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Framework for the Assessment of Genetic Testing in the Andalusian Public Health System

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Avda. de la Innovación s/n. Edificio ARENA 1
41020 Seville - SPAIN

Telephone +34 955006638, Fax +34 955006677
email: aetsa.csalud@juntadeandalucia.es

MÁRQUEZ-CALDERÓN, Soledad

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Authors: Soledad Márquez-Calderón and Eduardo Briones Pérez de la Blanca

Documentation: Antonio Romero Tabares, M^a Jesús Pírez Díaz

Translated from Spanish by Alison Turner Hanover and Manuel Gancayco Torralba.

External reviewers:

This document has considerably benefited from the contributions made by:

- Salud Borrego López
*Genetics and Reproduction Clinical Unit
Virgen del Rocío University Hospitals, Seville*
- Ana Carriazo Pérez de Guzmán
*Services Portfolio Service
Directorate General of Health Care
Andalusian Health Service*
- José Antonio Castilla Alcalá
*Reproduction Unit
Virgen de las Nieves University Hospital, Granada*
- José Expósito Hernández
*Oncologist. Virgen de las Nieves University Hospital,
Granada
Director of the Integral Oncological Plan of Andalusia*
- Ildefonso Hernández Aguado
*Professor of Preventive Medicine and Public Health
Miguel Hernández University, Elche*

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CONTENTS

1. INTRODUCTION	5
1.1. Context and justification of the report.....	6
1.2. Definition of genetic testing	9
2. TYPES OF GENETIC TESTS ACCORDING TO THE PURPOSE FOR WHICH THEY ARE USED.....	11
2.1. Tests to confirm diagnosis.....	11
2.2. Tests for screening purposes	11
2.3. Tests for predictive purposes	12
3. FRAMEWORK FOR THE ASSESSMENT OF GENETIC TESTING WITH THE AIM OF DECIDING THEIR INTRODUCTION INTO CLINICAL PRACTICE.....	14
3.1. What level and kind of evidence are required to move from research to use?.....	15
3.2. Assessment criteria for the introduction of genetic tests into the services portfolio	17
3.2.1. Assessment of the existing scientific evidence on the analytical validity of the test	18
3.2.2. Assessment of available scientific evidence on the clinical validity of the test.....	19
3.2.3. Assessment of available scientific evidence on the clinical utility of the test	21
3.2.4. Assessment of the social repercussions and ethical implications of the use of genetic testing in clinical practice	28
3.2.5. Estimate of the economic and organisational impact.....	30
4. FINAL CONSIDERATIONS	31
4.1. A document for updating in the future and as a basis for debate.....	31
4.2. Preparation of a guideline for decisions on the introduction of genetic tests into the services portfolio	32
4.3. The need to address other key issues not included in this report.....	33
5. REFERENCES	34
6. ANNEX I	38
LIST OF QUESTIONS BASED ON THE ACCE MODEL	38

1. INTRODUCTION

Knowledge of the impact of genetics on human health starts with the identification of associations between genetic variants and specific diseases through epidemiological studies (1,2). The derivation of causal relations on the basis of these studies is usually difficult since most diseases are multifactorial and there are also interactions among various genes and between genes and environmental factors.

The study of a genetic variant in the context of clinical practice is not considered (or should not be considered) until the causal relation between that variant and a specific health problem is sufficiently established. In other words, the basis for the development and use of genetic tests lies in the results of genetic epidemiology studies.

Once the assessment of a new genetic test is considered for its possible incorporation and use in clinical practice, the fundamental question to answer – as in any other intervention or health technology – is whether it produces any health benefit over the best existing alternative for the clinical conditions where it is to be applied (indication), and whether this benefit outweighs all possible risks.

At the same time, and following the trend of evidence-based medicine and outcome research, the comparison should be performed by means of well-designed studies and on the basis of relevant and final outcomes (as opposed to interim outcomes).

1.1. CONTEXT AND JUSTIFICATION OF THE REPORT

The field of human genetics is currently undergoing enormous development and will continue to do so in the future. The intensity of research into molecular genetics is leading to very rapid development of new genetic tests. In a survey conducted in 2002, it was found that in Spain tests based on molecular DNA analysis were available for 214 genetic diseases (3). In the United States, there are currently more than a thousand tests, approximately 760 of which are available in clinical practice and a further 325 are currently under investigation (GeneTests: <http://www.geneclinic.org>1). In Europe, the number of genetic tests is expected to multiply over the next few years. And all this is taking place in the absence of a regulatory framework to ensure the quality of the genetic diagnosis (4).

This context of constantly emerging new genetic tests is also characterised by the high expectations regarding their benefits in particular and the benefits afforded by genetics in general, both within the healthcare sector itself and among the general public. This does not exactly facilitate an objective and unbiased assessment.

These expectations may well be related – among other things – to certain specific cases of good results from the use of a test for a hereditary disease, such as phenylketonuria. In this particular health problem, there is a simple causal model and a high penetrance genotype (in cases with the genetic characteristic, the disease practically always occurs when a diet containing phenylalanine is given), an easily identifiable population, a reliable test used in the framework of a complete screening protocol and a treatment that is effective if started in time (1). Nevertheless, these circumstances are very rare, and they do not occur in common diseases, which are multicausal, associated with both environmental factors and various genetic factors. In these cases, the presence of a genetic variant can have a much lower predictive value. In fact, there is an inverse relation between the frequency of a genetic variation in the population and its penetrance (5).

Moreover, as in other technologies, genetic tests are products for which there is an enormous potential market, not only for this industry but also for other health product industries (as in the case of drugs where use would increase if genetic testing became more widespread). As a result, healthcare authorities, managers and professionals, as well as citizens are going to find themselves subjected to constant offers of new tests from industry in the near future, and this trend will increase as technology becomes more simplified, as is already occurring with multigene arrays (*biochips*).

The marketing plans of the health product industry are ever more ambitious and cover the entire possible spectrum of decision makers and pressure groups. In addition to the classical strategies of approaching medical professionals and their scientific societies, it is becoming increasingly more frequent to include a presentation of the product for those responsible for defining the services portfolio of the health services and patient associations. This is reason for concern in those cases in which the test to be introduced is supported by few studies that do not meet the appropriate criteria of methodological quality and have only evaluated the interim outcomes.

In the United States, marketing campaigns targeted directly at the population are emerging, like the one that was conducted by the supplier of the BRCA1/2 tests for breast and ovary cancer at the end of 2002 in some US cities, in spite of the fact that the data available on the clinical validity and utility of these tests in the general population is very limited. These campaigns achieved an increase in the use of genetic tests and the number of requests for referral to oncology and genetic services made by users to their doctors (6).

Unfortunately, experience now shows that in developed countries many genetic tests for common diseases are being offered for use in clinical practice before any studies have been conducted on the benefits and risks of interventions in subjects with genetic susceptibility (1) and even in cases where there is no effective treatment available (7).

In light of the above, the incorporation of genetic advances into health services warrants careful consideration and the establishment of

¹ Consulted on 14 December 2004.

frameworks and methods to assess new genetic tests, with the aim of incorporating into the services portfolio those that afford benefit to the health of the citizens and that do so in a cost-effective way. This framework will contain aspects in common with other frameworks for assessment of new technologies developed previously by the Andalusian Agency for Health Technology Assessment (AETSA, *Agencia de Evaluación de Tecnologías Sanitarias de Andalucía*) (8,9), along with specific aspects that take into account the particular nature of genetic testing.

