Clinical Guidelines for Genetic Screening Tests for Newborns

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1 Summary

- Although screening tests conducted comprehensively on groups of people to distinguish healthy people from those suffering from specific diseases are beneficial, they are conducted proactively when performed on newborns for diseases, so it may be beneficial in treatment if early diagnosis is made regardless of whether the newborns have relevant symptoms at birth.

- However, some genetic tests include chromosomal microdeletions or microduplications, which have no clinical diagnostic efficacy in healthy people. This raises concerns about various issues including the validity and necessity of such tests, the usefulness of the results, the potential for misuse of the genetic information of newborns, etc.

- Since genetic tests for diseases are conducted by request from medical institutions in accordance with Clause 3 of Article 50 of the Bioethics Act, physicians must consider the clinical significance of the corresponding tests including the necessity of conducting the test, method, and limitations or implications and use of the test results. as Also, why the tests are medically necessary for the subjects of the corresponding tests for the purposes of diagnosing, predicting and treating relevant diseases.

- In particular, when conducting tests other than a clinical genetic test for which their clinical utility for the diagnosis and treatment of a disease has been confirmed, it is appropriate to comprehensively check the characteristics of the tests, such as the purpose of the test, the gene or mutation to be detected, the type of specimen and the test method, etc. along with information on the analytical performance such as analytical accuracy, sensitivity and specificity, information on the clinical performance such as sensitivity and specificity, indications and contraindications of the test, clinical utility and detection limitations of the genetic test.

- Screening tests conducted on healthy newborns can be medically acceptable when a simple and efficient test is available, and the benefits of the test can be reasonably balanced against the economic and other necessary costs for cases that can provide therapeutic assistance through early detection using the test, and follow-up measures including further diagnostic testing, counseling and treatment to confirm diagnosis must be provided appropriately.

- Screening tests for newborns must be performed with the informed consent of the parents after they have been given and understood full explanation before conducting the test.

- Currently, screening tests for some congenital metabolic abnormalities (phenylketonuria, monogenic diabetes mellitus, homocystinuria, galactosemia, congenital hypothyroidism, congenital adrenal hyperplasia, and amino acid, organic acid, urea cycle and fatty acid metabolic abnormality using the tandem mass technique added after 2018) or auditory screening tests are available for all newborns for free after birth with the application of health insurance, and assertive implementation is necessary.

- Screening tests for newborns are not recommended even for treatable diseases that can be diagnosed early or for which the significant treatment effects can be proven if symptoms do not appear during the neonatal period and there is no specific treatment, resulting in insignificant benefits of the genetic screening test during the neonatal period.

- Generally, the likelihood that a gene variant identified through the test results will cause an actual disease is affected by penetrance, which can vary greatly in accordance with the corresponding disease. Therefore, genetic tests for newborns should be accompanied by an interpretation and explanation of test results including consultation with a clinical genetics specialist or genetic counseling. It should also be clearly explained that there are clinical limitations in predicting developmental delays, cognitive degradation and autistic disorders beyond the neonatal period based on a small number of chromosomal microdeletions or microduplications detected in asymptomatic newborns.

- In general, the possibility of the pathogenicity of variants analyzed in genetic screening tests is assessed by integrating a variety of evidence, including frequency of observation in the normal population, disease databases and literature reports. Accordingly, it is necessary to inform the possibility of change due to re-evaluation and to provide appropriate genetic counseling in accordance with the limitations of the results of the genetic screening test and the significance of positive/negative test results to avoid misunderstandings.

2 Overview

A Background

- Screening tests are conducted to distinguish people with specific diseases from healthy people. Since they are usually performed comprehensively on groups in the relatively simple format with high sensitivity, they raise significant social and ethical controversies in spite of their benefits.

