. Even if they think that it is in their best interest to refuse to know, such as to avoid any psychological harm, their avoidance does not negate the fact that others might also be harmed. This applies especially when children are involved, with Kielstein and Sass considering it a "duty to know" any information that might harm the child, thus being a responsible parent.[16] Even the Council of Europe stated that the right not to know is limited, with other concerns taking precedence where necessary, such as public safety, the protection of public health and for the protection of the rights and freedoms of others.[17]

This argument for the protection of others can take two forms. The first and stronger argument is that once information is uncovered that highly affects others in a negative fashion, then individuals lose their right not to know. They might even lose the right to keep their medical information confidential, as it is a clinician's duty to prevent harm. The second and weaker argument is that while the clinician is still under the obligation to respect the individuals' right not to know, by claiming this right people might be acting immorally, even though they might have a legal right to it.[18]

Another aspect to consider is the obligation each, and every member of society has not to impose unreasonable, avoidable burdens on others. In a society, everyone has, in theory, the freedom to pursue the life that one considers to be the best for oneself. No one has a right to constrain an individual, even if others do not agree with certain aspects of the individual's life. Nobody should be forced to change their values even if they might be considered irrational or potentially harmful to themselves.[19]

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15 Tassicker et al., "Problems Assessing Uptake of Huntington Disease Predictive Testing and a Proposed Solution," 66-70.

16 Rita Kielstein, and Hans-Martin Sass, "Right not to Know or Duty to Know? Prenatal Screening for Polycystic Renal Disease," *The Journal of Medicine and Philosophy* 17, no. 4 (1992): 395-405.

17 Council of Europe, *Convention for the Protection of Human Rights and Dignity of the Human Being*.

18 Ben Davies, "The Right not to Know and the Obligation to Know," *Journal of Medical Ethics* 46, no. 5 (2020): 300-303.

19 Ibid.

This does not mean, however, that each individual is free to do whatever one likes in pursuit of a good life. There are certain moral constraints that everyone still has to abide by. Suppose there are two paths that both lead to the same place. Then one should choose the path that inflicts the lesser amount of cost to others in society. No one should be legally forced to choose this path; however, it is the moral duty of each individual to do so.[20]

By choosing not to know about any actionable result, an individual might be forgoing treatment. When they do develop symptoms, the condition would be harder to treat and more expensive. If these individuals live in a country with a publicly funded healthcare system, they are placing a more considerable burden on society then they would have otherwise. This does not mean, however, that they should have been forced to know the information in the first place.[21]

While not all instances of choosing not to know impose unreasonable costs on others, there are various scenarios where this is the case. If, in these cases, we are all obliged to know the information, then this might seem relatively straightforward. One might agree with Rhodes, who stated that once someone has decided to perform a genomics test, they have decided to know all the information that is generated from it. If, on the other hand, they want to preserve their genetic ignorance, then they should not have the test performed. The professor states, therefore, that one cannot have an obligation to receive the results while at the same time having the right not to know.[22]

This, however, oversimplifies a complicated matter.[23] When arguing in favour of a right not to know, in a medical context, one is arguing in favour of the right not to be told unwanted information by medical professionals.[24] The main argument is the fact that one should not impose unreasonable burdens on others if these can be avoided. It is usually quite challenging, however, to know beforehand what constitutes an unreasonable choice. When

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20 Ibid.

21 Ibid.

22 Rosamond Rhodes, "Genetic Links, Family Ties, and Social Bonds: Rights and Responsibilities in the face of Genetic Knowledge," *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine* 23, no. 1 (1998): 10-30.

23 Niklas Juth, "The Right not to Know and the Duty to Tell: the Case of Relatives," *Journal of Law, Medicine & Ethics* 42, no. 1 (2014): 38-52.

24 Clair Morrissey, and Rebecca L. Walker, "The Ethics of General Population Preventive Genomic Sequencing: Rights and Social Justice," *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine* 43, no. 1 (2018): 22-43.

a patient decides not to know, the clinician does not know at that time whether the decision taken is unreasonable or not. The patient might have a valid reason for not wanting to know. Even were it to be unreasonable, it would still not be permissible for the clinician to try and force the patient to accept the information, as this would also affect those who have a valid reason why they are refusing to know the information. Considering, however, one of the difficulties of this subject is the lack of foreseeability, the clinician still has an obligation to explain the potential risks of not receiving medically relevant information.[25]

### 3.1.3. The Right to Choose

As can be seen from the arguments presented above, a person has a right not to know and this should be respected as long as it does not cause harm to others. Whether it should be respected if it causes harm to one's self is not as clear and is still up for debate. The ESHG recommends that,

> "(t)he patient's right not to know should be respected as far as reasonably possible, while allowing professionals to still inform the patient about specific findings of great importance for the patient's own health or that of his or her close relatives."[26]

As such, no system should be in place where secondary findings are given to an individual without their express consent. With this in mind, an opt-out system, as proposed by the ACMG guidelines, should not be put in place,[27] as one is assuming that the individuals would, in the vast majority, want to know their results. Also, using this system, the individuals' values and ethics are not given the importance that they deserve. By using this system, persons are given less time and information to figure out where they stand and what they would genuinely decide if they had all the necessary information.

For this right to be respected, a robust informed consent process has to be in place. The ESHG recommendations point out that the patient should be the one who decides whether to receive the information or not; however, they do not give any practical information about how this should take place.

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[25] Manne Sjöstrand, Stefan Eriksson, Niklas Juth, and Gert Helgesson, "Paternalism in the Name of Autonomy." *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine* 38, no. 6 (2013): 710-724.

[26] Guido de Wert et al., "Opportunistic Genomic Screening. Recommendations of the European Society of Human Genetics," *European Journal of Human Genetics* 29, no. 3 (2021): 365-377.

[27] David T. Miller et al., "ACMG SF v3. 0 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)," *Genetics in Medicine* 23, no. 8 (2021): 1381-1390.

## 3.2. Informed consent

One of the most important aspects of informed consent is autonomy. This principle, however, has to be balanced against other competing principles such as beneficence, non-maleficence, justice and solidarity. Thus while the autonomy of the tested individual is essential, it is not the only thing that should be taken into account when devising the informed consent process.[28]

For informed consent to occur correctly, there are four conditions that have to be met. The first is that the researcher or clinician has to provide adequate information to the tested individual, making sure that the information provided is easily understandable by the individual. The second condition is that the patient or research subject has to understand the information provided. The third condition is that the consent is given voluntarily, without undue influence, intimidation or manipulation by the researcher or clinician. The fourth condition is that there is a document signed by the research subject or patient which explicitly shows that consent is given.[29]

While all these conditions appear pretty straightforward, they are not as easily met as they seem. For example, how much information should be provided to the tested individuals in order as to meet the burden of providing adequate information. This matter is more complicated when secondary findings are possible, as the researcher or clinician has to provide information not only on the primary reason for the test but also on the additional results that may arise. The informed consent process is more complicated due to this fact, which results in various issues arising that researchers and clinicians do not usually face.[30]

### 3.2.1. Providing information

It is essential to consider in advance what information to provide to the patient. One of the conventional ways to do this is to provide all the information possible about the test to be performed, from explaining the aim and significance of the planned test to explaining all the

[28] Sebastian Schleidgen, and Kyle B. Brothers, "Informed Consent and Decision-making," in *Secondary Findings in Genomic Research,* ed. Martin Langanke, Pia Erdmann, and Kyle B. Brothers (Massachusetts: Academic Press, 2020), chap. 5, Kindle.

[29] Ibid.

[30] Susan M. Wolf et al., "Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations." *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 219-248.

secondary findings possible and the effect these would have on them as well as their family. It could be argued that this is the best possible method to choose as nothing is hidden from the patient, and because of this, they can make the best possible decision with all the information available to them.

