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Normative Issues in Next Generation Sequencing Gene Testing

†Na-Kyoung Kim

Department of Law, Sungshin Women's University, Seoul 02844, Korea

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†Corresponding author
Na-Kyoung Kim
Department of Law, Sungshin Women's University, Seoul 02844, Korea
Tel: +82-2-920-7459
E-mail: nakyoungkim@sungshin.ac.kr

ORCID
Na-Kyoung Kim
https://orcid.org/0000-0002-0961-5875

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Abstract

Despite the commercialization of Next generation sequencing (NGS) gene testing, only a few studies have addressed the various ethical and legal problems associated with NGS testing in Korea Here, we reviewed the normative issues that emerged at each stage of the wet analysis and bioinformatics analysis of NGS gene testing. In particular, it was in mind to apply various international guidelines and the principles of bioethics to actual clinical practice. Considering the characteristics of NGS testing, wet analysis of additional testing can be justified if presumptive consent is recognized. Furthermore, the medical relationship between diseases needs to be established and it should be clear that the patient would have given consent if the patient had been aware of the correlation between genes. At the stage of bioinformatics analysis, the question of unsolicited findings arises. In case of unsolicited and relevant findings, according to American College of Medical Genetics and Genomics (ACMG), a recognized relationship between genes and diseases needs to be established. In case of unsolicited and not-relevant findings, it is almost impossible to determine whether knowing or not knowing the findings is more beneficial to the patient. However, it seems to be certain that the psychological harm an individual may suffer from such information is likely to be greater if the disease is severe and if there is no cure. The list of genes for which the ACMG guidelines impose reporting obligations is a good reference for judgment.

Keywords: Next generation sequencing (NGS) gene testing, Informed consent, Presumptive consent, Incidental findings, Secondary findings, Unsolicited findings

INTRODUCTION

Next-generation sequencing (NGS) is rapidly becoming a routine component of clinical medical practice. While the clinical application of NGS testing for diagnosis of various diseases has been widely discussed, the ethical and legal implications remain rarely discussed. Gene testing consists of two elements, namely wet analysis and bioinformatics analysis (interpretation). Wet analysis refers to the stage of extraction of a patient's DNA and the use of NGS approach to identify nucleotide sequences. Bioinformatics analysis is the next stage, which is used to determine whether a gene mutation is present, and whether it can be identified as the cause of a particular disease. However, wet analysis and bioinformatics interpretation are indeterminate, and the spectrum of (possible) interpretation is wide. Hence, gene testing is considered to have an open structure, suggesting that gene testing itself is essentially a communication (Kim, 2015). If the structure of gene testing is dual and open, the patient ultimately needs to understand the structural features of gene testing and should be able to reinterpret

and construct the meaning of the test results.

In the case of NGS testing, the characteristics of gene testing appear in an amplified form. The unique characteristics of NGS pose a complex new problem, which is the problem of secondary finding; this problem of NGS widens the spectrum of interpretation further. Even when reporting secondary findings, the penetrance, severity, genetic strength on the concerned phenotype, preventability and/or presence of the treatment for the phenotype should be considered. This process is a kind of redesigning a patient's life through gene testing and in this process, it must be considered in detail, such as whether the patient would want to know about unexpected diseases or possibilities of new interpretation of the test genes that have not been revealed previously (Meiser et al., 2016). This study attempted to analyze these issues from ethical and legal perspectives by considering the nature of communication of gene testing. However, in Korea, ethical and legal discussions on NGS testing have not been sufficient, and the culture of genetic communication is not mature. Furthermore, specific clinical guidelines for the ethical issues posed by modern technologies, including NGS testing, have not been established sufficiently. Therefore, fundamentally, this study is oriented to spread awareness regarding these issues and explore clues to resolve them by considering the applicable laws and guidelines of the United States and Europe as well as general bioethics theories and principles. In particular, this study will ultimately provide an opportunity for development of the entire protocol for the complete process of genetic communication through a convergent and interdisciplinary work between a jurist and a physician, especially for NGS testing.

