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August 2005

Clinical validity and utility of genetic testing – the viewpoint of a clinical geneticist.

Definitions:

Clinical validity in genetic testing is a measurement of the accuracy (such as clinical sensitivity and specificity as well as predictive value) with which a test identifies or predicts a clinical condition.

Clinical utility refers to the ability of genetic test results, either positive or negative, to provide information that is of value in the clinical setting.

Although clinical validity and clinical utility are going to be important criteria in the decision making process of whether or not to offer and apply a genetic test, the development of standards and hence guidelines within the scientific community and health care providers of how to assess clinical validity and clinical utility are still in its infancy.

In order to establish such a framework, factors that will have to be considered include:

1. Scope of genetic testing
2. The clinical setting of genetic testing
2.1 Diagnostic
2.2 Predictive
2.3 For reproductive choice

1. Scope of genetic testing

The primary focus of genetic testing is to serve health purposes, which is the area to which this commentary is confined. Other potential applications are becoming visible, including genetic testing for employment purposes, insurance purposes, and, for genetic traits influencing physical and mental performance, to aid in educational choices and in forensic decisions. While genetic testing in medicine is sufficiently far advanced to argue for setting standards regarding clinical validity and clinical utility, genetic testing in the other named areas is currently of little practical importance. A recommendation would be here to warn against unfair discrimination in these areas in general terms, and mandate Human Genetics Commissions to be set up in all member states to observe these fields for the need of specific actions to be taken.

2. The clinical setting of genetic testing

Measures of clinical validity and clinical utility are likely to differ in scope and weight depending on the setting in which genetic testing is being performed. Numerical risk figures as a deciding factor, for example, could differ greatly depending on setting and impact of a condition: a 0.5% risk for Down's syndrome is universally seen as the lower bound of an indication for a prenatal test, whereas a 20% for developing breast cancer is seen (in France and Germany) as the lower bound at which to offer a search for a predisposing mutation. The utility of genetic testing will also depend on the way testing is integrated into genetic counseling. Pre-test counseling enables the counselee to make an informed choice, taking into account subjective benefits or threats that may follow from testing. An important element of post-test counseling is to assure that the counselee makes the best possible use of subsequent clinical management offers. The clinical validity of genetic tests is quite variable. In particular, the test sensitivity can be low due to allelic and/or locus heterogeneity (multiple alternative disease causing mutations in one gene and/or more than one gene is responsible for the disease), features which are the rule rather than the exception in most genetic conditions.

2.1 Genetic testing to diagnose a disease already manifest in the tested individual

In approximately one half of all known, usually rare, monogenic diseases the causative gene mutation is now principally identifiable, and, for a small number of frequent complex diseases, the predisposing genetic factors have been identified. If an individual is already clinically affected, genetic testing may thus serve to

- confirm a specific clinical diagnosis
- resolve a differential diagnosis

A correct genetic diagnosis may

- save the patient from undergoing other diagnostic procedures which may include risky and/or costly measures
- direct clinical management, including therapy
- be of psychological significance even in the absence of a specific therapy
- help to manage non-medical but individually important life planning aspects

In what way a positive test result influences the clinical management and hence outcome (clinical utility) is also variable. In the case of metabolic diseases, for example, specific therapies might ensue, whereas surgical interventions in dysmorphologies, as an other example, might be entirely independent from the underlying genetic cause. Any assessment of the clinical utility should, however, also include the benefits of sparing the patient from other diagnostic procedures, as well as the alleviation of the burden of not having a correct diagnosis. It is well known from empirical studies (www.eurordis.org) that a prolonged pre-diagnostic phase of symptomatic patients can be traumatic in itself to either the patient or his or her family (in particular parents of an affected child). Not having a diagnosis often causes general mistrust in the health service and hence generally lowered compliance and/or resorting to doubtful alternatives outside school medicine.

2.2 Genetic testing to predict the future health status of a healthy individual

Predictive genetic testing of seemingly healthy people can principally be applied individually or collectively. An individual approach is chosen when the person is at recognizably elevated prior risk to develop a specific disease because of a relevant family history. A collective approach could either be applied generally (e.g. newborn screening for metabolic disorders), or to subgroups preselected on the basis of risk factors. An intermediate approch is referred to as "cascade screening", where a patient's relatives, assumed to be unaware of their health status, are actively approached.

Genetic testing in healthy individuals at increased risk based on family history is frequently offered in the case of late-onset (adult age) disorders, particularly familial cancer (breast, bowel, thyroid, and others) and neurodegenerative disorders (including Huntington's disease and cerebellar ataxias), but also to children, if there is a proven clinical benefit ensuing from testing before adulthood. If, when there is allelic and/or locus heterogeneity, the particular disease causing mutation in an affected relative is known, or if there is genetic homogeneity, all measures of clinical validity usually approach 100%. Clinical utility of such testing will differ between conditions and will depend on the test result. If a disease is preventable (e.g. thyroid cancer by elective presymptomatic thyroidectomy), the benefits of a positive test result are obvious. If there are proven benefits of early detection, test-positives may be told to follow a stricter regimen of early detection protocols. If there are no known clinical benefits of early detection, a usually small minority of at-risk individuals nevertheless find it psychologically assuring to know the truth, and this fact alone may be clinically relevant. Undisputed benefits arise in test-negatives, who are nearly always released from psychological load, and find themselves in a situation to opt-out of otherwise burdensome and/or costly early detection programmes.