Even if, however, this seems to be the best option at face value, it is not so in practice. It is not possible to provide truly comprehensive information on all the secondary findings possible. Even if the secondary findings that would be looked for are restricted to the ACMG list, the list includes secondary findings about thirty-four different conditions. The clinician has to explain in detail about all of these conditions, most of which the patient would either have never heard of or have minimal knowledge about. If the main aim of the informed consent process is to cover the researcher or clinician legally, then this is a good approach.[31]

If, on the other hand, the aim is to help the patients to make the best possible choice, then this is not the correct approach to take. The patients would be so overwhelmed with all the provided information that it would stop them from making a 'good' decision that reflects their values and priorities.[32] A balance has therefore to be found between providing too much information and providing too little, as well as deciding what kind of information should be provided. Some suggest that the best way to promote autonomous decision-making is to give any patient only basic information about the test. On the other hand, it has also been suggested that all the information should still be given covering all the topics but in a simplified way so as to make it easier for any individual to understand why they are giving their consent.[33]

Finding the right balance is one of the main challenges faced during the informed consent process. Each individual is different, with each requiring different amounts of explanation. This is further complicated in the clinical setting by the fact that the possibility of secondary or incidental findings is discussed alongside the primary purpose of the test. This can lead the individual to confuse the two, attributing the risks and benefits of the secondary and

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31 John Lantos, "Informed Consent the Whole Truth for Patients?" *Cancer* 72, no. S9 (1993): 2811-2815.

32 Ibid.

33 Laura M. Beskow, N. Chantelle Hardy, Li Lin, and Kevin P. Weinfurt, "Simplifying Informed Consent for Biorepositories: Stakeholder Perspectives." *Genetics in Medicine* 12, no. 9 (2010): 567-572.

incidental findings with those of the primary purpose, and vice versa, causing them not to understand the primary purpose of the test.[34]

The impact the testing might have on the rest of the family must also be explained. This holds especially true when a child is tested, as the result will indirectly show the probable genetic status of the parents. As such, the whole family should be in agreement before testing is done to avoid getting any results by proxy. Also, knowing that a gene variant predisposing to a disease is present within the family may also cause problems within the extended family, who might resent the fact that this information now exists.[35] One of the main concerns that family members have is the fact that there is a risk of insurance discrimination. In countries where health insurance is the basis of the health system, this is a grave concern with long-term effects. While the rest of the family might not be barred from getting the insurance, the cost might be prohibitively high. These concerns are difficult to explain to the individual and their family as they will vary according to the results that they get. The individual would, therefore, not get an accurate picture of all the risks and benefits.[36]

All of this can be avoided in a research setting, if while drawing up a research study steps are taken, such as de-identifying any sample taken from a research subject. The individual should be informed that this procedure would be taking place and that any result produced during the research project cannot be traced back to a specific individual. The researchers could also explain to the subjects that these types of results could impact their lives in negative way, such as impacting their ability to get a job or a bank loan, which is one of the reasons the subjects are being shielded from these results.

There may be instances where the inclusion into the study is contingent on the participant accepting all the secondary findings generated. These types of studies would, for example, be examining how the participants would respond to the secondary findings generated, so it would make sense that inclusion into the study is based upon the participants' willingness to accept these types of results as it is the basis of the entire study. In these cases, it is vital that

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[34] Shannon Rego, Megan E. Grove, Mildred K. Cho, and Kelly E. Ormond, "Informed Consent in the Genomics Era," *Cold Spring Harbor Perspectives in Medicine* 10, no. 8 (2020): a036582.

[35] Mary-Anne Young, "The Responses of Research Participants and their Next of Kin to Receiving Feedback of Genetic Test Results Following Participation in the Australian Ovarian Cancer Study," *Genetics in Medicine* 15, no. 6 (2013): 458-465.

[36] Rego, et al., "Informed consent in the genomics era," a036582.

the informed consent process is carried out as diligently as possible.[37] Unfortunately, researchers may not be clinically trained to deal with what may be such emotional topics. In these types of studies, therefore, the inclusion of a genetic counsellor to the research team might be appropriate.

It is thus safe to say that no matter the circumstances, the informed consent process must be carried out. It is not necessary and quite impossible to go into detail about each and every gene, explaining in detail all the effects. As such, though the informed consent process is done to the best of the clinicians' ability, it is not possible for the patient to ever be fully informed. To make an informed decision, the explanation provided should include enough information about secondary findings so that the individual understands their implications, ideally also providing examples of what these results might be.

### 3.2.2. Models of Consent

As results might be generated outside of the primary purpose of the test, the traditional consent model is not adequate for this situation. There are various consent models that can be used in these cases. Each model has its own advantages and disadvantages, and their use is not mutually exclusive. Using one of the models does not preclude the use of another one, as they can be used in conjunction at will. In fact, it is usually good practice to do so.[38]

#### 3.2.2.1. Staged consent

Genomic studies, irrespective of their application, are typified by their complexity. As such, the informed consent process would be a very long and involved process if done at one go.[39] This is especially true in research where a project might have various different stages, from testing to questionnaires and interviews, as well as examining the participants' medical records and other additional data. Each step of the process has to be explained to the individual who would typically be unfamiliar with the process.[40]

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37 Schleidgen, and Brothers, "Informed Consent and Decision-making," chap. 5.

38 Ibid.

39 Eline M. Bunnik, A. Cecile JW Janssens, and Maartje HN Schermer, "A Tiered-Layered-Staged Model for Informed Consent in Personal Genome Testing." *European Journal of Human Genetics* 21, no. 6 (2013): 596-601.

40 Paul S. Appelbaum et al., "Models of Consent to Return of Incidental Findings in Genomic Research," *Hastings Center Report* 44, no. 4 (2014): 22-32.

A simplification of the process is thus necessary. By using the staged consent model, the participant would receive the same information; however, this information would be given in several different meetings. For each different stage of the process, a meeting is held to discuss the upcoming portion of the process. Studies have shown that patients or participants and their family would be interested in undergoing a staged consent process if this could be done through an online portal.[41] The researcher or clinician can also provide material that the individuals peruse at their own leisure with regard to the process, including the consent documents themselves. This would make the informed consent process less overwhelming for the potential patient or participant.

The discussion with regard to secondary findings would be separated from the initial informed consent process. In the beginning, they are merely informed that the production of secondary findings is possible and that they will be given other opportunities to decide whether they want to receive them or not. This would also be the time to give any additional materials to them about secondary findings that they might peruse at home, giving them time to familiarise themselves with the concept.[42]

Although this approach has its advantages, there are some drawbacks as well. These, however, can be overcome. One of the drawbacks is that if the clinician or researcher is not careful, they can inadvertently reveal information that the subject might not have wanted to know. If they ask whether the individual wants to receive the result of a particular secondary gene, then the individual would rightly infer that that gene yielded a positive result without having to be told outright. Even if the question is posed in broader terms, the individual might still infer that a result had indeed been generated without knowing what the specific result is. The individual might still feel trapped in accepting the result as he does not want someone else to know information about them that they do not know. All this can, however, be overcome with carefully designed procedures from the outset.[43]

Another downside of this method is the fact that it is time-consuming for the clinician and more complicated logistically. Instead of one meeting where all the necessary information is

41 Joon-Ho Yu, Seema M. Jamal, Holly K. Tabor, and Michael J. Bamshad, "Self-Guided Management of Exome and Whole-Genome Sequencing Results: Changing the Results Return Model," *Genetics in Medicine* 15, no. 9 (2013): 684-690.

42 Schleidgen, and Brothers, "Informed Consent and Decision-making," chap. 5.

43 Ibid.

given and consent obtained, each individual would have to be contacted multiple times, depending on the results found. This increases the risk of an individual being lost to follow-up and not receiving the necessary information. It also increases the cost of any genomic testing done. It might, therefore, not be practical in underfunded clinics with underserved patients who have limited or no access to the internet, as well as those who struggle with language and literacy barriers.[44]

#### 3.2.2.2. Modular Consent

The modular consent model utilises distinct elements that can be rearranged and reused. In the past, these consisted of consent templates that could be reused and often included complex language. While these are still in use, ideally, this approach is used to make the process more accessible to the tested individuals.[45] These could include premade multimedia tools such as animations or videos which explain the tests to be performed in simplified terms making them more understandable.[46] These would also help break the monotony of a long explanation, with the potential subject or patient feeling more involved and giving them a much-needed mental break. While these would be extremely useful, one of the main challenges to this approach is the lack of funding to produce bespoke material for each specific test. It is important to note that while the material may be reused from study to study, its content should be carefully evaluated to make sure that they are applicable to the new study. They have to be applicable scientifically as well as socially. The material must be written in a language all participants or patients will be able to understand without using any cultural context that the prospective individuals might not understand.

If funding is not an issue, these are ideal materials to help explain, mainly when used in conjunction with written and verbal explanations.[47] When used in conjunction with the staged consent model, these materials would be beneficial as the researcher or clinician would not

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44 Rego et al., "Informed consent in the genomics era," a036582.