The concern to advance in a planned manner in the field of genetics has been reflected in the III Andalusian Health Scheme, one of whose objectives is “To establish the intervention strategy in genetics, both in the field of research and in the provision of services”. This Health Scheme defines the assessment criteria for this objective as the development of the Assessment Framework for defining the services portfolio within the scope of medical genetics, a task assigned to the Andalusian Agency for Health Technology Assessment (10).

The aim of the present report is to provide a response to the mission assigned to the Andalusian Agency for Health Technology Assessment for the development of an Assessment Framework for the incorporation of new genetic tests into the services portfolio of the Andalusian Public Health System.

Therefore, the primary objective of this Assessment Framework is to propose the main dimensions and criteria that must be taken into account when deciding the incorporation of new genetic tests into the services portfolio of the Andalusian Public Health System. This proposal of criteria will subsequently serve as a basis for developing a decision-making tool or guideline. Moreover, the criteria that are put forward must be useful for

determining which genetic tests are in the research phase based on the scientific evidence available at a given point in time.

1.2. DEFINITION OF GENETIC TESTING

There is no broad agreement on the definition of a genetic test (11). In fact, the recommendations put forward in a recent European Commission document include the need for an overall consensus on this issue (12). The National Institutes of Health have considered genetic tests to be the analysis of DNA, RNA, chromosomes, proteins or certain metabolites, with the aim of detecting alterations related to a hereditary problem (<http://www.genetests.org>)². This can be done by means of (2):

- Molecular analysis of DNA or RNA related to a gene (direct test).
- Analysis of co-inherited markers with a gene causing a disease (linkage test).
- Analysis of proteins or other metabolites (biochemical or immunochemical test).
- Analysis of chromosomes (cytogenetic test).

These methods can be used alone or in combination. Sometimes, a screening strategy for a genetic disease may involve several tests, which are performed in series (i.e. only if one test is positive is the next one performed). For example, in some screening programmes for cystic fibrosis in the newborn, the first test performed is the determination of immuno-reactive trypsinogen in a drop of blood. Only when this test shows high values is DNA analysis subsequently performed (13).

Genetic tests share common aspects with other laboratory tests, although they also have specific characteristics of their own. (<http://www.genetests.org>)³.

- Results are generally applicable not only to the patient but also to other members of the family and to the children the

² Consulted on 29 July 2004.

³ Consulted on 16 July 2004.

patient might have in the future.

- Given that the majority of genetic problems are rare, genetic tests are generally performed only by specialised laboratories.
- They are usually performed within the context of a genetic outpatient clinic, which should include all aspects of genetic counselling, from information prior to the test and informed consent, to interpretation of the test and medical and psychological follow-up services when these are indicated (7).
- For a genetic test to be able to provide results with any clinical significance, several different methods may be required and other family members may have to be tested as well.

2. TYPES OF GENETIC TESTS ACCORDING TO THE PURPOSE FOR WHICH THEY ARE USED

In order to define an assessment framework, it is first of all necessary to place genetic testing within the different types of health technologies. These are technologies for a diagnostic purpose, which may be for confirmation of previous diagnoses, or intended for screening or estimating the predisposition to a particular health problem.

The majority of the genetic tests available for clinical use are intended to assist in the diagnosis of rare diseases. Only around 5% are applicable to common diseases with onset occurring in adulthood; in these cases the tests are generally used to identify variants of a gene associated with susceptibility to a disease in a family at high risk (for example: BRCA1 for breast cancer) (14). However, as genetic epidemiology advances, there is a tendency towards an increasing use of tests for the prevention and treatment of frequent health problems that present in adulthood (7). The impact of a test of this kind (for a common disease) can be enormous, given the high use implied in its application for the population as a whole.

Genetic tests can be classified according to purposes, i.e. confirmation of diagnosis, screening and predictive (2, 15).

2.1. TESTS TO CONFIRM DIAGNOSIS

Here the aim would be to confirm or rule out the diagnosis of a disease, prior to (prenatal test) or after birth. They are usually performed in diseases that have a clear genetic basis (cystic fibrosis, Down's syndrome, thalassaemia, etc.). Such testing may be considered following a positive screening test (prenatal or otherwise) or in persons who present symptoms consistent with the disease.

2.2. TESTS FOR SCREENING PURPOSES

These are in turn divided into various types:

- Prenatal screening: this is usually done in almost all European countries for the main chromosome aberrations and neural tube defects. It is based on serum tests combined with ultrasound imaging. In cases where the screening test is positive, diagnosis is confirmed by means of chromosomal analysis.
- Neonatal screening: this is performed for diseases where there is an effective treatment available, such as phenylketonuria and hypothyroidism. Generally, biochemical tests on a drop of blood are used as part of a screening strategy covering the whole newborn population. In positive cases, diagnostic confirmation is usually performed by means of a molecular test.
- Identification of carriers: in adults the identification of carriers can be of value, particularly for the purpose of reproductive counselling.

2.3. TESTS FOR PREDICTIVE PURPOSES

These tests cover a broad spectrum of diseases and acquired health problems, and their objective is to predict their onset in the future. They, in turn, include two types of test:

- Pre-symptom tests: these are tests that are conducted in problems where the penetrance of the gene is almost 100%. Some examples are Huntington's chorea, carcinoma of the colon in hereditary polyposis, some rare forms of Alzheimer's disease and some forms of hereditary carcinoma of the thyroid gland.
- Genetic predisposition tests: these are tests in which a certain genotype is associated with an increased risk of developing the disease. Some examples are hereditary cancer of the breast/ovary and hereditary cancer of the colon not associated with polyposis.

Other types of genetic predisposition tests are those used for frequent and multifactorial diseases, such as diabetes, cardiovascular disease, rheumatoid arthritis, etc. Falling into this category are some

commercial diagnostic kits available in the market, although few are clinically useful.

- Predictive tests of the response to a drug: although currently the number of tests available for this type of use in clinical practice is limited, pharmacogenomics can be expected to become one of the fields with the greatest future development and impact in terms of use and costs for the health system (16). An example is the detection of the HER2/neu oncogenes in breast cancer, where over-expression is associated with the response to treatment with trastuzumab (16). The purpose of this type of test is to predict the response to a treatment, and thereby provide drugs to those who are most likely to benefit from them and run a lesser risk of suffering adverse effects (2)

3. FRAMEWORK FOR THE ASSESSMENT OF GENETIC TESTING WITH THE AIM OF DECIDING THEIR INTRODUCTION INTO CLINICAL PRACTICE

SCOPE OF APPLICATION OF THE ASSESSMENT FRAMEWORK FOR GENETIC TESTING:

Although the assessment framework proposed in this document could be applicable to a large extent to any kind of genetic test (direct, linkage, cytogenetic, biochemical, etc.), it has fundamentally been developed in order to evaluate the inclusion of **genetic tests requiring DNA or RNA analysis** into the services portfolio of the Andalusian Public Health System .