ETHICAL AND LEGAL ISSUES IN THE STAGE OF WET ANALYSIS

In the course of carrying out NGS testing, it can happen that gene panels are added in the stage of wet analysis for any reason. Here, the first question arises, whether it is justified to expand the scope of the testing in such a way (Kim, 2022).

1. Informed consent

The legal principle asserts that any medical practice without the consent of the patient is not legitimate. Physicians' duty to explain all pertinent medical information to patients has been recognized as a clear legal obligation owing, in particular, to a paradigm shift in medical society, which emphasizes patient autonomy (for example of legal cases, see Texas Supreme Court, 1983; BGHZ, 1989; Korean Supreme Court, 1994; Korean Supreme Court, 2007).

1) Significance

Informed consent, that is, explanation and consent, is the first step of communication (O'Neill, 2008), especially from the perspective of genetic (or medical) communication. Informed consent is the process by which patients understand the medical test to be performed on them and accept their influence on their body and life. In this process, exchange of the patient's (subjective) understanding of his own body and the doctor's (objective) medical knowledge is included. In other words, the patient, on the one hand, can think about what and how much he can know about himself through gene testing. On the other hand, this process helps the patient eventually rebuild the interpretation of the test results (Kim, 2015). Through this hermeneutical circulation, the meaning of medical practice is reconstructed for the patient (Kim, 2015). According to the German philosopher Gadamer's expression of the meaning of medical communication from the standpoint of hermeneutics, only through this process will the doctor, "the Other", be able to guide the patient a little so that he knows how to find his own way (Gadamer, 2010) and the patient can secure the

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subjectivity of his body. In this context, it is legally required to impose procedural obligations on informed consent and genetic counseling in regulation of gene testing.

2) BioAct

In Korea, the Bioethics and Biosafety Act (BioAct, Korea) stipulates that any gene testing institution shall "fully explain the objectives and method[s] of the gene testing and the expected results and significance of the gene testing" (§51⑥) to test recipients and/or their representatives by law. Based on this explanation, a gene testing institution shall obtain written consent regarding the following matters: "1. Purpose of gene testing; 2. Management of the material for testing; 3. Withdrawal of consent, the protection of rights and information of the test, and other matters specified by Ordinance of the Ministry of Health and Welfare"(§51①). Here, the phrase "purpose of gene testing" requires that the extent of the diseases to be diagnosed must be (at least roughly) specified. In clinical situations, pretest counseling or pretest explanations of NGS testing have emphasized diseases or clinical indications rather than variable features or outcomes of individual genes. Each patient has unique health conditions and genetic makeup. As the effects of individual genes are variable, it is not possible or reasonable to explain the genes when informing the patients prior to the performance of gene testing.

2. Presumptive consent

1) Limitation of informed consent

In consideration of the BioAct guidelines, the question is whether the patient's consent to gene testing is likely to include not only a disease the patient was primarily diagnosed with but also another disease. Informed consent can be obtained in different forms at different times within any dynamic medical sequence that ultimately aims at the best possible treatment (Kim, 2007). A request for informed consent does not imply that the patient and the physician must speak about all details prior to medical intervention (Kim, 2007). Physicians' discretion is recognized in their responsibilities for medical practice. This discretion may include choosing the therapy option that the physician considers the most reasonable among the various possibilities of explanation associated with informed consent (Korean Supreme Court, 1994). In the case of gene testing, it is possible that the gene to be tested is associated with various diseases. Inversely, there is always an uncertainty as to whether the gene responsible for the disease to be tested is in fact clearly specified. This open structure caused by the complicated nature of the underlying science makes it more difficult to formalize the format and content of explanation in the process of gene testing (Kim, 2015). Then, could this difficulty in defining parameters justify testing for another disease? In particular, could wet analysis be expanded toward another disease?

2) Presumptive consent

(1) Requirements

According to the Korean Supreme Court, the hypothetical consent, which refers to an acceptance assuming that the patient did not listen to the doctor's explanation but the patient would have consented to the medical act provided the correct explanation was heard, is exceptionally allowed if "the patient's consent is clearly anticipated" (Korean Supreme Court, 2002; Korean Supreme Court, 2015). Given that NGS testing has recently emerged as an aspect of clinical practice, presumptive consent can only be considered under conditions of extremely exceptional exemption of physicians' legal responsibilities for additional gene testing. Additionally, the following

point should be explained to patients and consent based on this point should be obtained prior to the test: "gene testing of related diseases may be performed because secondary testing is an aspect of NGS testing." Moreover, when making ex-post judgments, it needs to be clarified the patient would have given consent if the patient had been aware of the correlation between genes.