- Although the majority of newborns may appear to be healthy, some may be suffering from diseases. Delays in detecting disease in the early stage with the opportunity to treat them in a timely manner can lead to irreversible and fatal damage or disability. For this reason, the neonatal screening test was introduced to learn about diseases and take necessary measures in advance to provide assistance in the treatment through early diagnosis, regardless of the presence of symptoms at birth. Thus, screening tests for some congenital metabolic abnormalities (phenylketonuria, monogenic diabetes mellitus, homocystinuria, galactosemia, congenital hypothyroidism, congenital adrenal hyperplasia, and amino acid, organic acid, urea cycle and fatty acid metabolic abnormality using the tandem mass technique added after 2018) or auditory screening tests are assertively recommended for all newborns for free with the application of health insurance.

- However, issues have been raised because genetic screening tests for healthy newborns have been implemented by some genetic testing centers recently. In particular, genetic screening tests include chromosomal microdeletions and microduplications that have no clinical diagnostic efficacy in healthy people, which has raised controversy about the usefulness of these tests. In addition to the validity and necessity of the tests and the usefulness of the results, there are also concerns about the possible misuse of genetic information of newborns due to screening tests.

- This is because the results of the genetic test do not necessarily imply the manifestation of a disease and cannot be used to provide therapeutic assistance or prevention, and on the contrary, early access to relevant information can be harmful.

Therefore, the aim of this guideline is to provide clinical determination criteria for genetic screening tests performed on generally healthy children with no special past family history of genetic traits or medical findings of specific diseases.

B Purpose of the guidelines

This guideline can be referred to when performing a screening test[1] of healthy newborns in medical institutions and is intended to provide a basis for clinical determination that the physician in charge needs to consider when executing or requesting the corresponding test using a genetic test[2] method.

1 It is a test for the purpose of detecting diseases in the early stage before symptoms appear in the test subject, and in the case of newborns, it is performed to detect treatable congenital metabolic diseases/genetic diseases in advance to improve the health of the patient and subsequent medical services through early treatment.

2 It refers to tests in accordance with Clause 15 of Article 2 of the Bioethics Act.

3 Genetic Tests in Accordance with the Bioethics Act

A General principles

1) Grounds for implementation

Genetic tests are performed for the purpose of personal identification, such as paternity, or for the purposes of diagnosis, treatment and prevention of disease in accordance with the [Bioethics and Safety Act] (hereinafter referred to as the "Bioethics Act"), and can only be performed at a genetic testing institution reported to the Korea Disease Control and Prevention Agency.

2) Purpose

Genetic tests are largely classified into the following five categories depending on the purpose for which they are performed (refer to Article 49 of the Bioethics Act and Appendix 5 of Article 46 of the Enforcement Regulations of the same Act).

1. Clinical genetic tests for the diagnosis and treatment of diseases
2. Genetic tests for the prediction of disease
3. Genetic tests for the prevention of diseases in accordance with nutrition, lifestyle and physical characteristics
4. Genetic tests for genetic ancestry such as searching for ancestors, etc.
5. Genetic tests for personal identification and confirmation of paternity

It must be possible to explain and confirm the purpose of the genetic test to be performed by the relevant institution, and in particular, since tests ❶ and ❷ can only be performed upon referral from a medical institution, the physician in charge of the medical institution requesting the test must be able to explain the purpose of the test to the patient. However, it is important that other tests are conducted based on the autonomy of the test subject.

B Disease-related genetic test

Genetic tests for "diseases" may be performed at or upon referral from a medical institution in accordance with Clause 3 of Article 50 of the Bioethics Act. The Act stipulates that a “genetic test for diseases” must be performed in a medical institution since it signifies that it is performed as a means of medical treatment. Accordingly, when a physician intends to perform a genetic test for the purposes of diagnosing, predicting or treating a disease in a patient as well as a healthy person prior to the onset of relevant symptoms, the physician must be able to explain the clinical significance of performing the genetic test, such as why the test is medically necessary for the test subject, the method, the limitations or implications of the results, and the utilization thereof.