The framework **refers to the assessment of genetic tests for evaluating their incorporation into the services portfolio and not to the assessment of genetic counselling services**. Genetic counselling is essential when genetic testing is performed (and this is stated in this assessment framework), although it is not necessarily linked to the performing of such tests.

As indicated earlier, the development of a genetic test is considered after an association between a certain genetic variant and a health problem has been identified in epidemiological studies. Once the test has been developed, a process of evaluational research should be launched in order to assess its utility and implications when used routinely in clinical practice. In this process, different phases with distinct objectives can be distinguished (1):

Phase of research into the performance of the genetic test

The objective should be to determine how the test runs compared with a gold standard in the laboratory and, subsequently, in certain groups

of people who might, theoretically, benefit from the information provided by the test (*analytical and clinical validity* of the test).

Phase of clinical research into the results of the genetic test

Once the analytical and clinical validity of a test has been proven, the next objective would be to determine its *clinical utility*, in other words, what health benefits it will provide and what adverse effects are entailed in performing the test (clinical utility, including effectiveness and safety aspects).

Phase of research into the impact on health services and on the population resulting from the routine use of the genetic test

In practice, this phase may partly overlap with the previous one. The objective would be to estimate the possible *organisational, economic, ethical and social implications* of using the genetic test in routine clinical practice.

The decision to incorporate new genetic tests into clinical practice should be based on an assessment of the evidence concerning how it runs and the health outcomes resulting from the interventions / decisions taken on the basis of the information provided by the test, in addition to an estimate of the social, ethical, organisational and economic implications of its inclusion in the services portfolio.

The methodology for these research phases will be addressed in greater detail later, but first of all it is necessary to examine the process of decision-making on the use of new genetic tests in clinical practice.

3.1. WHAT LEVEL AND KIND OF EVIDENCE ARE REQUIRED TO MOVE FROM RESEARCH TO USE?

When deciding to include a new genetic test in the services portfolio, a key issue is to determine when one can move from the

evaluative research process of the test to its use in practice. In other words, what kind of knowledge is required to take this step.

It could be taken for granted from the outset that a new genetic test must have complied with all the phases of research before being incorporated into clinical practice. The studies conducted must have proven that the test works well as a diagnostic tool, that it has a positive impact on health and there is a favourable assessment of the economic, organisational, social and ethical implications of its use.

The advantages of a model of this type are evident, since it would avoid the implementation of tests that are either of little use, have adverse effects or entail unnecessary costs. Nevertheless, an excessively rigid approach is not free from limitations. It must be taken into account that a large part of genetic tests are used for the purpose of predicting the future risk of disease and it is presumed that individuals at high risk will benefit from a series of preventive measures. The relevant outcomes in these cases can only be assessed in the very long term⁴. An assessment model that requires experimental studies covering the entire causal chain (from the genetic test to the health outcomes following intervention in test-positive cases) before any test can be used could curb benefits as a result of the delay in incorporating useful technologies (17). This could also lead to major tension within a system that is constantly pushing for the incorporation of innovations, running the risk of ending up using the test routinely, but disguised as research.

For this reason, in some cases it might be reasonable to introduce more flexible approaches, as in the case when a very effective, safe and acceptable treatment is already available for the disease which the new genetic test diagnoses, and when its use as a diagnostic test is clearly superior to the existing alternative. Nevertheless, this type of approach based on linking the pieces together (validity of the test on the one hand and effectiveness of the treatment on the other) also has major limitations. In fact, there are several examples in medicine where this strategy has led to erroneous conclusions, especially in the field of screening. In the case of

⁴ For example, in a genetic test that assesses the risk for developing a certain type of cancer in individuals with a family history of this type of cancer, where it is assumed that effective follow-up enabling early diagnosis is available and that early treatment reduces mortality, the study required would take years since the key outcome would be the number of deaths from cancer that are prevented.

genetic tests (above all predictive tests), these errors could be made, and it is therefore necessary in each case to determine the need for a full study (from the diagnostic test to the outcome of treatment) or to accept the strategy of performing separate studies for the validity of the diagnostic test and the efficacy of treatment. Section 3.2.3 (*Assessment of the existing scientific evidence on the clinical utility of the test*) provides more information on this subject.

3.2. ASSESSMENT CRITERIA FOR THE INTRODUCTION OF GENETIC TESTS INTO THE SERVICES PORTFOLIO

The decisions to incorporate any technology into the services portfolio must be based on the criteria of efficacy, effectiveness (acceptability of the technology, accessibility, facility for adequate use, etc.) and efficiency, along with a forecast of the economic impact and its impact on the organisation of services, together with the ethical and social aspects. These criteria are entirely applicable to genetic testing, although here certain areas require special emphasis and particular, specific issues should also be taken into account.

When addressing the issue of decision-making in the incorporation of a new genetic test into the services portfolio, it is necessary (1):

1. To assess the existing scientific evidence on the *performance* of the test, in other words, how it works as a diagnostic test (analytical validity and clinical validity).
2. To assess the existing scientific evidence on the results of the test (clinical utility and safety).
3. To conduct an assessment of the *social impact and ethical implications* of the routine use of the test in clinical practice.
4. To make an estimate of its impact on *the health services, at both the organisational and economic level*.

The first two points will be based, above all, on the studies conducted, both published and unpublished. In general, not much scientific evidence will be found for points three and four, and even where available, will have to be adapted to the local context. Therefore these points will generally involve estimations and considerations in each specific case.

The first step is to make a proper definition of the clinical condition (indication) where the genetic test is intended for use, along with the expected benefits (1).

A key aspect is to make a proper definition of the clinical condition (indication) where the use of the test is intended. This should be the first step in the process of assessing the incorporation of a new genetic test.

It has to be made clear at all times that the conclusions drawn from the assessment process and the final decision that is taken on the incorporation of the test into the services portfolio are only applicable to the indications that have been assessed and not to others.

Most of the genetic tests currently available are for rare diseases, although more and more tests are being developed for assessing the inherited risk of frequent health problems, such as breast cancer, cancer of the colon, thromboembolism, Alzheimer's disease, coronary heart disease, etc. (1).

3.2.1. ASSESSMENT OF THE EXISTING SCIENTIFIC EVIDENCE ON THE ANALYTICAL VALIDITY OF THE TEST

Analytical validity is the accuracy with which a laboratory test is capable of identifying a certain genetic variant (1, 14). It should be tested before its use both in the clinical context and for research purposes. It includes two types of parameters:

- Reliability of the test (*reproducibility*) in the context of clinical laboratories. This refers to the capacity to obtain similar results when the test is repeated by different observers or centres, or by the same observer, but under different conditions (18, 19).
- Sensitivity, specificity and predictive values in relation to the

genotype⁵. This concerns research at the laboratory level, comparing the genetic test with a reference standard in samples that include individuals with and without the genetic variant under study (14). The criteria used for defining these genotypes should be clearly established (reference standard).

Compared to other diagnostic tests, genetic tests are very complex as regards the assessment of analytical validity. On the one hand, it should be taken into account that the majority of genetic variants can be studied by different techniques (e.g., DNA sequencing, multigenetic arrays, functional tests) which may involve varying difficulties in their interpretation. The study of genetic variants may also be based on quantitative data that can then be categorised. Consequently, the different tests for identifying the same genetic variant may not have the same sensitivity and specificity; and the intra-and inter-observer reproducibility becomes an important assessment criterion. On the other hand, since many of the tests have been developed in each laboratory, the demonstration of their validity from the analytical perspective becomes extremely important.