Genetic factors associated with complex diseases usually confer minimal changes in relative disease risks. For none of these diseases have clinical validity and utility of such testing been properly evaluated, but these measures are likely to be low.

Predictive tests offered to the population at-large (e.g. newborn screening for phenylketonuria) are traditionally being offered with strict respect to the relevant WHO guidelines. These principles are

recently becoming eroded by newborn screening offers for extremely rare conditions and less clear clinical utility, paying tribute to technical developments.

2.3 Genetic testing to aid reproductive choice

2.3.1 Carrier testing

Carrier testing for autosomal-recessive disease is widely practiced in developed countries with ethnicities characterized by particularly high disease-causing allele frequencies, such as beta-thalassaemia in Mediterranian countries, or Tay-Sachs disease in Ashkenasim Jews. Such testing is usually carried out in the format of formal, community run programmes, with clinical validity and utility well established. Due to the high acceptance rates of such test offers, the prevalence of the diseases in question has sharply declined in these populations. In the USA, carrier testing is also being offered for cystic fibrosis (professional boards advising their members to offer such testing to the pregnant population). This contrasts with the situation in Germany, for example, where professional boards have advised against any population-wide screening, while supporting test offers to consanguinous couples or to those originating from a culture with established screening programmes.

Carrier testing for recessive and also (late-onset) dominant disorders is frequently sought by individuals who are at an elevated genetic risk due to family history and are planning a pregnancy. For such individuals a dilemma arises if family planning is considered a private matter and not a part of public health care (or not included in private health insurance), but if their health care provision system would consider it as a medical act to test for the same condition during pregnancy. This dilemma is further complicated by the discussion around the morality of the "tentative pregnancy" as a matter of principle. Most clinical geneticist would argue that genetic testing to enable reproductive choice prior to a pregnancy is a medical act and as such of high clinical utility.

2.3.2 Prenatal and preimplantative testing

Prenatal testing can be both diagnostic and predictive. Many of the aspects arising in the context of prenatal and preimplantative testing have thus already been discussed in chapters 2.1 and 2.2. Prenatal and preimplantative genetic testing and screening present the additional complication that both the interests of the developing human life (fetus, embryo) and of the pregnant or pregnant-to-be woman have to be considered. These interests may be congruent or conflicting, and clinical utility of testing may thus have different connotations.

Prenatal diagnosis may lead to specific therapeutic interventions or set the stage for early post-delivery management in the interest of the child, and some of these measures are of proven benefit (e.g. cortisol treatment of the pregnant women to prevent masculinisation in female fetuses affected by AGS). On the other hand, an adverse outcome of a prenatal test may lead the pregnant women to opt for termination of pregnancy. Although this prevents the birth of a child with a certain disease, this measure should not be seen as a way of disease prevention as discussed in chapter 2.2. If, as is the case in many national legal frameworks, termination of pregnancy is medically indicated in the interest of the mother, whose well-being would be endangered by a continuation of pregnancy, prenatal diagnosis and its consequences would be of undisputable clinical utility. The possible physical and psychological consequences of abortion must, however, be taken into account.

While the clinical validity of prenatal genetic testing is similar to postnatal measures, measures of clinical validity of prenatal screening employing maternal serum markers and/or fetal ultrasound are usually much lower.

Conclusions and outlook

It is premature to mandate ensurance that genetic testing in clinical services meet professional standards of clinical validity and utility, because there is as yet no consensus within the scientific community and among health care providers as to how clinical validity and clinical utility ought to be measured. It is to be expected that depending on type of disease, clinical setting, disease prevalence, economic constraints, as well as ethical, legal and social considerations, such standards will neither be universal nor comprehensive, and that standards might only be developed so as to give general guidance. The utility of genetic testing will also depend on the way testing is integrated into genetic counseling.It is foreseeable that standards will more easily be developed for frequent diseases, where approved procedures of evidence-based medicine can be applied. In the case of rare diseases a higher degree of opinion-based medicine and a case-by-case approach will need to be accepted when decisions for or against performing genetic tests have to be made. Largely unsolved problems are the level of numerical risk and the severity of any one condition that might set thresholds below which clinical utility of a test is no longer defendable. It can be argued that in private health care, it is entirely up to the client to make an informed choice, whereas in public health care systems with ressources usually limited by law, health economy aspects become part of the decision making process. Another unsolved problem is the scope of the term "clinical utility", whether it should be defined in a narrow sense or whether it should include psychological and social dimensions, including family planning.