With respect to disease-related genetic tests, there is a distinction between clinical genetic tests for which the clinical utility for the diagnosis and treatment of disease has been confirmed, and genetic tests for which sufficient clinical utility is yet to be confirmed but can be medically referred to. Therefore, before deciding whether to perform a genetic test, it is appropriate for a physician to review its clinical significance by comprehensively checking the characteristics of the test, including the purpose of the test, the gene or variant to be detected, the type of specimen and the test method, etc. along with information on analytical performance such as analytical accuracy, sensitivity and specificity, information on clinical performance such as sensitivity and specificity, indications and contraindications of the test, clinical utility and detection limits, etc.

C Test methods and procedures

1) Consent to genetic test

In order to confirm the clinical significance and legally perform the genetic test, the genetic test institution or the medical institution requesting the test must fully explain the purpose of the genetic test and the implications and limitations of the results to the test subject before collecting a specimen from the subject to be used for the genetic test, and obtain the written consent voluntarily prepared by the test subject (Attached Form No. 52, Genetic Test Consent Form).

Attachment 1 Attached Form No. 52, Genetic Test Consent Form

[Attached Form No. 52] of the Enforcement Rules of the Act on Bioethics and Safety

Genetic Test Consent Form

Consent Form Administration No.	

Test subject	Name	Date of birth
	Address	
	Tel. No.	Gender

Legal representative	Name	Relationship
	Tel. No.	

Genetic testing institution	Institution name	
	Tel. No.	

Genetic test	Purpose	[ ] 1. Genetic test for diagnosis and treatment of disease [ ] 2. Genetic test for disease prediction [ ] 3. Genetic test for the prevention of diseases in accordance with nutrition, lifestyle and physical characteristics [ ] 4. Genetic test to find genetic ancestry [ ] 5. Genetic test for personal identification and confirmation of paternity
	Items	

Institution requesting the test (in the case of test purposes of 1 and 2)	Name of medical institution	
	Physician requesting the test	

Pursuant to Article 51 of the [Act on Bioethics and Safet]y and Article 51 of the Enforcement Rules of the same Act, I have been fully informed and understand the purpose of the genetic test and the implications and limitations of the results thereof, and I voluntarily consent to the genetic test on myself as described above.

Date: (Yr/Mth/Day)

Test subject (signature or seal)

Legal representative (signature or seal)

Consultant (signature or seal)

210 mm× 297mm [White printing paper (80g/m^2) or Mid-quality paper (80g/m^2)]

* For additional genetic tests for the same subjects and purposes, you may add your signature below without completing a separate consent form.

	Date:	(Yr/Mth/Day)
Test subject		(signature or seal)
Legal representative		(signature or seal)
Consultant		(signature or seal)
	Date:	(Yr/Mth/Day)
Test subject		(signature or seal)
Legal representative		(signature or seal)
Consultant		(signature or seal)
	Date:	(Yr/Mth/Day)
Test subject		(signature or seal)
Legal representative		(signature or seal)
Consultant		(signature or seal)

Attached document	In the case of legal representative, power of attorney for representation.

Precautions

1. The results of this genetic test are preserved for 10 years and can be viewed if requested by the patient him/herself or his/her legal representative in accordance with Clause 2 of Article 52 of the Act.

2. If the test specimen cannot be preserved due to reasons such as the closure of the genetic test institution, the test specimen, test consent form, records on genetic information containing personal information and the management ledger will be discarded in accordance with the procedures prescribed by law. However, if the test subject requests the transfer of information and specimens to another testing institution or the Korea Centers for Disease Control and Prevention during preservation, they can be transferred.

3. Genetic test institutions shall not preserve, use or provide test specimens and related information for purposes other than those for which consent has been obtained. In order to use the test specimens remaining after the test for research purposes, the test subjects shall be fully informed of the purpose and field of the research and the scope of the information to be provided. If the subjects agree to donate the test specimen to human derivative research or a licensed human derivative bank, they shall additionally fill out the consent form for human derivative research in Attached Form No. 34 or the consent form for donation of human derivatives in Attached Form No. 41.

