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What is the clinical utility of genetic testing?

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Evidence-based guidelines on the use of genetic tests in clinical practice require a systematic assessment of their usefulness, which, following a commonly used framework proposed in 1998 by a U.S. Task Force on Genetic Testing, is commonly referred to as clinical utility.[1] Clinical utility in its narrowest sense refers to the ability of a screening or diagnostic test to prevent or ameliorate adverse health outcomes such as mortality, morbidity, or disability through the adoption of efficacious treatments conditioned on test results.[2] A screening or diagnostic test alone does not have inherent utility; because it is the adoption of therapeutic or preventive interventions that influences health outcomes, the clinical utility of a test depends on effective access to appropriate interventions. This use is consistent with standard practice in evidence-based medicine, which focuses on objective measures of health status to evaluate interventions. Clinical utility can more broadly refer to any use of test results to inform clinical decision-making. Finally, in its broadest sense, clinical utility can refer to any outcomes considered important to individuals and families (e.g., reproductive decisions and psychosocial support). The field of genetic services, notably genetic counseling for Mendelian disorders, has emphasized the latter aspects of genetic testing.[2]

This commentary was prompted by a discussion at a workshop on the evaluation of genetic testing sponsored by the Centers for Disease Control and Prevention (CDC) in January 2005. The participants were a diverse group of experts in evidence-based medicine and genetics. The term "clinical utility" was familiar to many participants, and those who used the term were confident that they knew what it meant. However, there was no consensus as to what the term meant, with subgroups holding to different interpretations. This diversity of opinion led us to reflect on the meaning of the term and to review its previous uses. We came to realize that different definitions corresponded to different analytic and disciplinary or policy perspectives.

We concur with Scheuner and Rotter[3] that multiple perspectives should be considered in the evaluation of genetic testing, a conclusion that we had already reached. This commentary is a first response to their recent editorial. Only by making different perspectives explicit is it possible to reach agreement on the key endpoints to use in evaluating genetic testing for different audiences and purposes. Although different groups will not necessarily agree on which endpoints are most important, which involves value judgments and priorities, we hope that we can contribute to the clarification of these differences of opinion. The utility of genetic testing has different dimensions (public health, clinical, personal, and social), and the term "clinical utility" may be too limiting.

In this commentary, we review the evolution of the concept of clinical utility of biochemical or molecular testing for genotypic variations associated with risk of disease. Potential health-related applications include screening, diagnostic, and carrier testing for single-gene disorders, testing of multiple loci to construct disease susceptibility risk profiles, and pharmacogenomic testing to predict drug–genome interactions. Most applications to date fall under the single-gene category, but more are expected for common diseases with complex genetic contributions and gene–environment interactions. We do not consider non–health-related uses of genotyping, such as testing for physical traits such as athletic ability.[4]

THE EVOLUTION OF THE CONCEPT OF CLINICAL UTILITY OF GENETIC TESTING

In 1997, the National Institutes of Health–Department of Energy Task Force on Genetic Testing proposed three criteria for the evaluation of genetic tests: analytic validity, clinical validity, and clinical utility.[1] By clinical utility, the report referred to "the balance of benefits to risks": "Before a genetic test can be generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks that accrue from both positive and negative results."[1] In enumerating potential benefits and risks, the Task Force explicitly included social and psychologic benefits and burdens or harms of genetic information, such as the ability to avoid the conception of an affected child, reduction of uncertainty, increase in anxiety or fear of discrimination, and complacency from negative test results that can result in unhealthful behaviors. That is, an assessment of the ethical, legal, and social implications (ELSI) of a genetic test was explicitly considered as an aspect of clinical utility.