3.2.2. ASSESSMENT OF AVAILABLE SCIENTIFIC EVIDENCE ON THE CLINICAL VALIDITY OF THE TEST

Clinical validity is the accuracy with which a test predicts a certain clinical outcome.

This is presented as sensitivity, specificity and predictive values⁶ in relation to a specific phenotype. Clinical validity is ascertained by means of epidemiological studies, fundamentally in cohorts and case-control studies, with the aim of determining the capacity of the test to diagnose or predict risks in a certain population (14).

⁵ Sensitivity is the proportion of individuals with the genotype under study (according to the reference standard) that are test-positive. Specificity is the proportion of individuals without the genotype that are test-negative. The positive predictive value is the probability that a test-positive individual has the genotype according to the reference standard. The negative predictive value is the probability that a test-negative individual really does not have the genotype according to the reference standard.

⁶ The positive predictive value of a test is the probability that a person who is test-positive has the disease. The negative predictive value is the probability that a person who is test-negative really does not have the disease. These values depend not only on sensitivity and specificity, but also on the prevalence of the disease in the population where the test is performed.

The result to which clinical validity refers will be the presence of current disease in the case of genetic tests used for diagnostic purposes, and the onset of the disease in the future in the case of tests used for measuring genetic susceptibility.

As mentioned above, a pivotal issue is the definition of the population where these studies are performed, since predictive values can change according to the prevalence of the particular health problem (18) and the distribution of the mutation. In fact, a very relevant criterion in the assessment of genetic tests is that there should be a reliable and valid mechanism for identifying the population on which the genetic test would be performed (29). For a given sensitivity and specificity, the predictive value of a test is proportional to the prevalence: the lower it is, the lower the ratio between true and false positives will be (5). In fact, many mutations that are associated with genetic susceptibility are initially defined in high-risk families (various members affected, onset of the disease at ages below the norm, etc.) and are then used in clinical practice in populations with a lower risk. This would cause a change in the predictive values.

Something similar occurs when there are interactions between genes or with environmental factors. When changing from one population to another with a different distribution of these other factors, the predictive capacity of the test will also change.

There is a major limitation that needs to be underscored and which occurs in many genetic tests regarding the estimation of the predictive value of a positive result, above all in the case of rare diseases. The problem is that many of these tests have a false positive rate that is close to zero, thereby complicating the calculation of the predictive value since it is very sensitive to small changes in the rate of false positives⁷ (21). How does one interpret a positive result in a person if no false positives have been found in previous studies, or just a very small number have been found in a very large population? In such cases, some authors suggest estimates by means of Bayesian methods starting from an *a priori* probability distribution of false positives and then calculating – on the basis

⁷ An example would be the following: a test that is conducted in the newborn to detect a disease with a prevalence of 1 in 250,000, where it can be assumed that the sensitivity is 100%. If the specificity were 100%, there would be no false positives and the positive predictive value would be 100%. But if there were just a minute rate of false positives (for example, 0.0077%), the positive predictive value would fall to 4.9%.

of that distribution plus the experience gathered from different studies – another probability distribution (*a posteriori*). The positive predictive values can then be estimated with these final distributions (21). These would be estimates that reflect the uncertainty of the false positive rates of the test (22), thereby providing useful information for patients.

In order to make an adequate assessment of studies on the clinical validity of genetic tests, the following key aspects should be taken into account (1).

- External validity: related to the definition of the study population (inclusion/exclusion criteria).
- Internal validity: related to the design used and the possibility of bias due to design and analysis: prospectivity / retrospectivity, case definition, selection of the comparison group, blinding when measuring the outcomes, verification of negative results and analysis taking into account possible modifying factors of the effect.
- Clinical relevance: related to the type of outcome measured (sometimes a single genetic variant can be associated with different outcomes, with different predictive values for each of them).

In a way, when defining the study population for determining clinical validity, a possible screening strategy is being anticipated. For example, it would not be the same case to consider screening a population for a polymorphism that is very frequent but with low penetrance as it would to consider screening family members of patients with a mutation that has high penetrance but is very rare in the general population.

3.2.3. ASSESSMENT OF AVAILABLE SCIENTIFIC EVIDENCE ON THE CLINICAL UTILITY OF THE TEST

Clinical utility is the probability that performing a test will have an effect in terms of health, considering both the effects of positive and negative results. It includes an assessment of the balance between benefits (effectiveness) and risks (safety). In order to achieve a health benefit, the following criteria have to be met:

- There must be a test with analytical and clinical validity.

- There must be an effective intervention in individuals in which the test is positive and/or a positive effect of the information in positive and/or negative cases (1, 13-14). Some authors draw attention to the fact of assuming *a priori* that genetic counselling is effective and that it entails an improvement in lifestyle. Nevertheless, this does not always occur and patients may sometimes even adopt fatalistic attitudes that lead to lesser motivation to change to healthier lifestyles (23).

Moreover, the benefit in terms of health will be closely linked to the severity of the disease that is diagnosed or predicted by the test, given that the outcome that is avoided will have a greater clinical significance if there is an effective treatment or method of prevention available.

When the genetic test is for **diagnostic purposes**, making the diagnosis by this method must afford some advantage over other methods. For example, genetic testing would be useful in cases where the definitive diagnosis by means of other types of tests requires more time and where such a delay is associated with a lower probability of benefiting from an effective treatment or a greater probability of having descendents with the disease.

When the genetic test is used for a **predictive purpose (predisposition to a disease)**, there must be evidence of a benefit from monitoring (i.e. regular follow-up to diagnose a disease in its early stages). For this purpose, an effective monitoring strategy for early diagnosis must be available, as there should be a treatment which, when started early, could improve survival, quality of life or other health outcomes (compared to late treatment).

In fact, the effectiveness of a screening test is questionable if asymptomatic subjects in whom the disease is detected early have the same outcome in health terms as those who seek medical care once they have developed symptoms (18, 20).

KEY POINTS ON CLINICAL UTILITY

- In cases where a diagnostic or screening *alternative* was already available prior to the genetic test, the genetic test has to provide major advantages over that alternative from the clinical point of view.
- A test may have excellent analytical and clinical validity and yet may not provide any significant advantage in either accuracy or predictive power when compared with the conventional diagnostic or screening method (for example: a biochemical parameter). If, in addition, the intervention or available treatment is only moderately effective, then the overall clinical utility of the genetic test would be minimal in comparison to conventional diagnosis or screening.

As in other screening tests, other possible results should be taken into account:

- Benefits derived from a negative test that rules out a serious disease.
Label of illness, above all if there is no effective treatment for the disease.
- Consequences of false positives (performing unnecessary interventions or treatments, psychological effects, unnecessary costs) and false negatives (delays in diagnosis and treatment, false sense of security).

Mention has already been made of the importance of defining the level of evidence that is to be required to move from research into genetic tests to their use in clinical practice. It is important to seek decision models that are not so rigid that they curb innovation, nor so flexible that they enable what has already happened with many emerging technologies to occur with genetic tests, i.e. their use on the basis of clinical grounds

without any adequate assessment of the balance between benefits and risks (1).

