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MINIREVIEW

IMPLEMENTING GUIDELINES FOR GENETIC TESTS IMPROVES PERSONALIZED DIAGNOSES IN MEDICAL PRACTICE

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RECEIVED: NOVEMBER 24TH, 2018
REVISED: NOVEMBER 29TH, 2018
ACCEPTED: NOVEMBER 30TH, 2018

Abstract

Implementing clinical practice guidelines, based on a systematic review of clinical evidence, is fundamental to sustain the decision-making procedures in patient care. Development of guidelines is needed for genetic tests regarding human genome/genes including cytogenetic tests, biochemical genetic tests and molecular genetic tests. Main aspects that should be considered when implementing guidelines for genetic testing regards 1) Usefulness of genetic test in patients who have already developed a disease; 2) Genetic testing for prenatal diagnosis, non-progressive carrier diagnosis and pre-symptomatic diagnosis; 3) Genetic testing for a minor or a person lacking the ability to make his/her autonomous decision; 4) Pharmacogenetic tests; 5) Genetic tests for multifactorial diseases. Since genetic tests of different diseases and disease-subgroups have been carried out in a wide range of medical fields, it is recommended that each national and international medical societies draw up and follow guidelines for each disease to obtain unique and universal diagnosis.

Keywords

Genetic test guidelines, Clinical practice guidelines, pharmacogenetic tests, multifactorial disease tests

Introduction

Today the relevance of medical genetics has permitted to improve the knowledge on etiopathogenesis and clinical aspects of monogenic (single-gene) diseases based on the identification of the causative genes [1]. Additionally, such improvements are leading to better and specific therapeutic strategies [2]. Furthermore, advantages of modern medical genetics achieved strong innovations to the fields of medicine and medical practice such as individual changes in pharmacological responses or the discovery of genetic factors associated with the onset of multifactorial disorders [3]. Therefore, actual developed genetic tests/diagnoses developed shed new light to all areas of medicine, providing personalized selections in preventive methods and treatments of pathologies. In this way, genetic tests/diagnoses have become one of the most important medical practices for all specialized physicians. Such revolution, however, does not make people forget to handle genetic information in the correct way, since it does not change throughout the individual's lifetime, and could also affect their biological relatives [4]. To emphasize this concept, it can be remembered that both diseases and clinical conditions based upon genetic variations, and genotypes should be involved in human diversities and not be considered as rare exceptions [5]. Both human diversity and identity should be respected. Considered the cited scenario, in order to provide better medical care to people, physicians and co-medical professional figures involved in genetic medicine should implement genetic tests/diagnoses appropriately and effectively in medical practice, paying proper attention to the specific characteristics of genetic information [6]. Since genetic tests of different diseases and disease-subgroups have been carried out in a

wide range of medical fields and departments, it is recommended that each medical society draw up and follow guidelines or a manual for each disease (group), field or specialty, to obtain unique and universal diagnosis.

Principal aims of genetic test guidelines

Development of guidelines is needed for genetic tests regarding human genome/genes including cytogenetic tests, biochemical genetic tests and molecular genetic tests (DNA/RNA tests) [7]. Speaking of "genetic tests" in the guidelines refers to analyzing germline alterations such as mutations or chromosomal abnormalities, or those related to germline alterations. The latter are commonly present in all cells that form an individual, and can be transmitted to the next generation as genetic information [8]. Such variants can be detected by testing any cell that constitutes the human body, such as peripheral blood, oral mucosa, nail, hair and skin fibroblast. In medical practice, genetic tests are performed for diagnoses of patients who have already developed a disease, but also for pre-symptomatic diagnosis, genetic predisposition tests, carrier detection, prenatal diagnosis, pharmacogenetic diagnosis, and newborn mass screening for congenital metabolic diseases [9]. In the meantime, the guidelines do not cover genetic tests to identify somatic mutations, variants acquired in somatic cells after fertilization or birth, and that will not be conveyed to the next generation [10]. However, although such alterations are evaluable in gene expression or chromosomal abnormality that occurred within cancer cells after fertilization, it could be useful to refer to these guidelines if they are possibly related with the genetic information of the germline.

Main features of genetic testing and its use in diagnosis [11]

The management of a genetic test should follow several important issues generally shared by common knowledge:

- Genotype or phenotype of tested individuals and of their relatives can be predicted with a relatively high probability.
- Disease development could be predicted beforehand with almost 100% accuracy.
- The genetic test will not change throughout the individual's lifetime.
- It is possible to make a diagnosis of non-progressive carriers (who will rarely develop the disease in the future, but carries a mutated gene, and the variant may possibly be transmitted to the next generation).
- It may be exploited for prenatal diagnosis.
- It is partially shared with biological relatives.
- If it is inappropriately handled or disclosed, it may cause a social disadvantage to the patient and their relatives.