45 Michael Ekstract et al., "Evaluation of a Web-based decision Aid for People Considering the APOE Genetic Test for Alzheimer Risk," *Genetics in Medicine* 19, no. 6 (2017): 676-682.

46 Patricia Birch et al., "DECIDE: A Decision Support Tool to Facilitate Parents' Choices regarding Genome-Wide Sequencing," *Journal of Genetic Counseling* 25, no. 6 (2016): 1298-1308; Yvonne Bombard et al. "The Genomics ADvISER: Development and Usability Testing of a Decision Aid for the Selection of Incidental Sequencing Results," *European Journal of Human Genetics* 26, no. 7 (2018): 984-995.

47 Miriam Kuppermann et al., "Effect of Enhanced Information, Values Clarification, and Removal of Financial Barriers on Use of Prenatal Genetic Testing: A Randomized Clinical Trial," *Journal of the American Medical Association* 312, no. 12 (2014): 1210-1217.

have to meet multiple individuals and explain the same thing multiple times. Though there is a higher initial cost, it would free up some of the time the researcher or clinician spends explaining the basic concept during the informed consent process, leaving them more time to answer any specific questions the subject or patient might have.

As the field of genomics has advanced at a rapid pace, there are not enough genetics clinicians to deal with the workload. Thus, the prepared material is made good use of by the other clinicians who are increasingly being faced with genomic information in their own practice. While they are enthusiastic about incorporating this new method, studies have shown that they are not comfortable explaining it to the patients, mainly due to their lack of confidence in their abilities and knowledge about genomics.[48] Although the materials are helpful, it is essential to note that over-reliance on these materials without good in-person communication can cause problems. The individuals might misunderstand certain aspects of the process without being able to clarify any questions that they might have.

While using pre-prepared informative materials might be helpful in the informed consent process, their impact is not fully known. As far as is currently known, they are beneficial; however, their efficiency is unknown with regard to patient knowledge and satisfaction, as well as whether they have an impact on the patient's well-being after the test.

#### 3.2.2.3. Family Consent

Any genetic test result generated might have implications not only for the tested individual but also for their biological family. Whilst not all genetic variants are inherited due to allele segregation during gamete formation, most of them are. Thus, if an actionable genetic variant is discovered in an individual, there is a high possibility that other members of the family also carry the same variant. When such a result is uncovered, a retroactive approach is therefore usually utilised called cascade testing, where family members who might be affected are contacted and encouraged to also seek testing.[49]

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[48] Irmgard Nippert et al., "Confidence of Primary Care Physicians in their Ability to Carry Out Basic Medical Genetic Tasks—A European Survey in Five Countries—Part 1," *Journal of Community Genetics* 2, no. 1 (2011): 1-11; June C. Carroll et al., "Primary Care Providers' Experiences with and Perceptions of Personalized Genomic Medicine," *Canadian Family Physician* 62, no. 10 (2016): e626-e635.

[49] Schleidgen, and Brothers, "Informed Consent and Decision-making," chap. 5.

The family consent model is a more proactive approach where any family members that might be affected by secondary findings are contacted before testing is done. The risks and benefits are explained to them, and they can decide whether they want to be informed if any results that may affect them are generated. They can thus give their informed consent beforehand and not be forced to accept the results. Contacting them after the result has already been generated implies that there are findings that might affect them. Using this model also opens up channels of communication that were not previously there, encouraging ongoing contact and facilitating the dissemination of results.[50]

This process, however, is quite a labour intensive as it involves finding out any individual that might be potentially affected in the family of each and every tested individual, contacting them, explaining the potential benefits and risks of secondary findings as well as going through a modified version of the informed consent process which has to be drafted in advance. The cost of all this might be prohibitively high, especially in research studies.

#### 3.2.2.4. Broad Consent

While the other consent models have mainly been designed for genomic studies, broad consent has already been used for other types of studies. When giving broad consent, the individual is giving their consent for their samples and results to be used in future studies. Categorical consent and tiered consent are also sometimes used. Categorical consent gives the researchers consent to use their data and samples for specific types of studies dealing with a specific disease, while tiered consent gives the same consent but to multiple specific categories.[51]

All these types of consent allow the researchers to use the samples and data generated during a study to be used in the future. This would mean that neither the researcher nor the subject would know at the time of consent what precisely the subject is consenting to, which is what makes this type of consent so controversial.[52] A solution to this is to anonymise any data gathered so that it cannot be traced back to the individual who donated it. By doing so, the

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[50] Jusaku Minari, Harriet Teare, Colin Mitchell, Jane Kaye, and Kazuto Kato, "The Emerging Need for Family-Centric Initiatives for Obtaining Consent in Personal Genome Research," *Genome Medicine* 6, no. 12 (2014): 1-3.

[51] Garrison Nanibaa'A et al., "A Systematic Literature Review of Individuals' Perspectives on Broad Consent and Data Sharing in the United States," *Genetics in Medicine* 18, no. 7 (2016): 663-671.

[52] Schleidgen, and Brothers, "Informed Consent and Decision-making," chap. 5.

research subject can give his broad consent easily while knowing that there are no future repercussions of doing so.

#### 3.2.2.5. Binning Model

There are ways that the testing procedure could be structured that can aid in the informed consent process. One of these is that the secondary findings are classified beforehand into various groups, depending on the outcome of said secondary findings, such as clinical actionability.[53] Thus, during the informed consent process, the question posed is whether they want to receive all of the results, some of them or none at all. This will lead to the individual questioning why this question is asked, as usually, it is the norm for all results to be given to the individual. An explanation can then be given about why this question is posed and why certain people might choose not to accept all or none of their results. An explanation such as this might be helpful to the individual who probably had never thought through a scenario like this to start thinking about all of the implications, especially those that might not have come to mind otherwise. They would start to think about what they value most and act accordingly, depending on what they value the most.[54]

Whichever method is used, it is important to keep in mind that the ultimate aim of the informed consent process is to help the patient or research subject understand what all these potential findings might mean to himself, as well as to his family. One might say that even though most focus on the duty to look for secondary findings, the duty to inform the patient or research subject is just as important.

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[53] Jonathan S. Berg, Muin J. Khoury, and James P. Evans, "Deploying Whole Genome Sequencing In Clinical Practice and Public Health: Meeting the Challenge One Bin at a Time," *Genetics in Medicine* 13, no. 6 (2011): 499-504

[54] Schleidgen, and Brothers, "Informed Consent and Decision-making," chap. 5.

# Conclusion

There are many ethical issues that concern the generation of secondary findings and the dissemination of these results. In the first chapter, an overview of how additional findings are generated was given, as well as how the ethical debate concerning these findings has evolved over the last decade or so. In the second chapter, whether clinicians and researchers have a duty to look for and communicate these results to the tested individuals was discussed. As various institutions worldwide have issued their own recommendations, two of the most influential ones were discussed at length. In the third chapter, the right not to know about additional findings was debated. To be able to exercise this right, a person must be sufficiently informed about the topic at hand, which is why the informed consent process is a very important topic. However, due to the complexity of the subject, the traditional informed consent process cannot be used in these instances. Thus, a new method has to be applied that best serves these circumstances.

Whether there is a duty by clinicians and researchers to inform patients and research subjects about secondary findings has been heavily debated. In terms of research, some argue that there is a duty to report additional findings based on the duty of easy rescue.[1] Most agree, however, that this reasoning is flawed. For the duty of easy rescue to apply, the costs to the research team must be smaller than the benefits reaped by the participants, which is clearly not the case. Researchers have, thus, no ethical duty to communicate additional findings to their subjects, as this would place the study under a lot of undue financial burden and would be time-consuming for the researchers.

Searching for secondary findings, on the other hand, would generate medical knowledge and thus would be of benefit to society and the common good. As funding for research is a continuous problem, all researchers try to make the most out of each sample that they collect. As such, each sample collected is usually used in multiple studies to reduce cost and maximise the scope of each study by increasing the overall available pool of samples. It is more

[1] Julian J. Koplin, Julian Savulescu, and Danya F. Vears, "Why Genomics Researchers are sometimes morally required to Hunt for Secondary Findings," *BioMed Central Medical Ethics* 21, no. 1 (2020): 1-11.

beneficial to society to reuse samples already collected as less subjects are inconvenienced or harmed.