In order to assess the evidence for the clinical utility of a genetic test, the ideal type of study is a clinical trial, which evaluates the complete intervention strategy (diagnostic tests and subsequent intervention), with a sufficiently long follow-up period to enable assessment of the final outcome.

In this trial, the subjects meeting the established inclusion criteria would be randomly assigned to the genetic test under study or to the alternative diagnostic or screening test. What is more frequently considered is the comparison of a strategy that includes the screening test plus the genetic test compared to the screening test alone. No matter what comparison is used, the same preventive or therapeutic intervention would be carried out in the positive cases of both arms of the clinical trial and the most relevant outcomes from the clinical point of view would be assessed.

Subjects with inclusion criteria

**Genetic test, alone or with
the usual diagnostic or
screening test**

**Usual diagnostic or screening
test**

**Long-term final outcomes, following the
preventive intervention or treatment in the
test-positive
cases of both arms of the trial**

When available, the aspects to be assessed in this type of clinical trials are:

- External validity: Definition of the population where the strategy has been tested (inclusion and exclusion criteria). It

is important to bear in mind that the same genetic variant can sometimes be associated with a range of health problems, and may be clinically useful for one and not for the others (for example, depending on whether or not there is an effective preventive intervention).

- Clear definition of the diagnostic and intervention alternatives.
- Internal validity: possibility of bias due to trial design and analysis (concealment, blinding when measuring results, verification of negative results, analysis of patients lost to follow-up, etc.).
- Relevance of the outcomes: measurement of all the important outcomes from a clinical point of view and magnitude of the difference in results between the two arms of the trial. The parameter used for assessing the magnitude of the difference is the *number needed to screen (NNS)* in order to avoid a certain event (whether this is the onset of the disease, its complications or death).

The NNS is affected by various components:

- Effectiveness of the intervention (NNT: number needed to treat in order to avoid an event).
- Follow-up time until the appearance of the outcome that is of interest.
- Frequency of the genetic variation in the study population.
- Penetrance of the genetic variant.
- Validity of the genetic test.

A randomised clinical trial and the evaluation of the complete strategy is feasible in cases where a large sample size is not required (e.g., the genetic variant has high penetrance and also the inclusion criteria select a population with a high prevalence of that variant) nor is a very long follow-up in order to obtain relevant results (e.g., assessment of a prediction test for the effects of a drug).

Nevertheless, in many cases these conditions are not met and other options could be assessed with regard to deciding on the incorporation of a new genetic test into clinical practice. In this case, the decision would be taken on the basis of different studies which separately measure different parts of the causal chain (a chain which starts with conducting a genetic test and ends with a major health outcome). Nevertheless, this approach has major limitations and must therefore be considered with caution.

In general, the NNS is going to give reasonable figures when dealing with high penetrance mutations in high-risk families, but not for such mutations in the general population or for low penetrance polymorphisms (5). All this, assuming there is a valid test and an effective intervention.

In these cases, the decision to incorporate the genetic test into clinical practice would be considered on the basis of the availability of two types of separate study:

- Assessment studies of the analytical and clinical validity of the test.
- Studies on the effectiveness of preventive or therapeutic intervention.

The aspects already commented above for studies on the analytical and clinical validity of the test, and the key aspects of the assessment of clinical trials on preventive or therapeutic intervention (internal validity, external validity, measurement of all the relevant health outcomes – both

benefits and risks – and the magnitude of the effects) should all be evaluated.

In any case, given the existing limitations when all that is available is the separate evidence on the validity of the diagnostic test and of the effectiveness of the treatment, the following points are worthy of mention.

First of all, in order to take the decision to introduce a genetic test into practice under these conditions, the level of requirements regarding existing studies has to be very high. In other words, the studies must have a high internal validity, with relevant outcomes (good predictive values, high magnitude of the beneficial effects of the treatment, safety of treatment) that could be generalised to the context where the test is to be used.

Secondly, in some cases it may be convenient for some tests to go through a period of conditional introduction subject to post-introduction information and surveillance systems. This type of strategy would enable clinical practice to be monitored by means of observational studies (cohort and case-control studies) which would enable information to be drawn from a lengthy follow-up and outcomes with greater clinical relevance. Some authors have suggested that this type of option would allow an analysis to be conducted that would bring together information from various studies by means of a systematic review and – if appropriate – meta-analysis (1, 14). In any event, this topic is under continual debate and for some authors, in the case of screening tests, trials with randomisation provide the only method that rules out certain types of bias (those related with lead time and length biases) (24).

All comments regarding the assessment of the utility of a genetic test refer to the context of decision-making for the test's incorporation into the services portfolio.

However, very often the balance between benefits and risks is assessed in a different way by each individual. For this reason, once a test is available for use in clinical practice, the affected person must always have the opportunity to assess the pros and cons of being subjected to the test, in line with his or her preferences, once the appropriate information has been duly provided.

3.2.4. ASSESSMENT OF THE SOCIAL REPERCUSSIONS AND ETHICAL IMPLICATIONS OF THE USE OF GENETIC TESTING IN CLINICAL PRACTICE

The evaluation of genetic tests cannot be limited to clinical results since there may be major social and ethical implications, some shared with other medical technologies and others that are more specific (2). These issues should be assessed, in spite of the difficulties involved in measuring some of them (1).

In a recent systematic review of the literature, a search was made for studies on the social, ethical and legal dimensions of technologies for assessing the risk of inherited cancer (genetic predisposition tests) (25). Of the 247 primary studies found, only 77 were of acceptable quality, which offers an idea of the scant experience available in conducting research that addresses these issues. The authors of this review highlight the number of key topics on which there is little or no information available. They also pinpoint the understanding of the psychological impact of the information that is provided when offering a genetic predisposition test to high-risk subjects (due to family background) as one of the major gaps in evidence. Once informed, such individuals may decide not to undergo the test. There have been very few studies focusing on these populations who reject genetic tests (25).

Some of the most outstanding ethical and social aspects that must be borne in mind when assessing a new genetic test are mentioned and illustrated below.

One of the main concerns in society regarding the use of genetic testing is the use of the information to discriminate against individuals, whether this be in relation to employment or to medical insurance (1, 2, 26). Nevertheless, this kind of inequality resulting from genetic information is one of the most difficult effects to study.

Another area of increasing concern and debate is the possibility of eugenics, based above all on the "risk" of the future development of a genetic disease (25).

A key topic is access to genetic tests and to treatments or interventions following a positive result. The risk of inequalities may grow in the light of the availability of new tests and treatments that are very costly

but have a major impact on health. Such a situation encourages those with a higher socio-economic level to seek such services in the private sector that the public health system cannot provide. The incorporation of genetic testing into practice has to take into account the feasibility, from the economic point of view, of equitable access both to the tests and to the ensuing treatments. This can be especially important in the case of pharmacogenomics (16).