For reference, the Guidelines for diagnostic NGS testing from the EuroGentest and the European Society of Human Genetics (ESHG Guidelines 2016) specifically refer to the "relationship between the aberrant genotype and the pathology" as a test requirement in the case of gene testing for diagnostic purposes (Statement 05 in this Guideline). More precisely, this guideline stipulates the following: "For diagnostic purpose[s], only genes with a known (i.e., published and confirmed) relationship between the aberrant genotype and the pathology should be included in the analysis" (Statement 05 in this Guideline). Of course, the "known" relationship is vague and can have different interpretations. However, even then, only a limited range of genes can be tested in the stage of wet analysis, according to this guideline. In other words, even if there exist medical relationship between diseases, the gene should not be included in the analysis unless it is a common and known causative gene, and presumptive consent for the gene cannot be recognized.

(2) Supplemental consideration: cost efficiency

Additionally, it is necessary to consider whether the cost efficiency of testing has a certain impact on the recognition of a patient's presumptive consent (post-presumption of consent). In NGS testing, simultaneous analysis of multiple genes of many people for various diseases greatly increases the cost-effectiveness of the testing (Fecteau, 2014; Gallego et al., 2016; ESHG, 2016). The cost efficiency of testing is an incongruous element that is removed from the nature of the medical treatment and from therapeutic communication between patients and physicians (Yi & Kim, 2017). The categorical imperative of the medical "life world" calls for the law to protect communication between medical subjects from the logic of capital as an element of the system (Habermas, 2011). In the case of NGS testing, however, considerations of cost efficiency may be beyond the regeneration of capital for healthcare providers. Patients may have a new desire to expand their medical information free of charge and plan their lives. If treatment is understood as holistic healing (Knoll, 2003), it is not always appropriate to exclude the possibility of meeting new patient needs. Most importantly, it must be ensured that the procedures involved in patient decision-making are based on accurate communication (i.e., procedures for understanding and reflection). Consideration of the efficiency of testing costs alone can never substitute patients' consent to testing, which is the most important basis of autonomy in medical practice. In the case of NGS testing, the process of understanding the rationale and characteristics of the test (i.e., the possibility of parallel testing for other diseases/genes) should be conveyed to patients as an essential prerequisite (Huang et al., 2014). If the minimum prerequisites, including this requirement, are met, the cost efficiency of such testing may be a mitigating factor in determining the medical relationship between diseases.

ETHICAL AND LEGAL ISSUES IN STAGES OF BIOINFORMATICS ANALYSIS AND REPORTING

Owing to the specificity of NGS testing, unsolicited and secondary findings can emerge in various ways in the process of interpretation of biological information. Here, important problems related to communication with the patient arise. Interpretation of the results of the wet analysis is, from the patient's point of view, a matter of relating the result to one's own life and ultimately accepting it. Regarding unsolicited and secondary findings, the range of information to be reported to the patient is particularly problematic (Facio et al., 2014). Here, the issue of informed consent is

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raised again but in a different context.

1. Basic principles for reporting

1) Global guidelines

From the general theory of informed consent and presumptive consent, which was examined above, abstract criteria for the scope of reporting in the bioinformatics analysis stage can be derived. However, there is a lack of official clinical guidelines for NGS testing based on this theory in Korea. Fortunately, clinical guidelines presented by the American and European academic societies and organizations have set important basic standards for this issue.

The American College of Medical Genetics and Genomics (ACMG) clearly stipulates a "responsibility to provide comprehensive pre- and post-counseling" to all patients in NGS-based testing (ACMG Recommendations 2013, Ver.1, Nr.3). Since the first formal recommendation for NGS testing, the ACMG has clearly stated that clinicians should "discuss with the patient the possibility of incidental findings" when clinical sequencing is ordered (ACMG, 2013). Specific content clarifies that "clinicians should alert patients to the possibility that clinical sequencing may generate incidental findings that may require further evaluation" (ACMG Recommendations Ver.1, Nr.3). Furthermore, the ACMG explains that this assures patients "the right to decline clinical sequencing if they judge the risks of possible discovery of incidental findings to outweigh the benefits of testing" (ACMG, 2013).