Using samples across multiple studies would not be possible if researchers had to contact each participant every time a new test is done and get their informed consent. As such, deidentifying samples is an easy solution to this problem, removing any privacy issue that may arise and streamlining the informed consent process. The informed consent process would use the broad consent model wherein a variety of diseases are explained to the individuals. The fact that none of the results can be traced back to the donor also has to be explained during the informed consent process along with an explanation why this is in the interest of both the research team as well as the research subject. It can be explained to the research subject that while there might be a benefit to knowing about additional findings, the risks of knowing outweigh any of the perceived benefits. Some of the risks include difficulty to get health insurance, to get employment and to get a bank loan, to name but a few. Once genetic information is known about an individual, this can be used in multiple ways, most of which are not in the interest of the tested individual.

I would therefore recommend that a broad consent method is used to maximise the research potential, while at the same time cause no harm to the research subject by deidentifying all samples as soon as they are collected. While researchers should look for secondary findings for research purposes, it is not recommended that these results are passed on to the participants.

In a clinical setting, the duty to look for secondary findings is not based solely on proportionality and the duty of easy rescue. Most arguments favour searching for secondary findings because doctors have a fiduciary duty to provide the best care possible to their patients. They consider searching for secondary findings to be a part of this duty.[2] It should be noted, however, that this type of testing is not yet licenced for diagnostics. Before any such result is communicated to the patient, it must be verified using validated methods. Not

[2] David T. Miller et al., "ACMG SF v3. 0 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)," *Genetics in Medicine* 23, no. 8 (2021): 1381-1390.

doing so could mean that unreliable results, such as false positive results, are given to the patient, and thus open the clinician to liability issues.

Others consider that these types of findings have to be looked for outside of the primary aim of a test to be a form of opportunistic screening. Another aspect in contention is that even when clinicians look for these findings, there is no consensus as to what constitutes a medically actionable variant. Though different institutions have issued their lists, these vary, showing that some medically actionable variants might not be as they seem. There is also an issue with justice since merely providing this type of opportunistic screening will benefit some but not others.[3]

The European Society of Human Genetics (ESHG) recommends that genetic tests should be as targeted as possible.[4] Thus, the generation of secondary findings should be avoided in the clinical setting for the time being. One of the reasons that is mentioned is the fact that scientific knowledge about this subject is not robust enough to justify integrating it into the healthcare system. The lack of scientific knowledge is a key factor why these types of findings should not be reported as yet. Doing so might cause more harm than good to the patients. It is this fact that, in my opinion, negates any argument in favour of reporting secondary findings. Once this field has advanced sufficiently such that it is proven that such results are beneficial and not harmful to the individuals tested, the first steps can be taken to incorporate it.

As such, for the time being, I would recommend that the search for secondary findings should be confined to pilot and evaluation studies to assess the proportionality of opportunistic genetic screening better. As it is a type of screening, before any system is put in place, it must conform to the general framework that is usually used for screening, including the fact that there must be clear benefits to the population before it can be put in place.

Many types of pilot and evaluation studies should be utilised. One of these should be to find the prevalence of actionable variants in different populations so a list can start being built tailored to every population. No framework can be put in place without first doing this as the

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[3] Guido de Wert et al., "Opportunistic Genomic Screening. Recommendations of the European Society of Human Genetics," *European Journal of Human Genetics* 29, no. 3 (2021): 365-377.

[4] Ibid.

results produced in one population can vary drastically from those found in another. The ethnicity of the population in question plays a major role in the results. Currently, most of the genetic information is not the same for each ethnicity with one being overrepresented. This has to be corrected as all members of a society should be represented within the reference material used. Ideally a project, like the 100,000 Genomes Project,[5] should be put in place to assess this.

Studies should also be conducted to determine how to incorporate this screening into the healthcare system. Each system is different; thus, this situation does not have a one size fits all. Each system's capacity to incorporate every aspect of this screening, including integrating the preventative treatments that could result from this testing, has to be evaluated. When the time comes to incorporate it, a robust framework has to be built to avoid the ethical pitfalls embedded in this topic as much as possible. Attention has to be given to the ethical principles of proportionality, respect for autonomy, justice and solidarity, making sure that they are respected as much as possible.

A robust, well-designed informed consent process should be implemented in every framework. The form this should take depends on where and in what circumstances it will be used. The various models provide a basis, as discussed in section 3.2.2. Each population and healthcare system will have different needs and challenges. The models that I would recommend are the staged and modular models, both of which can be modified to suit different situations. These two models when combined should produce the most useful procedure.

I would recommend that before the test is done, the patient is first contacted for informed consent purposes. During this first meeting, the primary purpose of the test should be discussed at length. The possibility that a secondary finding is found should also be discussed in broad terms. It should be explained to the patient what this term means and give examples of the types of findings that might crop up. The types of findings should be categorised by the effect that they have, for example, those associated with a heart condition should be placed in the same category.

[5] Genomics England, "100,000 Genomes Project," last accessed October 28, 2022, https://www.genomicsengland.co.uk.

During this first meeting, the modular model can also be used. This can be done by giving the patient access to premade materials explaining all this new information. As it is a complicated matter, they do not have to make the decision immediately, but should be given some time to get to terms with all the new information. A web site can be made with all the information so that all patients or subjects can view it at their own convenience. This can include presentations and videos as well as a frequently asked questions section. A second meeting should be scheduled where the patient can ask any remaining questions and then choose whether they want to know all types of findings, none at all or to know only one of the categories only.

Once the clinician has the results in hand, the patients are contacted again. The primary result should be given to them. Then, the clinician should ask again whether they want to know their results. Once they confirm that they have not changed their mind, the secondary results, if there are any, can be given to the patient. Thus using the staged and modular models combined to make sure that the informed consent process is taking place correctly.

Using the method described would honour patient's values, including their right not to know, which can be respected as long as no harm is inflicted on others. Should the patient decide not to know, the data generated should not analysed for secondary findings, thus preventing any ethical dilemmas from arising. Situations may still occur where the individual changes their mind about wanting to know after the results have already been generated. Should the results generated be potentially able to prevent harm to the patient or others, they cannot be ignored. As such, an ethics board should be formed to deal with this type of situation on a case-by-case basis, considering the validity of the result, its utility and actionability, and who is potentially in harm's way.

While the informed consent process should be structured in such a way as to facilitate the individuals' understanding, ideally, genetic counselling is also provided. Genetic counselling is a communication process that aims to provide individuals with information tailored according to each person's needs, helping them decide whether to undergo testing and what to do with the results. This can take place before the test is done to help the individuals understand all the implications of the test and afterwards to help the person to understand

the results. The informed consent process itself might include a session with a genetic counsellor.[6]

While a genetic counsellor should have a sound knowledge of genetics, this is not the only prerequisite. A genetic counsellor is mainly a counsellor whose aim is to help individuals to uncover their values and preferences. They are trained on how to communicate best, actively listen and empower the person to make choices that are consistent with their values.

One of the main issues that genetic counsellors face is the complexity of the topic they must explain. As previously discussed, genetic changes interact with each other and with other environmental factors, some of which can affect a person's health. Some of these effects are preventable, while others are not. There are even others whose effects we do not know yet. All this can be confusing even for those well-versed in genomic testing. It is even more so for the members of the general public. While the informed consent process seeks to inform and educate all who will undergo the test, being well-informed on the scientific aspects of the test is not enough. The person must also know their underlying values and priorities, considering their past experiences. Despite their importance, most people have not pondered this as they are not topics that come up in daily life. The genetic counsellor aims to lead the individuals to evaluate their values and priorities for the first time.[7]

Another essential factor they must explain is that, as previously mentioned, this field is rapidly evolving. What today is considered a variant of undetermined significance might in the future be recognised as a risk factor for a specific disease and vice versa. This is quite difficult to explain and causes two problems. The first is that the list of genes tested for secondary findings, as well as their subsequent variants, and their significance will vary significantly over time. While a person can be given a list, which can be explained to them, there is no guarantee that this will remain valid. As such, instead of a specific list of genes that are risk factors, these could be grouped according to type. The individual can then decide whether they want a specific type of result instead of choosing to know the specific result. The downside of this approach is that a person might still not understand what these categories mean, not having

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6 Sebastian Schleidgen, and Kyle B. Brothers, "Informed Consent and Decision-making," in *Secondary Findings in Genomic Research,* ed. Martin Langanke, Pia Erdmann, and Kyle B. Brothers (Massachusetts: Academic Press, 2020), chap. 5, Kindle.