The report of the Task Force on Genetic Testing[1] led to the chartering in 1998 of a Secretary's Advisory Committee on Genetic Testing. In a report that called for enhanced federal oversight of genetic testing, the Secretary's Advisory Committee on Genetic Testing followed the Task Force in stating: "Clinical utility takes into account the impact and usefulness of the test results to the individual, the family, and society. The benefits and risks to be considered include the psychological,

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social, and economic consequences of testing as well as the implications for health outcomes."[4] Even in the absence of clear benefit in reducing the burden of illness and death, benefits such as the minimization of diagnostic delays, reproductive health planning, and psychosocial support were considered as constituting evidence of clinical utility.[5]

Many investigators have distinguished clinical utility, defined in terms of impacts on morbidity and mortality resulting from the use of test results, from ELSI, which refers primarily to the psychosocial outcomes of testing. For example, an influential article stated: "Clinical utility refers to the likelihood that the test will lead to an improved health outcome."[6] In that article, health outcomes referred to endpoints such as diagnosed cancer or mortality. Social issues, such as discrimination, stigmatization, and psychologic harms, were separately listed under a fourth category, ELSI.

The term clinical utility was elaborated by the *A*nalytic validity, *C*linical validity, *C*linical utility, and *E*thical, legal and social implications (ACCE) project that was carried out by the Foundation for Blood Research with support from the CDC.[7] Clinical utility in the ACCE framework was broadened to include contextual or implementation issues (e.g., availability of resources to support testing and data on acceptability in practice). The ACCE project addressed five clinical scenarios, involving tests for genotypes associated with cystic fibrosis, breast and ovarian cancer, hemochromatosis, venous thromboembolism, and colorectal cancer. Although the primary focus of clinical utility in the ACCE framework was put on the use of test results to inform the adoption of remedies to avoid clinical manifestations, that is, morbidity or mortality, the investigators suggested that clinical utility could also be associated with endpoints such as psychologic benefits from testing family members for Huntington disease.[7]

Reports from the CDC and other groups influenced by the ACCE model have associated clinical utility with health benefits, defined in terms of clinical endpoints.[8] For example, a CDC report that evaluated newborn screening for cystic fibrosis defined clinical utility as the "net balance of health outcomes," referring to endpoints such as growth, lung function, hospitalizations, and infections.[9] Further, earlier diagnosis of cystic fibrosis influences clinical management of the disease, allowing for prompt administration of pancreatic enzymes and aggressive treatment of infections, therapies that are believed to improve outcomes. Psychosocial risks and benefits to individuals and families were also considered in the report, but separately from clinical utility. The Genetic Testing Network Steering Group and the Public Health Genetics Unit in the United Kingdom have also adopted the ACCE framework and refer to "outcomes" and "net benefit" without specifying which endpoints should be included under clinical utility.[10]

CLINICAL UTILITY, VALUE OF INFORMATION, AND OTHER ATTRIBUTES

The ability to inform clinical practice and to influence outcomes not directly related to health status may also be important benefits of genetic testing. A proposed framework for the evaluation of diagnostic testing in general clinical medicine provides a useful hierarchy for considering the potential benefits of genetic testing.[11] Beyond feasibility and validity of the test, four levels of impacts are considered: diagnostic thinking, therapeutic choice, patient outcome, and societal impacts. Diagnostic thinking refers to the value of information in understanding the diagnosis, cause, and prognosis. Therapeutic choice refers to the use of test results in clinical management of an individual with a diagnosed disorder. Patient outcomes refer to endpoints such as mortality or quality of life, and societal impacts include cost-effectiveness. From the clinical perspective, diagnostic thinking and therapeutic choice may constitute the basis of clinical utility, even absent data on health outcomes.

The potential informational benefits of genetic testing to individuals and families have received increased popular attention. In particular, demand from consumers and marketing by commercial laboratories and test developers have emphasized the value of information per se. This includes direct-to-consumer marketing of nutrigenomic, immunogenomic, and cardiogenomic profiles.[2] The potential value of genotypic information to individuals includes better understanding of their own prognosis, risk, or susceptibility to disease, or that of family members to disease, whether that knowledge affects clinical management decisions or not. The ability to understand the cause or diagnosis of a disorder or to predict the risk of developing a disorder at a later time may be viewed by many people as important benefits even in the absence of specific interventions to reduce morbidity or mortality. For example, a survey of preferences for adult cancer screenings reported that the majority of respondents considered screening to be of value even if positive test results would not lead to any change in action or outcomes and regardless of invasive procedures after false-positive screens.[12]