4. The genetic test institution or the medical institution requesting the test shall fully explain to the test subject the purpose and test items of the genetic test to be performed, the management method of the test specimens, how to withdraw consent, the rights and information protection of the test subject, the disposal or transfer of the test specimen and related records in the event of the temporary cessation of business or closure of the genetic test institution, the retention period and management method of the genetic test result records, and the limitations of the genetic test results.

The consent form must clearly state the purpose of the test and the items to be performed, and the name of the medical institution and the physician requesting the test. The purpose and method of the test as well as the significance of the predicted test results must be explained in a manner that is easy for the test subject to understand. Genetic tests must be conducted on the principle of voluntary written consent of the test subject, and if the test subject is incapable of consenting, consent may be given by a legal representative. Moreover, genetic tests on minors must be authorized by having a legal representative give consent on behalf of the minor. Although written consent may be exempted for clinical genetic tests conducted directly by medical institutions for the diagnosis and treatment of diseases and for the immediate disposal of test specimens after testing, genetic test consent must be obtained in the event of requesting tests other than clinical genetic tests or making a request to testing institutions for such tests.

However, if there are special reasons such as the identification of a corpse or an unconscious person, or if there are applicable provisions in other laws, obtaining consent for a genetic test may be exempted in accordance with Clause 5 of Article 51 of the Bioethics Act.

2) Requesting genetic tests

When a medical institution wants to conduct a genetic test related to a disease, it may request the corresponding test from a genetic test institution. When requesting a genetic test, the medical institution must provide a copy of the consent form with the removal or encryption of personal identifiable information such as the name and phone number of the test subject.

The medical institution requesting a genetic test must be capable of making a determination about the clinical necessity of the test or the results of the test because it must be able to make a medical determination about the diagnosis or treatment of the disease being requested. For example, a genetic test for the diagnosis of colorectal cancer or the selection of a targeted cancer therapy cannot be requested by a dental clinic that is not related to the corresponding treatment.

Since a request for a genetic test is made by a medical institution that determines that a genetic test for a specific disease is necessary for the corresponding patient or subject, the request may be made in writing, including a copy of the genetic test consent form and the

signature of the requesting physician on a request form that records the items of genetic test requested, the name of the disease and the reason for the request. Moreover, when a copy of the genetic test consent form is provided by including the name of the requesting institution, and the name and signatures of the requesting physician, the name of the disease and the reason for the request must be recorded in the medical record.

D Precautions when requesting the test

When requesting a genetic test for a disease, the requesting physician must keep the following in mind:

1. A genetic test for a disease must be requested from a genetic testing institution by a medical institution by reviewing the need for conducting the test in accordance with the clinical determination of a physician.
2. In particular, it is prohibited to ask a third party such as a genetic test institution or pharmaceutical company that is not a medical institution to make a request for a genetic test for a disease.
3. Genetic tests are conducted in the order of explanation of the purpose of the genetic test and the implications of the results, followed by preparation of a consent form, collection of the test specimen, and request for the test. With the exception of tests that can be requested directly by the test subject,[3] the explanation, consent form and collection of the test specimen must be conducted by a medical institution.
4. The results of a genetic test for a disease conducted by a medical institution through a referral to a testing institution must be explained and provided to the patient by the physician at the medical institution, and it is important to explain the purpose and results to the patient sufficiently to prevent them from experiencing unnecessary anxiety.

3 This refers to so-called direct-to-consumer (DTC) genetic tests, which are genetic tests that do not include tests for disease and are recognized by the Minister of Health and Welfare as necessary for the prevention of disease, such as genetic tests for nutrition, lifestyle and physical characteristics, genetic ancestry, such as searching for ancestors, and personal identification and confirmation of paternity.