7 Ibid.

sufficient medical knowledge. When the person receives the result, they might be surprised, not having realised they had given their consent.[8]

As previously mentioned, genomics is an area of study that blurs the line between research and clinical care, causing them to overlap somewhat. It is difficult for the patient or research subject to distinguish between healthcare procedures and research, mainly when they occur in the same place or at the same time. The patients' doctor might also be a researcher who conducts medical research during their medical practice which means that the research might be taking place in a hospital. The research subject might automatically assume that any procedure taking place in a hospital to be a normal medical procedure. It might be impossible for the patient to know whether the procedure is meant for research or clinical care as they might be the same, as is sometimes the case in genomics. Tests conducted for a particular clinical reason could also be used as research material. A patient would feel that there is no other choice but to submit to the testing if they want to know the result of their or their child's genetic condition.[9]

All of this can lead to a diagnostic misconception by the tested individual, wherein they decide to take part in a study to get a diagnostic result.[10] To avoid this issue, it should be clearly explained to the participant that the main aim of the study is the generation of new scientific and medical knowledge during the informed consent process. Research is done for the common good, not for the benefit of the research subjects themselves. As such, other options can be explained to them, such as the availability of private testing, if this service is not provided by the national health care system. Doing so would decrease as much as possible the number of people who feel that they have no choice but to participate in a research study to receive their medical diagnosis.[11]

8 Ibid.
9 Ibid.
10 Ibid.
11 Ibid.

# Bibliography


Ackerman, Jaeger P., Daniel C. Bartos, Jamie D. Kapplinger, David J. Tester, Brian P. Delisle, and Michael J. Ackerman. "The Promise and Peril of Precision Medicine: Phenotyping Still Matters Most." *Mayo Clinic Proceedings* 91, no. 11 (2016): 1606-1616.

Adler, Arnon, Valeria Novelli, Ahmad S. Amin, Emanuela Abiusi, Melanie Care, Eline A. Nannenberg, Harriet Feilotter et al. "An International, Multicentered, Evidence-Based Reappraisal of Genes Reported to Cause Congenital Long QT Syndrome." *Circulation* 141, no. 6 (2020): 418-428.

American College of Medical Genetics Board of Directors. "ACMG Practice Guidelines: Incidental Findings in Clinical Genomics: A Clarification." *Genetics in Medicine* 15, no. 8 (2013): 664-6.

Andermann, Anne, Ingeborg Blancquaert, Sylvie Beauchamp, and Véronique Déry. "Revisiting Wilson and Jungner in the Genomic Age: A Review of Screening Criteria over the Past 40 Years." *Bulletin of the World Health Organization* 86 (2008): 317-319.

Andorno, Roberto. "The Right not to know: An Autonomy based Approach." *Journal of Medical Ethics* 30, no. 5 (2004): 435-439.

Appelbaum, Paul S., Erik Parens, Cameron R. Waldman, Robert Klitzman, Abby Fyer, Josue Martinez, W. Nicholson Price, and Wendy K. Chung. "Models of Consent to Return of Incidental Findings in Genomic Research." *Hastings Center Report* 44, no. 4 (2014): 22-32.

Behjati, Sam, and Patrick S. Tarpey. "What is Next Generation Sequencing?" *Archives of Disease in Childhood-Education and Practice* 98, no. 6 (2013): 236-238.

Bentley, Amy R., Shawneequa Callier, and Charles N. Rotimi. "Diversity and Inclusion in Genomic Research: Why the Uneven Progress?" *Journal of Community Genetics* 8, no. 4 (2017): 255-266.

Berg, Jonathan S., Ann Katherine M. Foreman, Julianne M. O'daniel, Jessica K. Booker, Lacey Boshe, Timothy Carey, Kristy R. Crooks et al. "A Semiquantitative Metric for Evaluating Clinical Actionability of Incidental or Secondary Findings from Genome-Scale Sequencing." *Genetics in Medicine* 18, no. 5 (2016): 467-475.

Berg, Jonathan S., Muin J. Khoury, and James P. Evans. "Deploying Whole Genome Sequencing In Clinical Practice and Public Health: Meeting the Challenge One Bin at a Time." *Genetics in Medicine* 13, no. 6 (2011): 499-504.

Beskow, Laura M., N. Chantelle Hardy, Li Lin, and Kevin P. Weinfurt. "Simplifying Informed Consent for Biorepositories: Stakeholder Perspectives." *Genetics in Medicine* 12, no. 9 (2010): 567-572.

Birch, Patricia, S. Adam, N. Bansback, R. R. Coe, J. Hicklin, A. Lehman, K. C. Li, and J. M. Friedman. "DECIDE: A Decision Support Tool to Facilitate Parents' Choices regarding Genome-Wide Sequencing." *Journal of Genetic Counseling* 25, no. 6 (2016): 1298-1308.

Bombard, Yvonne, Marc Clausen, Chloe Mighton, Lindsay Carlsson, Selina Casalino, Emily Glogowski, Kasmintan Schrader et al. "The Genomics ADvISER: Development and Usability Testing of a Decision Aid for the Selection of Incidental Sequencing Results." *European Journal of Human Genetics* 26, no. 7 (2018): 984-995.

Borra, Ronald J. H., and A. Gregory Sorensen. "Incidental Findings in Brain MRI Research: What Do We Owe Our Subjects?" *Journal of the American College of Radiology* 8, no. 12 (2011): 848-852.

Borry, Pascal, Mahsa Shabani, and Heidi Carmen Howard. "Is there a Right Time to Know?: The Right not to Know and Genetic Testing in Children." *Journal of Law, Medicine & Ethics* 42, no. 1 (2014): 19-27.

Bowling, Kevin M., Michelle L. Thompson, Gregory M. Cooper. "How Secondary Findings are Made." In *Secondary Findings in Genomic Research*, edited by Martin Langanke, Pia Erdmann and Kyle B. Brothers. Massachusetts: Academic Press, 2020. Kindle.

Bredenoord, Annelien L., N. Charlotte Onland-Moret, and Johannes J. M. Van Delden. "Feedback of Individual Genetic Results to Research Participants: In Favor of A Qualified Disclosure Policy." *Human Mutation* 32, no. 8 (2011): 861-867.

Brothers, Kyle B., Martin Langanke and Pia Erdmann. "Introduction." In *Secondary Findings in Genomic Research*, edited by Martin Langanke, Pia Erdmann and Kyle B. Brothers. Massachusetts: Academic Press, 2020. Kindle.

Bunnik, Eline M., A. Cecile JW Janssens, and Maartje HN Schermer. "A Tiered-Layered-Staged Model for Informed Consent in Personal Genome Testing." *European Journal of Human Genetics* 21, no. 6 (2013): 596-601.

Burke, Wylie, Armand H. Matheny Antommaria, Robin Bennett, Jeffrey Botkin, Ellen Wright Clayton, Gail E. Henderson, Ingrid A. Holm et al. "Recommendations For Returning Genomic Incidental Findings? We Need To Talk!" *Genetics in Medicine* 15, no. 11 (2013): 854-859.

Carroll, June C., Tutsirai Makuwaza, Donna P. Manca, Nicolette Sopcak, Joanne A. Permaul, Mary Ann O'Brien, Ruth Heisey et al. "Primary Care Providers' Experiences with and Perceptions of Personalized Genomic Medicine." *Canadian Family Physician* 62, no. 10 (2016): e626-e635.

Centers for Disease Control and Prevention. "Tier 1 Genomics Applications and their Importance to Public Health." Last modified March 6, 2014. https://www.cdc.gov/genomics/implementation.

Council of Europe. *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine.* 1997.

Cho, Mildred K. "Understanding Incidental Findings in the Context of Genetics and Genomics." *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 280-285.

Chow, Andrew, and Katharine J. Drummond. "Ethical Considerations for Normal Control Subjects in MRI Research." *Journal of Clinical Neuroscience* 17, no. 9 (2010): 1111-1113.

Cochrane, A. L., and W. W. Holland. "Validation of Screening Procedures." *British Medical Bulletin* 27, no. 1 (1971): 3-8.

Darnell, Andrew J., Howard Austin, David A. Bluemke, Richard O. Cannon III, Kenneth Fischbeck, William Gahl, David Goldman et al. "A Clinical Service to Support the Return of Secondary Genomic Findings in Human Research." *The American Journal of Human Genetics* 98, no. 3 (2016): 435-441.

Davies, Ben. "The Right not to Know and the Obligation to Know." *Journal of Medical Ethics* 46, no. 5 (2020): 300-303.