Two key ethical issues should be highlighted. The first concerns the balance between the benefits and risks of genetic testing and who should strike that balance. To the extent that people have different values and preferences, it is important that they be the ones to take the decision to undergo genetic testing (12). Nevertheless, this contrasts with reality where medicine is still set within a paternalistic model and where a broad sector of society sometimes prefers this type of health care model. As stated recently in a European Commission report, counselling must be provided in a “non-directive” way (2) and this involves respecting the right of not wanting to receive information on the risk linked to genetic characteristics. At the same time, informed consent is complicated by the complexity of the information that is required and by the relevance of the results of genetic testing, not only for the individual who undergoes the test but also his/her family. This is directly related to the second important ethical aspect. First of all, a key question is whether the information resulting from a genetic test can be given to a family member without the approval of the person who underwent the test (27). Similarly, when the person accepts that information be provided and the family is informed, then the ethical dilemma may arise of whether or not information on future risks should be provided to those who have not requested such information.

Currently, most of the legislation in Europe requires the consent of the individual before providing the information to family members. Only under very exceptional circumstances can action of any other kind be considered (2).

Another important issue is that of conducting genetic tests in children. In most health centres, tests performed in children are strictly confined to those cases in which the diagnosis is essential for the management of the disease or its treatment (2, 28). In this way, the right of the individuals to decide is protected in the event they do not wish to receive certain information in the future.

3.2.5. ESTIMATE OF THE ECONOMIC AND ORGANISATIONAL IMPACT

Before deciding to incorporate new genetic tests into clinical practice, an estimate of the requirements and costs to organise and maintain all the related services should be made. These would include:

- The genetic tests *per se*.
- Genetic counselling services, which have a role both before and after the tests (1), and which include both the index case and family members.
- Care and treatment circuits for subjects with a positive result.

The economic impact of introducing genetic tests is difficult to estimate. The costs derived from conducting the tests are usually small compared to those entailed in monitoring, prevention and treatment (29). For example, in the case of certain tumours, detection tests have been developed for mutations that predict the response to treatment with cytostatic drugs; and although the tests are not expensive, the costs of the resulting treatment are fairly high (16).

In any case, the fundamental parameter for decision-making is the cost-effectiveness of the diagnosis or screening strategy with the new genetic test compared with other alternatives.

4. FINAL CONSIDERATIONS

4.1. A DOCUMENT FOR UPDATING IN THE FUTURE AND AS A BASIS FOR DEBATE

The European Commission has recommended that all key players should pool their efforts to optimise future advances in healthcare that could stem from genetic studies, whether in relation to the prevention or the treatment of diseases (2). Moreover, most of the assessment frameworks for genetic tests in use are under constant review, while even the framework of the European Union is still in the development phase. In this context, this document should be revised and updated in the future, in line with any future developments. Moreover, this document should serve as a basis for discussion with public healthcare system managers and professionals, since both their opinions and viewpoints and those of citizens should be built into any future review.

Discussion and consensus are particularly important on certain issues that some authors have termed “the grey areas” of technology assessment, and which have already been indicated in this report:

- a. There are no clear standards on what the scale of the benefits should be (in terms of effectiveness, efficiency and other assessment criteria) for a new technology to deserve to be included in the coverage provided by the public health system.
- b. Many technologies are introduced into practice based on information that is incomplete, ambiguous or may even have been lost.
- c. Once it has been decided that a new technology will be provided within the public health system, within a short period of time the technology itself and the context often may change, meaning that the aims, effects and costs also change.

4.2. PREPARATION OF A GUIDELINE FOR DECISIONS ON THE INTRODUCTION OF GENETIC TESTS INTO THE SERVICES PORTFOLIO

A guideline for decision-making would be useful so as to facilitate the assessment process for genetic testing to be included in the services portfolio. Proposed below are some suggestions for this guideline:

- The preparation of the guideline should focus on specifying and simplifying the main assessment criteria that comprise the conceptual framework proposed in this document.
- The support system for decision-making proposed in the guideline should distinguish between compulsory assessment criteria (minimum criteria) and the desirable or optimum assessment criteria. All the possible decisions that can be taken following the assessment of a genetic test based on the guideline should also be specified.
- The working group preparing the guideline should include professionals involved in the services portfolio decision-making process as well as in the health care of the patients in whom genetic tests can be considered.
- Once the guideline has been developed, a provisional implementation of certain genetic tests would be advisable in order to determine whether changes should be made to facilitate their use in clinical practice.

In order to define the criteria of the assessment framework in the guideline, a list of specific questions to be answered could be used. An initial list is proposed, based on the ACCE⁸ model (13), which was in turn drawn up on the basis of the recommendations issued by the Advisory Committee on Genetic Testing of the United States Department of Health and Human Services⁹. This list is shown in Annexe I.

⁸ ACCE: Analytic validity / Clinical validity / Clinical utility / Ethical, legal & social implications.

⁹ *Enhancing the oversight of genetic tests: Recommendations of the SACGT (Secretary's Advisory Committee on Genetic Testing).*

4.3. THE NEED TO ADDRESS OTHER KEY ISSUES NOT INCLUDED IN THIS REPORT

As emphasised from the beginning of the report, the main objective of this assessment framework is to assist in the decision-making process for the incorporation of new genetic testing into the services portfolio. Other key issues in the use of these tests in clinical practice have not been included in the report, although it must be stressed that these should be addressed.

It would be of little use to take the decision to incorporate a new genetic test following full assessment and confirmation of its validity and clinical utility without ensuring optimal conditions for performing such a test in clinical practice, as follows:

- Laboratories with appropriate quality controls, preferably with accreditation to perform genetic analysis. An important initiative in this field is to take part in quality control networks for the genetic diagnosis of different diseases.
- Accessible and properly organised genetic counselling services.
- Well-established treatment and follow-up circuits for patients and family members.
- Procedures that guarantee access to all of the above (tests, genetic counselling, treatment and follow-up), regardless of the place of residence within the territorial boundaries of Andalusia.

5. REFERENCES

- 1) Burke W, Atkins D, Gwinn H, Guttmacher A, Haddow J, Lau J et al. Genetic test evaluation: information needs of clinicians, policy makers, and the public. *Am J Epidemiol* 2002; 156: 311-318.
- 2) McNally E, Cambon-Thomsen A, Brazell C, Cassiman JJ, Kent A, Lindpaintner K et al. Ethical, legal and social aspects of genetic testing: research, development and clinical applications. Brussels: European Commission / Community Research, 2004.
- 3) Rueda J, Briones E. Servicios de diagnóstico genético para las enfermedades hereditarias en España. EUR 20516 EN. Seville: Institute for Prospective Technological Studies, 2002.
- 4) Ibarreta D, Bock AK, Klein C, Rodríguez-Cerezo E. Towards quality assurance and harmonisation of genetic testing services in the EU. EUR 20977 EN. Seville: Institute for Prospective Technological Studies, 2003.
- 5) Vineis P. Genetic tests in populations: an evidence-based approach. In: Khoury MJ, Little J, Burke W, editors. *Human Genome Epidemiology. A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease*. Oxford: Oxford University Press, 2004. pp 207-216.
- 6) Jacobellis J, Martin L, Engel J, VanEenwyk J, Bradley LA, Kassim S, et al. Genetic testing for breast and ovarian cancer susceptibility: evaluating direct-to-consumer marketing – Atlanta, Denver, Raleigh-Durham, and Seattle, 2003. *MMWR* 2004; 53: 603-606.
- 7) Wang C, Gonzalez R, Merajver SD. Assessment of genetic testing and related counseling services: current research and future directions. *Soc Sci Med* 2004; 58: 1427-1442.
- 8) Briones E, Loscertales M, Pérez MJ en nombre del Grupo GANT. Guía de adquisición de nuevas tecnologías en los centros sanitarios de Andalucía. Seville: Andalusian Agency for Health Technology Assessment, 1999.