4 Medically Allowed Screening Tests for Newborns

A Basic principles

- Although screening tests for newborns may vary depending on national and local public health systems, including the environment in which health services are provided, screening test items and methods can be reflected by listening to the opinions of relevant medical institutions and experts.

- For screening tests conducted on all newborns, evidence of benefits from pre-symptomatic screening tests is required, including high-quality randomized controlled tests, etc. However, evidence is not always easy to obtain and sometimes requires long-term follow-up.

- Therefore, it is necessary to establish a multidisciplinary committee composed of appropriately qualified healthcare professionals to identify what should be screened, what tests are needed and a management plan so that the screening test program is managed effectively.

- It is important that these programs ensure that screening tests identified as beneficial are performed on all possible newborns.

- The general principles by which screening tests for newborns are medically acceptable and recommended include the following:

  1. Screening tests of healthy newborns should be conducted when early detection by testing can lead to helpful therapeutic intervention.
  2. Mass screening tests of all newborns may be conducted when reliable, simple and efficient testing methods are available, and the benefits of such a test are reasonably balanced against the economic and other costs required.
  3. When an abnormality is identified by a screening test of newborns, follow-up care, including additional diagnostic tests for confirmation, counseling and treatment, should be provided appropriately.

- Screening tests of newborns should be conducted with the informed consent of the parents and a full explanation and understanding before testing, and the right to refuse any information or tests they do not want to know about without being subjected to any disadvantages.

- Special attention needs to be exercised in relation to genetic tests, including the establishment of regulations to ensure the protection of personal information and to secure the confidentiality of the child or family.

B Clinical determination of genetic screening tests

- Although recent advances in genetic analysis service technology have made genetic testing more accessible, including a reduction in testing costs, screening tests for newborns should be conducted prudently by considering the general principles outlined above.

- Caution should be exercised for screening tests for newborns for diseases that do not manifest during the neonatal period such as developmental disabilities and autism symptoms, and for which early diagnosis is difficult, clinical efficacy as a screening test is low, and appropriate follow-up treatment based on test results is absent.

- Even for conditions that can be diagnosed early or for which early detection is important for prognosis, screening through genetic tests during the neonatal period is also not recommended for diseases that do not develop symptoms during the neonatal period and for which there is no specific treatment and therefore no significant benefit can be obtained from a screening test.

- Representative examples of screening tests for newborns are listed below:

  - ☑ (Phenylketonuria) is a representative disease that is screened in a mass screening test at the earliest possible age since its early diagnosis and a protein-restricted diet can prevent severe neurological abnormalities.
  - ☑ With the introduction of tandem mass spectrometry in the 2000s, early diagnosis of about 50 congenital metabolic disorders, including amino acid metabolism disorders, organic acid metabolism disorders and fatty acid metabolism disorders, has become possible, thereby preventing serious and long-term complications in patients.

- However, if a medical institution wants to perform a genetic test for a disease on healthy newborns, the physician in charge must be able to explain the rationale or clinical significance for performing the test.

- Although genetic test institutions must currently report a genetic test for a disease in order to perform the test, the fact that the test is reported does not mean that the clinical significance has been confirmed.

- Specifically, with the exception of genetic tests for some monogenetic diseases, most of the genetic test items currently reported are diagnostic genetic tests aimed at the detection of chromosomal microdeletions, microduplications or chromosome number abnormalities, which are performed when the associated target disease is clinically suspected.

- However, these diagnostic genetic tests, including tests for the detection of chromosomal microdeletions, microduplications and chromosome number abnormalities, do not have a high positive predictive value in asymptomatic, healthy newborns who do not have a clinical reason for testing, and so are not recommended for a screening test.

- Physicians should prudently make a decision on whether to perform a test by taking into account the recommended or exclusion criteria presented above, and ensure that parents are fully informed and consent is obtained before testing.

C Recommendations

- The most important principle of genetic screening tests for healthy newborns is that the "foremost priority must be put on the interest of the newborn" for whom the test will be conducted.