De Wert, Guido, Wybo Dondorp, Angus Clarke, Elisabeth Dequeker, Christophe Cordier, Zandra Deans, Carla G. van El et al. "Opportunistic Genomic Screening. Recommendations of the European Society of Human Genetics." *European Journal of Human Genetics* 29, no. 3 (2021): 365-377.

Dheensa, Sandi, Gabrielle Samuel, Anneke M. Lucassen, and Bobbie Farsides. "Towards a National Genomics Medicine Service: the Challenges facing Clinical-Research hybrid Practices and the Case of the 100 000 Genomes Project." *Journal of Medical Ethics* 44, no. 6 (2018): 397-403.

Duncan, Rony E., and Martin B. Delatycki. "Predictive Genetic Testing in Young People for Adult-Onset Conditions: Where is the Empirical Evidence?" *Clinical Genetics* 69, no. 1 (2006): 8-16.

Durmaz, Asude Alpman, Emin Karaca, Urszula Demkow, Gokce Toruner, Jacqueline Schoumans, and Ozgur Cogulu. *BioMed Research International*. "Evolution of Genetic Techniques: Past, Present, and Beyond." Last modified March 22, 2015, https://www.hindawi.com/journals.

Dworkin, Ronald, and Jeremy Waldron. *Theories of Rights.* Oxford: Oxford University Press, 1984.

Ekstract, Michael, Golde I. Holtzman, Kye Y. Kim, Susan M. Willis, and Doris T. Zallen. "Evaluation of a Web-based Decision Aid for People considering the APOE Genetic Test for Alzheimer Risk." *Genetics in Medicine* 19, no. 6 (2017): 676-682.

Fowler, Sara A., Carol J. Saunders, and Mark A. Hoffman. "Variation among Consent Forms for Clinical Whole Exome Sequencing." *Journal of Genetic Counseling* 27, no. 1 (2018): 104-114.

Gaille, Marie and Ruth Horn. "The ethics of Genomic Medicine: Redefining Values and Norms in the UK and France." *European Journal of Human Genetics* 29, no. 5 (2021): 780-788.

Geisinger. “MyCode Genetic Conditions.” Accessed on October 29, 2022. www.geisinger.org.

German Reference Centre of Ethics in the Life Sciences. “Legal Aspects.” Accessed October 21, 2022. https://www.drze.de.

Genomics England. “!00,000 Genomes Project.” Accessed October 28, 2022, https://www.genomicsengland.co.uk.

Gliwa, Catherine, and Benjamin E. Berkman. "Do Researchers Have an Obligation to Actively Look for Genetic Incidental Findings?" *The American Journal of Bioethics* 13, no. 2 (2013): 32-42.

Green, Robert C., Jonathan S. Berg, Wayne W. Grody, Sarah S. Kalia, Bruce R. Korf, Christa L. Martin, Amy L. McGuire et al. "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing." *Genetics in Medicine* 15, no. 7 (2013): 565-574.

Haer-Wigman, Lonneke, Vyne van der Schoot, Ilse Feenstra, Anneke T. Vulto-van Silfhout, Christian Gilissen, Han G. Brunner, Lisenka ELM Vissers, and Helger G. Yntema. "1 in 38 Individuals at Risk of a Dominant Medically Actionable Disease." *European Journal of Human Genetics* 27, no. 2 (2019): 325-330.

Harris, John, and Kirsty Keywood. "Ignorance, Information and Autonomy." *Theoretical Medicine and Bioethics* 22, no. 5 (2001): 415-436.

Hart, Julian Tudor. "The Inverse Care Law." *The Lancet* 297, no. 7696 (1971): 405-412.

Häyry, Matti, and Tuija Takala. "Genetic Information, Rights, and Autonomy." *Theoretical Medicine and Bioethics* 22, no. 5 (2001): 403-414.

Hirschberg, April Malia, Gayun Chan-Smutko, and William F. Pirl. "Psychiatric Implications of Cancer Genetic Testing." *Cancer* 121, no. 3 (2015): 341-360.

Hofmann, Bjørn. "Incidental Findings of Uncertain Significance: To Know or not to Know - That is not the Question." *BMC Medical Ethics* 17, no. 1 (2016): 1-9.

Hoggard, Nigel, Gail Darwent, David Capener, Iain D. Wilkinson, and Paul D. Griffiths. "The High Incidence and Bioethics of Findings on Magnetic Resonance Brain Imaging of Normal Volunteers for Neuroscience Research." *Journal of Medical Ethics* 35, no. 3 (2009): 194-199.

Holtzman, Neil A. "ACMG Recommendations on Incidental Findings Are Flawed Scientifically and Ethically." *Genetics in Medicine* 15, no. 9 (2013): 750-751.

Illes, Judith, Allyson C. Rosen, Lynn Huang, R. A. Goldstein, Thomas A. Raffin, G. Swan, and Scott W. Atlas. "Ethical Consideration of Incidental Findings on Adult Brain MRI in Research." *Neurology* 62, no. 6 (2004): 888-890.

Illes, Judy, John E. Desmond, Lynn F. Huang, Thomas A. Raffin, and Scott W. Atlas. "Ethical and Practical Considerations in Managing Incidental Findings in Functional Magnetic Resonance Imaging." *Brain and Cognition* 50, no. 3 (2002): 358-365.

Illes, Judy, Matthew P. Kirschen, Emmeline Edwards, L. R. Stanford, Peter Bandettini, Mildred K. Cho, Paul J. Ford et al. "Incidental Findings in Brain Imaging Research." *Science* 311, no. 5762 (2006): 783-784.

Isidor, Bertrand, Sophie Julia, Pascale Saugier-Veber, Paul-Loup Weil-Dubuc, Stephane Bezieau, Eric Bieth, Jean-Paul Bonnefont et al. "Searching for Secondary Findings: Considering Actionability and Preserving the Right Not to Know." *European Journal of Human Genetics* 27, no. 10 (2019): 1481-1484.

Juth, Niklas. "The Right not to Know and the Duty to Tell: the Case of Relatives." *Journal of Law, Medicine & Ethics* 42, no. 1 (2014): 38-52.

Joly, Yann, Ida Ngueng Feze, and Jacques Simard. "Genetic Discrimination and Life Insurance: A Systematic Review of the Evidence." *BioMed Central Medicine* 11, no. 1 (2013): 1-15.

Joly, Yann, Katie M. Saulnier, Gladys Osien, and Bartha M. Knoppers. "The Ethical Framing of Personalized Medicine." *Current Opinion in Allergy and Clinical Immunology* 14, no. 5 (2014): 404-408.

Kalia, Sarah S., Kathy Adelman, Sherri J. Bale, Wendy K. Chung, Christine Eng, James P. Evans, Gail E. Herman et al. "Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing, 2016 Update (ACMG SF V2. 0): A Policy Statement of the American College of Medical Genetics and Genomics." *Genetics in Medicine* 19, no. 2 (2017): 249-255.

Khera, Amit V., Heather Mason-Suares, Deanna Brockman, Minxian Wang, Martin J. VanDenburgh, Ozlem Senol-Cosar, Candace Patterson et al. "Rare Genetic Variants Associated with Sudden Cardiac Death in Adults." *Journal of the American College of Cardiology* 74, no. 21 (2019): 2623-2634.

Khera, Amit V., Mark Chaffin, Krishna G. Aragam, Mary E. Haas, Carolina Roselli, Seung Hoan Choi, Pradeep Natarajan et al. "Genome-wide Polygenic Scores for Common Diseases Identify Individuals with Risk Equivalent to Monogenic Mutations." *Nature Genetics* 50, no. 9 (2018): 1219-1224.

Kielstein, Rita, and Hans-Martin Sass. "Right not to Know or Duty to Know? Prenatal Screening for Polycystic Renal Disease." *The Journal of Medicine and Philosophy* 17, no. 4 (1992): 395-405.

Knoppers, Bartha Maria, and Ruth Chadwick. "Human Genetic Research: Emerging Trends in Ethics." *Nature Reviews Genetics* 6, no. 1 (2005): 75-79.

Knoppers, Bartha Maria, Yann Joly, Jacques Simard, and Francine Durocher. "The Emergence of an Ethical Duty to Disclose Genetic Research Results: International Perspectives." *European Journal of Human Genetics* 14, no. 11 (2006): 1170-1178.

Koplin, Julian J., Julian Savulescu, and Danya F. Vears. "Why Genomics Researchers are sometimes Morally Required to Hunt for Secondary Findings." *BioMed Central Medical Ethics* 21, no. 1 (2020): 1-11.