Essential aspects in genetic testing practice

Several points have to be taken in account when conducting a genetic test, depending on the patient and on the purpose of the test.

1) Usefulness of genetic test in patients who have already developed a disease [12]. In this case, genetic testing is principally conducted to confirm a diagnosis that is highly suspected from clinical examination, or for the differential diagnosis that should be realized. Tests are performed if considered useful from clinical and genetic perspectives after their clinical and analytical validation. Analytical validity refers to, for example, a condition where the test method has been fully defined and related quality controls have been performed for highly reproducible results. Such estimation is based upon negative rate when the subject has not any mutation, positive rate when the subject carries mutations, the presence of quality control program and the procedure of confirmation. Clinical validity, instead, regards the condition that enough implications are given to the test results. It is based upon specificity (negative rate when the examinee has no disease), sensitivity (positive rate when the examinee has the disease), positive and negative predictive values, morbidity of the disease, genotype-phenotype correlation. Finally, clinical utility refers to clinical advantages, as the ability to diagnose target disease, obtaining information about patient's future prospects, including appropriate prevention and therapy. The evaluation is based upon the influence of the test result to the patient, and effective support to him. If an examinee requires multiple genetic tests, order and purposes of the tests should be carefully determined from a clinical point of view. Patients should be informed about scopes and implication (including expected merits and demerits to the examinees) of the tests at a specific time before realize them, as well as the potential conditions that after

the results will be obtained and the fact that the genetic outcomes gathered by the tests may influence their relatives. The manager physicians should confirm that the examinees have fully understood these concerns, and support their independent choice to undergo genetic testing or less. Therefore, it is important to obtain a written informed consent from the examinees after the explanation and support. In details, the examinee's attending physician should perform the informed consent or assent before genetic testing, and if necessary, should organize genetic counseling of an expert so that the examinee can receive support for autonomous decision-making. Genetic test outcomes should be clearly and easily explained to the patients to allow them to fully and adequately understand the results following a flow of exams. A diagnosis should not only consist of genetic examination results, but it has to comprise both clinical and genetic information. Furthermore, genetic tests are useful not only to diagnosis establishment, but also for the medical practice using the data concerning genotype-phenotype correlation come from results. Nevertheless, when it is arduous to establish the pathologic significance of a novel mutation and where the penetrance of disease is considered to be less than 100%, result interpretation has to be particularly evaluated. Finally, as soon as diagnosis is confirmed, it is fundamental to provide the patient with sufficient information about prognosis, progress, therapy and medical care of the pathology.

2) Genetic testing for prenatal diagnosis, non-progressive carrier diagnosis and pre-symptomatic diagnosis [13]. All these tests should be conducted after an appropriate genetic counseling session, a process needed to help people understand and adapt to the medical, psychological and familial implications of genetic contributions to pathology. This procedure includes: 1) evaluation of family and medical histories to assess the disease probability of occurrence or recurrence; 2) education on the genetic scenario, test, management, prevention, resources and research; 3) informed choice (autonomous and independent decision with enough information) and counseling for the promotion of the adaptation to risk and the actual condition. It is opportune that all medical doctors acquire basic knowledge and skills for genetic counseling. Medical doctors and institutes involved in genetic tests/diagnoses should be prepared to provide genetic counseling or introduce a genetic counselor when necessary.
   - *Prenatal diagnosis* [14]: includes methods involving biochemical and molecular genetics, cytogenetic, as well as cytological and pathological methods, using fetus samples such as chorionic villi, amniotic fluid, etc.; pre-implantation genetic diagnosis. Due to involvement of many medical, social and ethical issues in prenatal diagnosis, the test/diagnosis should be performed complying with the views of the competent health authorities, and after providing the examinee with appropriate genetic counseling.
   - *Diagnosis of non-progressive carrier* [15]: they do not develop a disease and thus generally require no treatment. Therefore, genetic testing of their diagnosis should not be done without the examinee's consent unless there is a special reason.
   - *Pre-symptomatic diagnosis* [16]: when it allows the prediction of disease development beforehand with almost 100% accuracy, the genetic test(s) should be realized after the patient has sufficiently understood the information concerning the available preventive method(s) and therapeutic strategies of the pathology. When results will be disclosed, the patient should receive full explanation about the characteristics and natural history of the disease once again, and he should obtain appropriate medical information to maintain his health. Primarily, when conducting a disease pre-symptomatic diagnosis for which preventive method(s) before, or effective therapies after the onset are unavailable, support and care for the patient's psychological health are essential before and after the test.