- 9) Castellano MM, Santos B, Briones E, Villegas R, Bautista FJ. Evaluación de la implantación de una guía de incorporación de nuevos medicamentos en un hospital. *Rev Calidad Asistencial* 2004; 19: 312-318.
- 10) Consejería de Salud, Junta de Andalucía. Metas y líneas prioritarias de actuación. Tercer Plan Andaluz de Salud 2003-2008. Seville: Consejería de Salud, Junta de Andalucía, 2003.
- 11) Regenauer A, Schmidtke J. Genetics. Basis for medicine in the 21st century. An introduction to genes, diseases and genetic tests. München: Munich Reinsurance Company, 1998.
- 12) McNally E, Cambon-Thomsen A, Brazell C, Cassiman JJ, Kent A, Lindpaintner K et al. 25 recomendaciones sobre las repercusiones éticas, jurídicas y sociales de los tests genéticos. Brussels: European Commission / Community Research, 2004.
- 13) Haddow JE, Palomaki GE. ACCE: a model process for evaluating data on emerging genetic tests. In: Khoury MJ, Little J, Burke W, editors. *Human Genome Epidemiology. A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease*. Oxford: Oxford University Press, 2004. pp 217-233.
- 14) Gwinn M, Khoury MJ. Epidemiologic approach to genetic tests: population-based data for preventive medicine. In: Khoury MJ, Little J, Burke W, editors. *Human Genome Epidemiology. A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease*. Oxford: Oxford University Press, 2004. pp 195-206.
- 15) Department of Health. Our inheritance, our future. Realising the potential of genetics in the NHS. London: Department of Health / National Health Service, 2003.
- 16) Phillips KA, Veenstra DL, Ramsey SD, Van Bebber SL, Sakowski J. Genetic testing and pharmacogenomics: issues for determining the impact to healthcare delivery and costs. *Am J Manag Care* 2004; 10: 425-432.
- 17) Steinberg EP, Tunis S, Shapiro D. Insurance coverage for experimental technologies. *Health Aff* 1995; 14: 143-158.

- 18) U.S. Preventive Services Task Force. Guide to clinical preventive services, 2nd ed. Baltimore: Williams & Wilkins, 1996.
- 19) Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. for the Methods Work Group, Third U.S. Preventive Services Task Force. Current methods of the U.S. Preventive Services Task Force. *Am J Prev Med* 2001; 20 (3 Suppl): 21-35.
- 20) Goel V for Crossroads 99 Group. Appraising organized screening programmes for testing for genetic susceptibility to cancer. *BMJ* 2001; 322: 1174-1178.
- 21) Smith JE, Winkler RL, Fryback DG. The first positive: computing predictive value at the extremes. *Ann Intern Med* 2000; 132: 804-809.
- 22) Winkler RL, Smith JE. On uncertainty in medical testing. *Med Decis Making* 2004; 24: 654-658.
- 23) Marteau T, Lerman C. Genetic risk and behavioural change. *BMJ* 2001; 322: 1056-1059.
- 24) Grimes DA, Schulz KF. Uses and abuses of screening tests. *Lancet* 2002; 359: 881-884.
- 25) Kmet L, Lee RC, Cook LS, Lorenzetti D, Godlovitch G, Einsiedel E. Systematic review of the social, ethical, and legal dimensions of genetic cancer risk assessment technologies. Calgary: Alberta Heritage Foundation for Medical Research, 2004.
- 26) Burgermeister J. Switzerland has opened door to genetic discrimination, say ethicists. *BMJ* 2004; 329: 70.
- 27) Parker M, Lucassen A. Genetic information: a joint account? *BMJ* 2004; 329: 165-167.
- 28) McConkie-Rosell A, Spiridigliozzi GA. "Family matters": a conceptual framework for genetic testing in children. *J Genet Couns* 2004; 13:9-29.
- 29) Ontario Report to Premiers. Genetics, Testing & Gene Patenting: Charting New Territory in Healthcare. Ontario: Ontario Report to Premiers, 2002.

- 30) Giacomini M, Miller F, Browman G. Confronting the "gray zones" of technology assessment: evaluating genetic testing services for public insurance coverage in Canada. *Int J Technol Assess Health Care* 2003; 19: 301-316.

6. ANNEX I:

LIST OF QUESTIONS BASED ON THE ACCE MODEL¹⁰ (13)

Health problems and context

1. What is the health problem that is to be studied?

It should be a relevant problem and should be defined on the basis of clinical characteristics, not on laboratory results (example: hypercholesterolaemia would not be considered as a health problem, instead the problem would be cardiovascular disease).

2. What genetic tests are associated with the health problem?

There can sometimes be more than one relevant test (for example, in deep vein thrombosis, DNA analysis for Leiden factor V and for prothrombin genes can be performed).

3. Is it known whether there are polymorphisms or mutations in other genes that offset the effect of the mutation under study?

There can sometimes be mutations in other genes which influence the correlation of the mutation under study and the phenotype, as they have effects which offset that of the mutation of interest.

4. In what clinical context is the genetic test going to be conducted?

It has to be defined whether the test is going to be conducted to confirm a diagnosis, to identify the susceptibility to a disease, for screening purposes or in order to determine the probability of a certain response to a treatment.

5. What is the initial selection strategy for the screening population?

It must be made clear whether this concerns screening of family members of a index case, of patients with symptoms, the newborn with a family history, prenatal test, etc.

6. What other questions or tests are to be used in the strategy for selecting the candidate population for the genetic test?

These may concern criteria that are used simultaneously or in series (for example, only if one criterion is positive should one move on the following one).

Analytical validity

7. Are there commercially available kits or are the tests prepared in each laboratory?

8. Is the genetic test quantitative or qualitative?

In general, the results of DNA tests are qualitative (mutation present or absent), although they are sometimes quantitative (example: number of repetitions of base pair sequences in the fragile X chromosome syndrome). Although in practice quantitative results are usually reclassified, they should be considered as continuous variables in the study of analytical validity.

9. What is the sensitivity of the test in relation to the genotype?

Proportion of positive results when the mutation is present. Sensitivity should be presented with its confidence interval. External assessments, published studies on validation and comparison of methods can all stand as sources of information on sensitivity. Only samples with a known genotype can be used to calculate sensitivity directly.

10. What is the specificity of the test in relation to the genotype?

Proportion of negative results when the mutation is not present. For DNA tests this has to be close to 100%. The problem is to obtain accurate estimates since the confidence intervals using binomial distribution are broad and very large samples would be needed in order to narrow them down.

11. If necessary: how was confirmation performed to tackle the problem of false positives?

Confirmatory analyses are only usually performed for positive results and are important above all when a certain assay is known to produce this type of result occasionally. Confirmation can be achieved through a second analysis of the same sample or by using a different technology.

¹⁰ ACCE: Analytic validity / Clinical validity / Clinical utility / Ethical, legal & social implications.