Additionally, the ESHG Guidelines (2016) stipulate that "it should be decided—at the laboratory, institute or national level—whether patients are offered opt-in [or] opt-out options to get additional information besides the initial diagnostic result" (ESHG, 2016). It is further stated that "the clinical (genetic) center needs to set up an unsolicited and secondary findings protocol" to "specify whether unsolicited findings and carrier status are reported" (ESHG, 2016). Based on the two guidelines, the following principles should first be applied in the bioinformatics analysis stage of NGS testing. First, it should be explained to patients that unsolicited and secondary findings may result from testing. Accordingly, patient consent should be obtained regarding the extent of information to be received regarding unsolicited and secondary findings.

2) Right not to know

In 1997, the United Nations Educational, Scientific and Cultural Organization (UNESCO) adopted the Universal Declaration on Human Genome and Human Rights. As stipulated in article 5c of this declaration, "the right of each individual to decide whether or not to be informed of the results of genetic examination and the resulting consequences should be respected." This prescribes the right not to be informed (i.e., "the right not to know") regarding gene testing and its results (Chadwick, 2014). The importance of "the right not to know" is emphasized not only in clinical guidelines but also in the positive law, such as in the German Gene Testing Act (Recht auf Nichtwissen). Concerning informed consent in gene testing, §9. ② nr.5 of this Act stipulates that the explanation is included in particular "5. the right of the person concerned not to know, including the right not to take note of the test result or parts of it, but to have it destroyed." Furthermore, according to §8 ① of this act, the patient should make a "decision as to whether and to what extent the testing result is to be [reported] or destroyed" when deciding upon the extent of gene testing for purposes of treatment. This is a regulation to secure autonomy in the context of individual genetic information by synchronizing the right of knowing and the right of not knowing.

2. Reporting of unsolicited and secondary findings

In NGS testing, however, even if a patient has specified the extent to which the information about findings should be conveyed, there is always the possibility of the emergence of additional information related to a specific disease that the patient has identified, but whose association has not been considered by the patient in advance. Furthermore, there also exists the possibility of additional information (unrelated to the disease that a patient has specified) about which the patient would want to know. In this context, it is often said that it is not always desirable not to tell patients the results of unsolicited and secondary findings (Facio et al., 2014). It is also said that if the emphasis is placed only on the patient's self-determination, results that are rather contradictory to "the duty of care of patients" may arise in a problematic situation related to NGS testing (Egalite et al., 2014). This ambiguity in the reporting problem is a function of the underlying science of genes—as the knowledge of genes deepens, new understandings may emerge. For example, modern medicine may reveal that more than one gene can cause multiple symptoms in various organs or can cause medically different diseases.

1) Unsolicited but relevant secondary findings

If a mutation emerged at the stage of the wet analysis was not intentional, that is, unsolicited, and if exploration of the mutation and validation of this finding is acceptable, then should the bioinformatics analysis-based interpretation of this finding be reported to the patient? As mentioned above, due to the specificity of NGS testing methods, the possibility of newly discovered causative genes in diseases can appear in many cases. Therefore, the likelihood of this type of testing being performed and/or the number of patient requests for such testing may increase.

The ACMG imposes the following restrictions on the range of secondary findings to be reported "by the laboratory to the ordering clinician." According to the Recommendation Statement of ACMG, except the case of minimum list of genes (78 genes) in the guideline, "only variants that have been previously reported and are a recognized cause of the disorder or variants that have been previously unreported but are of the type that is expected to cause the disorder, as defined by prior ACMG guidelines, should be reported" (ACMG, 2013; ACMG, 2022). Since this criterion is applied to the scope of information that "the laboratory should report to the doctor", it is a separate concern whether "the doctor must report it to the patient" even if the criteria mentioned are met. However, it can be said that these criteria are the minimum prerequisites that must be met in order for a physician to report to a patient.