Kuppermann, Miriam, Sherri Pena, Judith T. Bishop, Sanae Nakagawa, Steven E. Gregorich, Anita Sit, Juan Vargas et al. "Effect of Enhanced Information, Values Clarification, and Removal of Financial

Barriers on Use of Prenatal Genetic Testing: A Randomized Clinical Trial." *Journal of the Americal Medical Association* 312, no. 12 (2014): 1210-1217.

Landrum, Melissa J., Jennifer M. Lee, Mark Benson, Garth R. Brown, Chen Chao, Shanmuga Chitipiralla, Baoshan Gu et al. "ClinVar: Improving Access to Variant Interpretations and Supporting Evidence." *Nucleic Acids Research* 46, no. D1 (2018): D1062-D1067.

Langanke, Martin, Pia Erdmann, Wenke Lieke, and Kyle B. Brothers, "Concept, History and State of Debate." In *Secondary Findings in Genomic Research*, edited by Martin Langanke, Pia Erdmann and Kyle B. Brothers. Massachusetts: Academic Press, 2020. Kindle.

Lantos, John. "Informed Consent the Whole Truth for Patients?" *Cancer* 72, no. S9 (1993): 2811-2815.

Lek, Monkol, Konrad J. Karczewski, Eric V. Minikel, Kaitlin E. Samocha, Eric Banks, Timothy Fennell, Anne H. O'Donnell-Luria et al. "Analysis of Protein-Coding Genetic Variation in 60,706 Humans." *Nature* 536, no. 7616 (2016): 285-291.

Lewis, Cathryn and Oliver Pain. "Genetics Helps Estimate the Risk of Disease – But How Much Does It Really Tell Us?" Last modified January 26, 2022. https://theconversation.com.

Manrai, Arjun K., Birgit H. Funke, Heidi L. Rehm, Morten S. Olesen, Bradley A. Maron, Peter Szolovits, David M. Margulies, Joseph Loscalzo, and Isaac S. Kohane. "Genetic Misdiagnoses and the Potential for Health Disparities." *New England Journal of Medicine* 375, no. 7 (2016): 655-665.

McDougall, Rosalind. "Rethinking the 'Right not to Know'." *Monash Bioethics Review* 23, no. 1 (2004): 22-36.

McGuire, Amy L., Steven Joffe, Barbara A. Koenig, Barbara B. Biesecker, Laurence B. McCullough, Jennifer S. Blumenthal-Barby, Timothy Caulfield, Sharon F. Terry, and Robert C. Green, "Ethics and Genomic Incidental Findings," *Science* 340, no. 6136 (2013): 1047-1048.

McKenna, Aaron, Matthew Hanna, Eric Banks, Andrey Sivachenko, Kristian Cibulskis, Andrew Kernytsky, Kiran Garimella et al. "The Genome Analysis Toolkit: a MapReduce Framework for Analyzing Next-generation DNA Sequencing Data." *Genome Research* 20, no. 9 (2010): 1297-1303.

Miller, David T., Kristy Lee, Wendy K. Chung, Adam S. Gordon, Gail E. Herman, Teri E. Klein, Douglas R. Stewart et al. "ACMG SF v3. 0 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)." *Genetics in Medicine* 23, no. 8 (2021): 1381-1390.

Miller, Franklin G., Michelle M. Mello, and Steven Joffe. "Incidental Findings in Human Subjects Research: What Do Investigators Owe Research Participants?" *The Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 271-279.

Minari, Jusaku, Harriet Teare, Colin Mitchell, Jane Kaye, and Kazuto Kato. "The Emerging Need for Family-Centric Initiatives for Obtaining Consent in Personal Genome Research." *Genome Medicine* 6, no. 12 (2014): 1-3.

Mohammed, Saira, Zaneta Lim, Paige H. Dean, James E. Potts, Jessica NC Tang, Susan P. Etheridge, Alice Lara et al. "Genetic Insurance Discrimination in Sudden Arrhythmia Death Syndromes: Empirical Evidence from a Cross-Sectional Survey in North America." *Circulation: Cardiovascular Genetics* 10, no. 1 (2017): e001442.

Morin, S. H. X., J. F. L. Cobbold, Adrian K. P. Lim, Joseph Eliahoo, E. Louise Thomas, Sanjeev R. Mehta, Giuliana Durighel, Julie Fitzpatrick, Jimmy D. Bell, and Simon D. Taylor-Robinson. "Incidental Findings in Healthy Control Research Subjects using Whole-Body MRI." *European Journal of Radiology* 72, no. 3 (2009): 529-533.

Moret, Celine, Alex Mauron, Siv Fokstuen, Periklis Makrythanasis, and Samia A. Hurst., "Defining Categories of Actionability for Secondary Findings in Next-Generation Sequencing." *Journal of Medical Ethics* 43, no. 5 (2017): 346-349.

Morrissey, Clair, and Rebecca L. Walker. "The ethics of general population preventive genomic sequencing: rights and social justice." *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine* 43, no. 1 (2018): 22-43.

Morrison, Michael, Harriet Teare, Gabrielle Bertier, James Buchanan, Yasmin Bylstra, Clara Gaff, Leigh Jackson et al. "Implications of Secondary Findings for Clinical Contexts." In *Secondary Findings in Genomic Research,* ed. Martin Langanke, Pia Erdmann, and Kyle B. Brothers, chap. 8. Massachusetts: Academic Press, 2020. Kindle.

Nanibaa'A, Garrison, Nila A. Sathe, Armand H. Matheny Antommaria, Ingrid A. Holm, Saskia C. Sanderson, Maureen E. Smith, Melissa L. McPheeters, and Ellen W. Clayton. "A Systematic Literature Review of Individuals' Perspectives on Broad Consent and Data Sharing in the United States." *Genetics in Medicine* 18, no. 7 (2016): 663-671.

Nippert, Irmgard, Hilary J. Harris, Claire Julian-Reynier, Ulf Kristoffersson, Leo P. Ten Kate, Elizabeth Anionwu, Caroline Benjamin et al. "Confidence of Primary Care Physicians in their Ability to Carry Out Basic Medical Genetic Tasks—A European Survey in Five Countries—Part 1." *Journal of Community Genetics* 2, no. 1 (2011): 1-11.

Petersen, Britt-Sabina, Broder Fredrich, Marc P. Hoeppner, David Ellinghaus, and Andre Franke. "Opportunities and challenges of whole-genome and-exome sequencing." *BioMed Central Genetics* 18, no. 1 (2017): 1-13.

Public Health Genomics Foundation. "Managing incidental and pertinent findings from WGS in the 100,000 Genomes Project." Last modified April, 2013. www.phgfoundation.org.

Pujol, Pascal, D. Stoppa Lyonnet, T. Frebourg, J. Blin, M. C. Picot, C. Lasset, C. Dugast et al. "Lack of Referral for Genetic Counseling and Testing in BRCA1/2 and Lynch Syndromes: A Nationwide Study Based on 240,134 Consultations And 134,652 Genetic Tests." *Breast Cancer Research and Treatment* 141, no. 1 (2013): 135-144.

Pujol, Pascal, Pierre Vande Perre, Laurence Faivre, Damien Sanlaville, Carole Corsini, Bernard Baertschi, Michèle Anahory et al. "Guidelines for Reporting Secondary Findings of Genome Sequencing in Cancer Genes: the SFMPP Recommendations." *European Journal of Human Genetics* 26, no. 12 (2018): 1732-1742.

Project EURAT. "Cornerstones for an ethically and legally informed practice of Whole Genome Sequencing: Code of Conduct and Patient Consent Models." Last modified May, 2016. https://www.uni-heidelberg.de/md/totalsequenzierung.

Ravitsky, Vardit, and Benjamin S. Wilfond. "Disclosing Individual Genetic Results to Research Participants." *The American Journal of Bioethics* 6, no. 6 (2006): 8-17.

Rego, Shannon, Megan E. Grove, Mildred K. Cho, and Kelly E. Ormond. "Informed Consent in the Genomics Era." *Cold Spring Harbor Perspectives in Medicine* 10, no. 8 (2020): a036582.

Rhodes, Rosamond. "Genetic Links, Family Ties, and Social Bonds: Rights and Responsibilities in the face of Genetic Knowledge." *Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine* 23, no. 1 (1998): 10-30.

Richardson, Henry S., "Ancillary-Care Obligations," Last modified August 11, 2021. https://academic.oup.com.