12. Has an internal quality control programme been defined and has it been monitored externally?

Quality control programmes refer to laboratory procedures designed so that the tests run correctly (quality reagents, well-calibrated equipment, etc.). These may follow recommendations of professional organisations and be accredited externally. A key aspect of these programmes is quality control performed on control samples (samples with known genotype, negative and positive, which are used as controls in the assays). The failure rate in the analysis of these samples is a key indicator of quality.

13. Has the intra-laboratory variability been measured?

This question applies to quantitative tests, making repeated measurements on a single sample.

14. What is the reproducibility between laboratories?

Evidence must be presented of the reproducibility of the results in different laboratories using either the same or a different technology.

Analytical validity

15. What is the sensitivity of the test in relation to the phenotype?

Proportion of positive results when the disease is present (or will be in the future). When the test is negative in an individual with the disease (false negative) it is not usually due to an error of the test, but because there are other causal agents distinct from the mutation under study.

16. What is the specificity of the test in relation to the phenotype?

Proportion of negative results when the disease is not present (or will not be in the future). Positive results in individuals without the disease (false positive) can occur due to error in the test, although it is more frequently due to the lack of penetrance of the gene.

17. Are there methods for resolving false positives within a reasonable length of time?

Clinical false positives are relatively rare when penetrance is high and frequent when penetrance is low. The problem here is that individuals who really do not have or will not develop the disease would be treated. As

a result, when the genetic test gives a positive result, there may be other diagnostic tests that can rule out the disease when it is not present.

18. What is the prevalence of the disease in the defined context?

Prevalence is important for estimating positive and negative predictive values. It is also important to bear in mind that prevalence may vary depending on certain population characteristics (for example, among racial groups), which means that predictive values have to be assessed for each population group.

19. What are the positive and negative predictive values?

These values are calculated taking into account the test's sensitivity and specificity, clinical sensitivity and specificity and prevalence.

20. What is the relationship between genotype and phenotype?

There are two important aspects in this relation. One is the concept of penetrance, which really corresponds to the positive predictive value. The other is that different mutations of a single gene can give rise to different forms of the disease.

21. What is known about other genetic or environmental factors that can modify the effect of the genotype under study?

The information on interactions between genes or between gene and environmental factors may be important in predicting individual risk.

Clinical utility

22. What is the natural history of the disease?

This can help to determine whether or not it is important to incorporate the genetic test into clinical practice, and also to define the ideal age for performing the test.

23. Is there any effective and acceptable intervention or other kind of benefit derived from performing the genetic test?

This issue is crucial. If the health problem cannot be avoided or has no effective treatment, then it is difficult to justify its detection in clinical practice. Nevertheless, one possible benefit in unavoidable cases where no treatment is available may be that uncertainty is dispelled (e.g., family members of individuals with Huntington's chorea).

24. Is there any information on the degree of participation that can be expected (of all those to whom the test is offered, what percentage of individuals would accept to undergo the test)?

This type of information can provide an idea of the acceptability of the test.

25. Is it possible to have good accessibility to the intervention?

It is important to explore this aspect of introducing a new genetic test into practice, including accessibility to genetic counselling, apart from any therapeutic or preventive intervention. The lack of accessibility could considerably reduce the effectiveness of the intervention in the susceptible population.

26. What are the health risks that may result from performing the test and the intervention?

The possible adverse effects that should be taken into account are the morbidity and mortality associated with the use of other diagnostic or therapeutic procedures following a positive result in the genetic test. It is also important to determine if information is available on other risks such as anxiety and the effect of "label of illness" in those cases with a positive test.

Implications for the health services

27. What are the services required for using a new genetic test in clinical practice?

In other words, what services will have to be organised to provide for the care needs of patients both before and after the genetic test (genetic counselling service, prevention programmes, provision of new diagnostic tests, delivery of treatments, etc.). This would also include quality control programmes for the clinical laboratories involved.

28. What is the foreseeable impact on the use of services?

This refers to estimating the use of health resources following a positive test, both by patients and by family members, including all possible services (from genetic counselling to the delivery of treatments).

29. What human, material and economic resources are required for the provision of the necessary services?

This is a question of making the necessary calculations to estimate the resources required to cope with the demand expected from each of the components of the genetic services. For this purpose, the starting point should be the resources that are already available followed by assessment of whether they are sufficient or whether additional resources are required. Here, it is useful to consult with experts and analyse resources on other similar programmes.

30. What are the possible economic benefits associated with conducting a genetic test?

The analysis of benefits is generally limited to financial benefits in terms of reducing care costs. Nevertheless, the ideal analysis should quantify other types of benefits such as the increase in life expectancy and quality of life.

31. Are there any results from pilot studies on the implementation of the genetic test?

Pilot studies assessing the transition of tests from the research phase to routine application in health care practice may be available. These studies can provide some indication concerning the response of individuals to the genetic tests (acceptance, decision-making process), as well as economic information.

32. Are there any educational materials available that are effective in making the information readily understandable?

It may sometimes be necessary to translate or adapt materials from other contexts and to validate them so that the information can be readily understood by those with a lower level of education. These materials would assist in the process of informed consent.

Ethical and social implications

Pilot studies can provide information on the possible social impact and ethical issues, although actually the overall experience obtained from using genetic tests can be useful for making an assessment. With this experience, recommendations can be drawn up and strategies planned to avoid a negative impact.

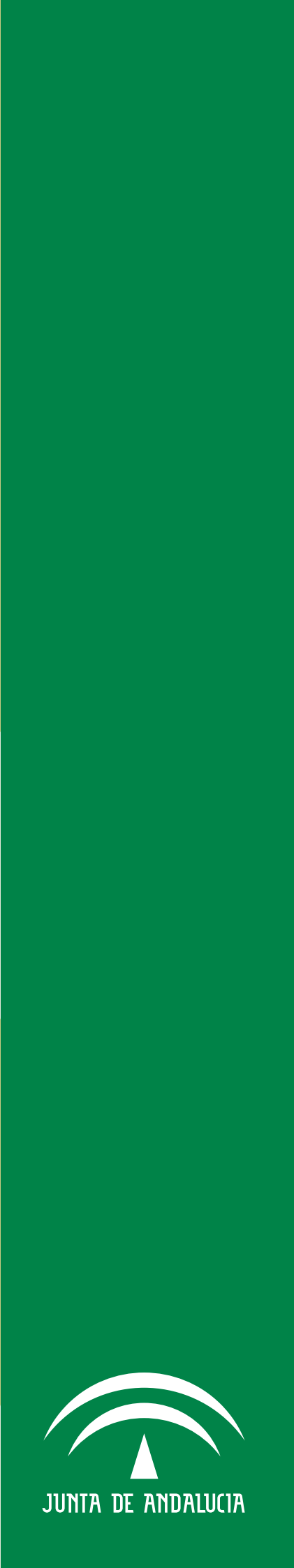
33. What information is available on the impact of the test in terms of stigmatisation, discrimination and inequality in health?

34. What procedures are useful in making informed consent effective?

35. What are the key aspects for achieving confidentiality and privacy?

36. What are the implications of performing a genetic test on the family of the individual who undergoes the test?

37. Are there any legal issues concerning the ownership of the data and samples, the patent of the test or other related issues?



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