3) Genetic testing for a minor, or a person lacking the ability to make his/her own autonomous decision [17]. In this case the consent must be provided by an individual standing as a surrogate representative, who should decide

after a thoughtful consideration of the patient's beneficence in his/her health care. It is opportune to obtain an authorization from the examinee after giving the explanation of the test at a level corresponding to the patient's ability. Similar situation regards genetic testing of diseases developing before adulthood if their pre-symptomatic diagnoses are useful in the management of the patient's healthcare. In the meantime, genetic tests for a minor with non-progressive carrier or pre-symptomatic diagnosis of pathology that may develop in and after adolescence should not be realized in principle by the consent from the patient's surrogate, but should be postponed until the examinee reaches adulthood and becomes able to independently make a decision.

4) Pharmacogenetic tests [18]: included in pharmacogenomic tests, it analyzes germline genetic variations. Because the genetic data obtained presents the unique characteristics as undermentioned, the information can be managed, in a different way from the genetic information of monogenic diseases, as ordinary clinical data in medical practice by referring to the specific guidelines. Based upon the definitions of Pharmacogenomics and Pharmacogenetics as "a study on the variation of DNA and the characteristics of RNA associated with response to drugs" and "a part of pharmacogenomics, and a study on the mutation of DNA sequence associated with response to drugs", respectively, these guidelines define and cover tests regarding germline genetic data in association with response to drugs as pharmacogenetic tests:
   - They may help to avoid drug dangerous side effects or drugs with only little effect to the patient.
   - Appropriate dosing amount can be evaluated.
   - The evaluating abilities of the phenotype based on genotype are not necessarily high.

5) Genetic tests for multifactorial diseases (genetic predisposition diagnosis) [19]. To date a huge number of genetic factors involved in multifactorial diseases are known, and genetic tests for such pathologies to prevent their onset are expected to be developed for clinical application. Tests used to predict such multifactorial disorders have the following characteristics:
   - Obtained results represent the risk (probability) of disease onset.
   - A high prediction power of phenotype based on genotype is not required.
   - Both genetic and environmental factors are involved in disease development, with different contribution degrees for each pathology.

Individual genetic information management [20]

Clinician and specialists accessing patients' genetic data are required to fully understand individual features of genetic information and handle them appropriately. If a genetic test is realized on a patient already showing symptoms, obtained results should be recorded in the medical documents as any other clinical test, and have to be shared by all physicians and specialists involved in the care of the examinee. Moreover, all individual obtained data, as any other medical information, is subject to confidentiality, and it must not be disclosed to any third-party including patient's relatives without his consent. When an individual genetic diagnosis is advantageous for the health management of patient's relatives, disclosure of the genetic data to the relatives may be considered if such information is requested to implement effective prevention and treatment. Basically, patient's consent would be necessary in such cases but, considering the best interest of his relatives, the examinee's genetic information may be disclosed, even if patient's consent cannot be obtained. Disclosure to patient's relative should be performed through consultation with the ethics committee of the relevant medical institution.

Genetic Counseling [21]

Genetic counseling represents a fundamental part of genetic tests/diagnoses, and is realized at an opportune time when needed. It provides information but also psychological and social support, in order to allow patient to make a decision autonomously. Therefore, it is beneficial that the attending doctor, expert of specific pathology, cooperates with a specialist in genetic counseling, acting as a medical team. If results from genetic counseling can infringe on the privacy issue, thoughtful response is needed, for example, by describing and keeping the contents

of counseling independent from the usual medical record.

Conclusion

Implementing a genetic test/diagnosis requires that the attending doctors of each clinical division have enough knowledge and experience in genetics. Because data on genetic test/diagnosis is continuously updated, the clinicians involved are encouraged to keep updated with the latest research in order to apply such information to their medical practice. It is opportune that they cooperate with medical geneticists, evaluating the specific features of the disease and the clinical area targeted for the genetic test. Moreover, medical institutes should fully perceive aims and contents of these guidelines, in order to continue education/enlightenment of physicians and healthcare experts involved in the genetic test/diagnosis regarding the basic knowledge of medical genetics and the appropriate handling of individual genetic information [22]. It is also useful for medical institutes to realize a system for opportune implementation of genetic medicine, a field that can make rapid progress and that will improve various medical sectors. There is a need for each national and international medical societies to provide education/enlightenment regarding the appropriate genetic medicine and counseling regarding pathologies in each medical area.