2) Unsolicited and non-relevant secondary findings

The question of great consequence raised in the bioinformatics analysis stage is whether the patient should be informed if mutations are found, which are secondary but not-relevant. The guidelines and bioethical principles mentioned above may serve as initial criteria.

(1) Patient's choice

The possibility of secondary but non-relevant findings needs to be explained to the patient while establishing the test protocol, that is, prior to gene testing. Furthermore, it is also desirable in the process of pre-counseling to allow the patient to choose whether results must be disclosed. A patient's "right not to know" related to unsolicited and non-relevant findings is, above all, due to the possibility that the patient will be psychologically harmed by knowing certain information. Specifically, "the right to pursue happiness"(§10 Korean Constitutional Law) may be a valid legal or philosophical basis for any individual's right not to know. Additionally, "the right to free development of personality" in Kant's philosophy may be the ultimate basis for this legality (Kant,

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2011). In this context, it is a matter of subjective judgment whether or not the knowledge of any genetic information benefits the individual; the objective balancing of conflicting interests is impossible. Therefore, the patient's consent is the most important factor for reporting the findings.

(2) Plan for the future vs. open future

However, due to the characteristic of NGS testing, "detailed prior explanations of all conceivable outcomes are often not possible" (Deutscher Ethikrat, 2013). Often, the consent process might not have been performed because it was unforeseeable whether consent will be required in the future. Furthermore, patients are not always equipped with the ability to understand the disease and its influence completely. Patients with the disease often lack skills or energy for cognitive activity (O'Neill, 2002). What makes patient decisions more difficult with gene testing is that personal predictions about future life are always uncertain. On the one hand, knowledge can increase our "capacity to plan for the future" (Bortolotti & Widdows, 2011). On the other hand, the freedom of not-knowing guarantees an "open future" for everyone (Feinberg, 2006). One example involves the question of whether people in the high-risk group for Huntington's disease as determined by family history are likely to seek predictive information about onset through relevant gene testing. A study shows that only about 20% of the people in risk groups were genetically tested, even though 57%–84% of them showed an interest in predictive testing (Creighton et al., 2003). There is no clear answer as to whether knowledge is beneficial or not. Furthermore, it is said that the psychological harm of knowing is not clear and that "there is no consensus about what is more beneficial in terms of psychological well-being" (Bortolotti & Widdows, 2011). In this context, it is not always desirable to say that reporting is not allowable if there is no self-made decision, nor is it desirable to report unconditionally if consent is provided.

(3) Multifaceted genetic counseling

Then, is there no additional requirement to be met when the patient's prior consent is the primary criterion for reporting unsolicited and non-relevant secondary findings in NGS testing? Conversely, if there is no prior decision on reporting such findings from the patient, is there no other criterion to assess whether a follow-up reporting is necessary?

Concerning informed consent, above all, assuming that the patient is "abstractly rational" and "telling everything without leaving anything out" is not a good basis for physicians' obligation to explain (Wachsmuth & Schreiber, 1985; Kim, 2007). It should be conceded that informing a patient may be justified when the patient's "weakened" position is taken fully into account. Therefore, it seems to be of utmost importance that genetic counseling related to unsolicited and non-relevant findings is conducted in a professional and multi-faceted manner and not just formally, considering the patient's situation or psychological state. Only then, it will be possible to say that the patient was able to decide whether to submit to knowing or not knowing the result of gene testing. Additionally, it is regrettable that Korea's BioAct lacks explicit provisions on the genetic counseling process.