- It is appropriate to conduct tests that do not have a "direct medical benefit" to newborns or children in their infancy when accompanied by abnormalities and symptoms (such as developmental delays and congenital anomalies) that are suggestive of disease rather than for the screening purpose on an asymptomatic subject.

- If the results of a genetic test indicate that the manifestation of a disease is uncertain and the time of manifestation is not during the neonatal period or infancy of the subject, it is recommended that the test be withheld until a rationale for its implementation is established.

  - (Example) Diseases such as fragile X syndrome or dyslexia, for which there is no evidence of medical benefit during the neonatal or infancy period, are inappropriate for a screening test of newborns.

- It is important for the medical staff to fully explain to parents the meaning, limitations and treatment options for newborns or infants before and after testing.
- The medical staff needs to act as gatekeepers in determining whether a test is needed for the test subject by ensuring that tests that are not medically meaningful are not implemented.
- In general, genetic tests for the purpose of screening should not be conducted on healthy and asymptomatic newborns. However, if it is performed, it should be carefully managed by including collaboration with a clinical genetics expert and genetic counseling to interpret and explain the test results.

5 Core Questions and Answers

A When can genetic screening tests for newborns be conducted?

»» Currently, since screening tests for some congenital metabolic abnormalities (phenylketonuria, monogenic diabetes mellitus, homocystinuria, galactosemia, congenital hypothyroidism, congenital adrenal hyperplasia, and amino acid, organic acid, urea cycle and fatty acid metabolic abnormality using the tandem mass technique added after 2018) or auditory screening tests are available for all newborns for free after birth with the application of health insurance, assertive implementation is necessary.

»» However, screening tests for newborns should be conducted with a high level of caution for diseases that are difficult to diagnose at an early stage or that do not affect the prognosis of treatment, including developmental disorders and autism symptoms that have low diagnostic accuracy, do not occur during the neonatal period and lack appropriate follow-up treatment in accordance with the test results.

»» In particular, even for treatable diseases that can be diagnosed at an early stage or for which treatment can be shown to be highly effective, screening tests through genetic tests of newborns are not recommended if symptoms do not appear during the neonatal period, there is no specific treatment and the benefit of a screening test is not significant.

B How should test results from genetic screening tests on newborns be explained?

»» Generally, the likelihood that a gene variant identified through the results of the test will cause an actual corresponding disease is affected by its penetrance, which can vary greatly in accordance with the disease. Therefore, it is recommended that the interpretation and explanation of test results be accompanied by collaboration with a clinical genetics specialist or genetic counseling.

»» In particular, it should be clearly explained that there are clinical limitations in predicting developmental delays beyond the neonatal period, cognitive degradation and autistic disorders based on a very small number of chromosomal microdeletions or microduplications detected in asymptomatic newborns.

»» In addition, the possibility of the pathogenicity of variants analyzed in genetic screening tests is assessed by integrating a variety of evidence, including frequency of observation in the normal population, disease databases and literature reports. Accordingly, it is necessary to inform the possibility of change due to re-evaluation.

C What counseling is necessary after a genetic screening test for newborns?

»» It is necessary to provide appropriate genetic counseling in accordance with the limitations of the results of the genetic screening test and the implications of positive/negative test results.

»» In particular, in the case of a positive result, it is recommended to provide information on the need for confirmatory testing for the corresponding disease, further evaluation of the various clinical manifestations associated with the disease, and the need for long-term observation and examinations. Also, the provision of accurate information on the penetrance and diversity in the expression of the disease, the long-term prognosis, the existence of possible treatments, introduction to self-help patient groups and self-study materials on the disease, impact on the family and recurrence rates, the need for analysis of other family members, etc. are recommended. However, since a negative result does not necessarily mean that the corresponding disease is not present, caution should be exercised not to mislead and provide undue reassurance to the patient and his/her family.

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