References

1. Oda H, Kastner DL. Genomics, Biology, and Human Illness: Advances in the Monogenic Autoinflammatory Diseases. Rheum Dis Clin North Am 2017;43:327-345.
2. Cristoferi L, Nardi A, Invernizzi P, Mells G, Carbone M. Individualizing Care: Management Beyond Medical Therapy. Clin Liver Dis 2018;22:545-561.
3. Campbell DD, Li Y, Sham PC. Multifactorial disease risk calculator: Risk prediction for multifactorial disease pedigrees. Genet Epidemiol 2018;42:130-133.
4. Fonhus MS, Dalsbo TK, Johansen M, Fretheim A, Skirbekk H, Flottorp SA. Patient-mediated interventions to improve professional practice. Cochrane Database Syst Rev 2018;9:CD012472.
5. Ahluwalia SC, Chen C, Raaen L, Motala A, Walling AM, Chamberlin M, O'Hanlon C, Larkin J, Lorenz K, Akinniranye O, Hempel S. A Systematic Review in Support of the National Consensus Project Clinical Practice Guidelines for Quality Palliative Care, Fourth Edition. J Pain Symptom Manage 2018.
6. Parimbelli E, Marini S, Sacchi L, Bellazzi R. Patient similarity for precision medicine: A systematic review. J Biomed Inform 2018;83:87-96.
7. Tack V, Dufraing K, Deans ZC, van Krieken HJ, Dequeker EMC. The ins and outs of molecular pathology reporting. Virchows Arch 2017;471:199-207.
8. Scally A. Mutation rates and the evolution of germline structure. Philos Trans R Soc Lond B Biol Sci 2016;371.
9. Swanson A, Goldberg JD. Industry perspectives on prenatal genetic testing. Semin Perinatol 2018;42:314-317.
10. Saini N, Gordenin DA. Somatic mutation load and spectra: A record of DNA damage and repair in healthy human cells. Environ Mol Mutagen 2018;59:672-686.
11. Sandler S, Alfino L, Saleem M. The importance of preventative medicine in conjunction with modern day genetic studies. Genes Dis 2018;5:107-111.
12. Higashi MK, Veenstra DL. Managed care in the genomics era: assessing the cost effectiveness of genetic tests. Am J Manag Care 2003;9:493-500.
13. Allen S, Young E, Bowns B. Noninvasive prenatal diagnosis for single gene disorders. Curr Opin Obstet Gynecol 2017;29:73-79.
14. Post AL, Mottola AT, Kuller JA. What's New in Prenatal Genetics? A Review of Current Recommendations and Guidelines. Obstet Gynecol Surv 2017;72:610-617.
15. Cohn-Hokke PE, Holstege H, Weiss MM, van der Flier WM, Barkhof F, Sistermans EA, Pijnenburg YA, van Swieten JC, Meijers-Heijboer H, Scheltens P. A novel CCM2 variant in a family with non-progressive cognitive complaints and cerebral microbleeds. Am J Med Genet B Neuropsychiatr Genet 2017;174:220-226.
16. Tracy A, Buckley CD, Raza K. Pre-symptomatic autoimmunity in rheumatoid arthritis: when does the disease start? Semin Immunopathol 2017;39:423-435.
17. Chapman SM, Maconochie IK. Early warning scores in paediatrics: an overview. Arch Dis Child 2018.
18. Daly AK. Pharmacogenetics: a general review

on progress to date. Br Med Bull 2017;124:65-79.
19. Quinn E, McGee R, Nuccio R, Pappo AS, Nichols KE. Genetic Predisposition to Neonatal Tumors. Curr Pediatr Rev 2015;11:164-78.
20. Alhazzani W, Lewis K, Jaeschke R, Rochwerg B, Moller MH, Evans L, Wilson KC, Patel S, Coopersmith CM, Cecconi M, Guyatt G, Akl EA. Conflicts of interest disclosure forms and management in critical care clinical practice guidelines. Intensive Care Med 2018;44:1691-1698.
21. Resta RG. What have we been trying to do and have we been any good at it? A history of measuring the success of genetic counseling. Eur J Med Genet 2018.
22. LePoire E, Basu B, Walker L, Bowen DJ. What do people think about genetics? A systematic review. J Community Genet 2018.