Saelaert, Marlies, Heidi Mertes, Elfride De Baere, and Ignaas Devisch. "Incidental or Secondary Findings: An Integrative and Patient-inclusive Approach to the current Debate." *European Journal of Human Genetics* 26, no. 10 (2018): 1424-1431.

Sanghvi, Rashesh V., Christian J. Buhay, Bradford C. Powell, Ellen A. Tsai, Michael O. Dorschner, Celine S. Hong, Matthew S. Lebo et al. "Characterizing Reduced Coverage Regions Through Comparison of Exome and Genome Sequencing Data Across 10 Centers." *Genetics in Medicine* 20, no. 8 (2018): 855-866.

Schleidgen, Sebastian, and Kyle B. Brothers. "Informed Consent and Decision-making." In *Secondary Findings in Genomic Research*, edited by Martin Langanke, Pia Erdmann and Kyle B. Brothers. Massachusetts: Academic Press, 2020. Kindle.

Schmidt, Carsten Oliver, Katrin Hegenscheid, Pia Erdmann, Thomas Kohlmann, Martin Langanke, Henry Völzke, Ralf Puls, Heinrich Assel, Reiner Biffar, and Hans Jörgen Grabe. "Psychosocial Consequences and Severity of Disclosed Incidental Findings from Whole-Body MRI in a General Population Study." *European Radiology* 23, no. 5 (2013): 1343-1351.

Schuol, Sebastian, Christoph Schickhardt, Stefan Wiemann, Claus R. Bartram, Klaus Tanner, Roland Eils, Benjamin Meder et al. "So Rare We Need to Hunt for Them: Reframing the Ethical Debate on Incidental Findings." *Genome medicine* 7, no. 1 (2015): 1-7.

Severin, Franziska, Pascal Borry, Martina C. Cornel, Norman Daniels, Florence Fellmann, Shirley Victoria Hodgson, Heidi C. Howard et al. "Points to Consider for Prioritizing Clinical Genetic Testing Services: A European Consensus Process Oriented at Accountability for Reasonableness." *European Journal of Human Genetics* 23, no. 6 (2015): 729-735.

Shevchenko, Yuriy, and Sherri Bale. "Clinical versus Research Sequencing." *Cold Spring Harbor Perspectives in Medicine* 6, no. 11 (2016): a025809.

Siddiki, Hassan, Joel G. Fletcher, Beth McFarland, Nora Dajani, Nicholas Orme, Barbara Koenig, Marguerite Strobel, and Susan M. Wolf. "Incidental Findings in CT Colonography: Literature Review and Survey of Current Research Practice." *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 320-331.

Sjöstrand, Manne, Stefan Eriksson, Niklas Juth, and Gert Helgesson. "Paternalism in the Name of Autonomy." *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine* 38, no. 6 (2013): 710-724.

Tabor, Holly K., Benjamin E. Berkman, Sara Chandros Hull, and Michael J. Bamshad. "Genomics Really Gets Personal: How Exome and Whole Genome Sequencing Challenge the Ethical Framework of Human Genetics Research." *American Journal of Medical Genetics* Part A 155, no. 12 (2011): 2916-2924.

Tan, Nina, Laura M. Amendola, Julianne M. O'Daniel, Amber Burt, Martha J. Horike-Pyne, Lacey Boshe, Gail E. Henderson et al. "Is "Incidental Finding" the Best Term?: A Study of Patients' Preferences." *Genetics in Medicine* 19, no. 2 (2017): 176-181.

Tassicker, Roslyn J., Betty Teltscher, M. Kaye Trembath, Veronica Collins, Leslie J. Sheffield, Edmond Chiu, Lyle Gurrin, and Martin B. Delatycki. "Problems Assessing Uptake of Huntington Disease Predictive Testing and a Proposed Solution." *European Journal of Human Genetics* 17, no. 1 (2009): 66-70.

ThermoFisher Scientific. "When Do I Use Sanger Sequencing vs NGS?" Accessed 12/10/2021. https://www.thermofisher.com/blog.

Timmermans, Stefan, and Mara Buchbinder. "Patients-in-waiting: Living between Sickness and Health in the Genomics Era." *Journal of Health and Social Behavior* 51, no. 4 (2010): 408-423.

Turner, Heather, and Leigh Jackson. "Evidence for Penetrance in Patients without a Family History of Disease: A Systematic Review." *European Journal of Human Genetics* 28, no. 5 (2020): 539-550.

UNESCO. *Universal Declaration on the Human Genome and Human Rights.* 1997.

Van der Giessefn, J. A. M., E. Van Riel, M. E. Velthuizen, A. M. van Dulmen, and M. G. E. M. Ausems. "Referral to Cancer Genetic Counseling: Do Migrant Status and Patients' Educational Background Matter?" *Journal of Community Genetics* 8, no. 4 (2017): 303-310.

Van El, C. G., M. C. Cornel, P. Borry, R. J. Hastings, F. Fellmann, S. V. Hodgson, H. C. Howard et al. "ESHG Public and Professional Policy Committee. Whole-genome Sequencing in Health Care. Recommendations of the European Society of Human Genetics." *European Journal of Human Genetics* 21, Suppl 1 (2013): S1-5.

Wahlin, Tarja-Brita Robins. "To know or not to know: A Review of Behaviour and Suicidal Ideation in Preclinical Huntington's disease." *Patient Education and Counseling* 65, no. 3 (2007): 279-287.

Walsh, Roddy, Kate L. Thomson, James S. Ware, Birgit H. Funke, Jessica Woodley, Karen J. McGuire, Francesco Mazzarotto et al. "Reassessment of Mendelian Gene Pathogenicity Using 7,855 Cardiomyopathy Cases and 60,706 Reference Samples." *Genetics in Medicine* 19, no. 2 (2017): 192-203.

West, Kathleen McGlone, Erika Blacksher, and Wylie Burke. "Genomics, Health Disparities, and Missed Opportunities for the Nation's Research Agenda." *Journal of the American Medical Association* 317, no. 18 (2017): 1831-1832.

Wilfond, Benjamin S., and Kathleen Nolan. "National Policy Development for the Clinical Application of Genetic Diagnostic Technologies: Lessons from Cystic Fibrosis." *Journal of the American Medical Association* 270, no. 24 (1993): 2948-2954.

Wilson, James Maxwell Glover, Gunnar Jungner, and World Health Organization. *Principles and Practice of Screening for Disease*. 1968.

Wolf, Susan M. "The Challenge of Incidental Findings." *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 216-218.

Wolf, Susan M., Frances P. Lawrenz, Charles A. Nelson, Jeffrey P. Kahn, Mildred K. Cho, Ellen Wright Clayton, Joel G. Fletcher et al. "Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations." *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 219-248.

Woodward, C. I., and A. P. Toms. "Incidental Findings in "Normal" Volunteers." *Clinical Radiology* 64, no. 10 (2009): 951-953.

Wouters, Roel H. P., Rhodé M. Bijlsma, Geert W. J. Frederix, Margreet G. E. M. Ausems, Johannes J. M. van Delden, Emile E. Voest, and Annelien L. Bredenoord. "Is It Our Duty to Hunt for Pathogenic Mutations?" *Trends in Molecular Medicine* 24, no. 1 (2018): 3-6.

Young, Mary-Anne. "The Responses of Research Participants and Their Next of Kin to Receiving Feedback of Genetic Test Results Following Participation in the Australian Ovarian Cancer Study." *Genetics in Medicine* 15, no. 6 (2013): 458-465.

Yu, Joon-Ho, Seema M. Jamal, Holly K. Tabor, and Michael J. Bamshad. "Self-guided Management of Exome and Whole-Genome Sequencing Results: Changing the Results Return Model." *Genetics in Medicine* 15, no. 9 (2013): 684-690.

Zamora, Bernarda, Francois Maignen, Phill O'Neill, Jorge Mestre-Ferrandiz, and Martina Garau. "Comparing Access to Orphan Medicinal Products in Europe." *Orphanet Journal of Rare Diseases* 14, no. 1 (2019): 1-12.

Zerres, Klaus, Simone Heidemann, Hildegard Kehrer-Sawatzki, Wolfram Kress, Peter Wieacker, Sabine Rudnik-Schoeneborn, Ute Hehr et al. "Statement of the German Society for Human Genetics on genetic Additional Findings in Diagnosis and Research." *Medizinische Genetik* 25, no. 2 (2013): 284-286.