(4) Duty of reporting

In the absence of a patient's ability to choose whether or not to know the results of gene testing, it is not easy—perhaps even impossible—to determine whether the harm of informing a patient of the outcomes is greater than that of not informing, particularly from a third party's point of view. The harm an individual may suffer from knowing about the genetic inevitability of a disease is likely to be greater if the disease is severe and if there is no cure. The ACMG specifies 78 genes that should always be examined by laboratories and reported to physicians when the results of clinical

sequencing are evaluated (ACMG, 2022). These listed genes seem to be selected considering the magnitude or certainty of harm as mentioned. If gene defects are found within these parameters, the laboratory must always report the details to the ordering clinician. In particular, the ACMG guidelines clearly state that "in selecting a minimal list that is weighted toward conditions for which penetrance may be high and intervention may be possible, we felt that clinicians and laboratory personnel have a fiduciary duty to prevent harm by warning patients and their families about certain incidental findings and that this principle supersedes concerns about autonomy." (ACMG, 2013). Based on this statement, the ACMG first specifies "high penetrance" and the "possibility of intervention" as criteria for screening genes for which reporting duties may prevail in cases where patients have not made advance decisions or issued advance directives (ACMG, 2013; ACMG, 2022). Additionally, the criterion of "clinical utility", stating that treatment based on test results is possible even with genetic tests, has already been proposed as an acceptance criterion for general gene testing (See GEKO, 2013; McGuire et al., 2013). According to ACMG, the listed 78 genes also met the requirement of "verifiability by other diagnostic methods" (ACMG, 2013; ACMG, 2022). Furthermore, the ACMG clarifies that the establishment of its guidelines "did not favor offering the patient a preference as to whether or not their clinician should receive a positive finding from the minimum list of incidental findings described in these recommendations" (ACMG, 2013). In this context, the ACMG seems to take the following position: even if a clinician has not discussed the possibility of secondary findings with a patient in clinical sequencing and the laboratory reports bad results pertaining to information about the 78 genes prescribed by the ACMG, the clinician must reevaluate the patient's (and the family) history and inform the patient about the disease accordingly. In the end, these 78 genes can be considered as examples of cases where the doctor's professional decisions can generally be more rational than patient choices.

CONCLUSION

In summary, the most important requirement in NGS testing is sufficient communication between healthcare providers and patients regarding the characteristics of testing methods and the possibility of secondary findings. In medical law, this is called informed consent. However, considering the characteristics of NGS testing, wet analysis of additional testing can be justified if presumptive consent is recognized (Kim, 2022). Furthermore, the medical relationship between diseases needs to be established and it should be clear that if the patient had known there was a link between the genes, he would have consented to the testing (Kim, 2022). Additionally, in some exceptional cases, it cannot always be denied that cost efficiency in NGS testing may be a slightly mitigating factor toward the requirement of testing for medical relationships between diseases. However, at least a procedure for understanding the rationale and characteristics of NGS testing should have been provided in advance to the patient discussed herein.

At the stage of bioinformatics analysis, a more difficult question, the question of unsolicited findings arises. In case of unsolicited and relevant findings, according to the ACMG Guidelines, a recognized/confirmed relationship between genes and diseases need to be established. In case of unsolicited and not-relevant findings, it is almost impossible to determine whether knowing or not knowing the findings is more beneficial to the patient. However, it seems to be certain that the psychological harm an individual may suffer from such information is likely to be greater if the disease is severe and if there is no cure. The list of genes for which the ACMG guidelines impose reporting obligations is a good reference for judgment. Additionally, particularly in medical practice, it should not be forgotten that a patient is in a vulnerable position. The goal of genetic communication is not to reveal all the details to the patient, but rather to provide a chance

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to ponder upon the pros and cons of knowing and not knowing and thus act according to the patient's decision.If a patient is not given the opportunit to make his or her own choices and if it is not possible to treat or prevent the disease, it is appropriate not to inform the patient that the a mutation has been discovered (Kim, 2022).

Lastly, in Korea, there are no legal standards or official clinical guidelines for NGS testing, as suggested by ACMG or EuroGentest. Above all, genetic counseling, one of the most important communication elements in gene testing, is not legislated in Korea. Hence, Korean law lacks the most basic understanding of gene testing. As above mentioned, the patients should understand the nature of each gene testing and the implication of the testing results in the future. Furthermore, a patient's support is essential to recognize the possible emergence of new genetic information in the dynamic process of gene testing and to share the concerns (See Meiser et al., 2016). The provision of informed consent alone is not sufficient; if only informed consent is emphasized formally, the process of communication may become superficial (O'Neill, 2002). Finally, legislation for comprehensive genetic communication, including genetic counseling, is needed.

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