The shift to a broader perception of benefits is particularly noticeable in newborn screening, the one type of genetic testing that takes place within the public health sector in the United States. In the past, newborn screening was initiated and justified in terms of the prevention of deaths and severe disability through initiation of special diets and other therapies in the first months after birth. Increasingly, parent advocates and experts are arguing for the expansion of newborn screening at least in part on the basis of benefits to families, including reductions in diagnostic odysseys, the ability of parents to avoid having subsequent affected children, and the parents' "right to know" if their child has a serious genetic disease or risk of disease. This paradigm shift, if implemented in newborn screening, will have important implications for public health policy and genetic testing.[13] Translation of individual nonhealth benefits into societal values and decisions on how they should factor in the allocation of scarce public health resources are complex issues.

Our own perspective is that of public health, and we have argued elsewhere that health impacts that can be measured at the population level are crucial for setting public priorities for health interventions and for assessing the public health utility of genetic testing.[8,14] Contrary to a recent commentary on our

work,[3] this does not mean that we do not consider other perspectives to be important. We understand that from the clinical perspective there can be value in diagnostic testing even without evidence of improved health outcomes, and that testing may be incorporated in clinical practice on that basis.[11] Further, we agree that consumers have a legitimate interest in obtaining access to services that they consider to provide good value for money, and we believe that they should have the freedom to use their own resources in this way. Nevertheless, it is questionable that third-party payers, public or private, should be obligated to pay for services that lack a demonstrable health impact.

We believe that whatever the perspective, outcomes need to be measured using objective metrics. For example, Scheuner and Rotter[3] argue that even in the absence of genotype-specific interventions, genetic testing may lead to incremental population health benefit if (1) the interventions are more effective in people with particular genotypes, (2) persons with specific genotypes are more compliant in the uptake of interventions, and (3) genotype results are integrated into overall risk assessment along with nongenetic data. These arguments are plausible, but there are few empiric data presently available to support them.

CONCLUSION

As the availability of genetic tests expands, especially in the area of susceptibility to common chronic diseases, and pressures for coverage by payers increase, it is important to evaluate the outcomes that matter to decision-makers. These outcomes include not just clinical endpoints but other factors as well. Because of its association with clinical endpoints, the term "clinical utility" may be too restrictive; we suggest that utility is a more encompassing concept of net benefit. In particular, we suggest that psychosocial, ethical, legal, and social issues be considered as sources of social utility because they contribute to the net balance between benefits and harms of genetic testing for tested individuals, their families, and the population at large. Although we propose a broad definition of utility of genetic testing, including clinical and social, we continue to believe that improvements in health outcomes—morbidity, mortality, and disability—should be primary endpoints in assessments of the utility of genetic testing.[8]

Decision-makers or stakeholders may have varying opinions as to which outcomes are considered relevant. Therefore, the types of outcomes that must be considered in evaluating the utility of a genetic test depend on the purpose of the test and the audience of decision-makers. For a state-funded public health program, the impact on morbidity and mortality is likely to be the most critical factor. Coverage decisions by third-party payers may be based in large part on perceptions that test results are useful for timely or accurate diagnosis and clinical management. For a test that is offered to families in a clinical setting on a voluntary basis, the value of information for making career, residential, and reproductive decisions takes on greater relevance.

In 2004 the CDC launched the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative to conduct evidence-based assessments of specific genetic and genomic applications. The EGAPP Working Group, a nonfederal independent panel, is currently compiling a list of outcomes from which to select specific outcomes to be addressed in assessments of pilot topics over the next 2 years. We hope the experience gained from the EGAPP initiative will lead to an enhanced dialogue among stakeholders as to which specific endpoints are important for assessing specific genetic tests rather than a "one size fits all" evaluation of the utility of genomic applications.

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