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## Genetic Services Policy Project Final Report

### **Chapter 4: The Role of Cost-Effectiveness Analysis in Decision Making about Genetic Services**

As the number of genetic tests on the market has increased rapidly, so has the number of cost-effectiveness analyses evaluating genetic technologies. Our literature review identified 63 peer reviewed articles that systematically compared costs with some measure of benefit (e.g., years of life saved or gained, bad events prevented, cases detected) between 1990 and 2004 (Carlson et al. 2005; Veenstra et al., 2007).

Several factors contribute to the increase in popularity of the cost comparative studies. First, genetic technology is growing at a pace that prohibits reliance on the traditional guide to appropriate use of medical service: clinical experience. Second, the new technology often comes with a hefty price tag. BRCA1/2 testing, for example, can cost nearly \$3,500 (www.dnadirect.com). Coverage decisions of insurance companies and other third party payers have important consequences for test use, insurance premiums, and profits of both payers and test manufacturers. Third, Medicare is both a large and a public payer, without the option of either raising premiums or dropping enrollees in response to higher health care expenditures. A fourth factor is the increased amounts of public and private research funding available to conduct cost comparative studies.

This trend would appear to be strictly positive. When faced with decisions that have important clinical and economic consequences, what could be wrong with basing these decisions on careful empirical analysis? Plenty, according to a recent article published by Booz Allen Hamilton (Caruso 2008). In “The Myth of Cost-Benefit Analysis,” Caruso writes, “Cost-benefit analysis is also inappropriate for products or processes over which there are disagreements about benefits or about which outcomes are important, such as new medical technologies like genetic testing” (page 5). This chapter will draw upon both our literature review and our own cost-effectiveness analysis (CEA) of A1555G testing for aminoglycoside-induced hearing loss in cystic fibrosis patients (Carlson et al. 2005; Veenstra et al., 2007) to examine the strengths and weaknesses of cost comparative studies for genetic technologies.

#### Definitions

There are a number of approaches to cost comparative studies. All share the same basic conceptual framework: costs or negative consequences of a decision or action (e.g., administering the test) are listed on one side of the balance sheet and benefits or positive consequences are listed on the other. From this point, however, differences arise. In *cost-benefit analysis* (C/B), all costs and benefits are monetized to facilitate comparison. This approach is typically used when analysts wish to compare very dissimilar choices: Are scarce research dollars more productively invested in developing a new genetic test or a more fuel efficient car? *CEA*, by contrast, focuses on comparing decisions with sufficiently similar outcomes that they can be compared using dollars per unit of outcome. The most common outcomes used in analyses of medical technology are life years (LYs) gained or saved or quality-adjusted life years

(QALYs).<sup>1</sup> Other outcomes are also used for specific purposes, including cases detected, cases prevented, births averted, and carriers detected (Carlson et al. 2005). Thus, CEA could address a comparison between alternative means to reducing mortality: Are research dollars more productively invested in developing a new genetic test for diabetes or for breast cancer? CEA theoretically eliminates the need for analysts to monetize the value of a life—an empirically difficult and ethically challenging undertaking. We will return to this point later.

In our literature review, these two types of cost comparative approaches accounted for 19 percent (C/B) and 53 percent (CEA) respectively of the 63 studies reviewed. The remaining four studies used cost minimization, a variant of CEA. In the discussion that follows, we will focus our analysis on CEA as the most commonly used technique in the genetics area (although our comments and conclusions apply equally to cost-benefit analysis).

### Strengths

The primary strength of CEA is the logical framework it provides for decision making. This framework is applicable to most situations. The 63 studies we found analyzed genetic technologies in 13 different disease areas. CEA provides a structure through which the analyst can identify a wide range of costs and benefits associated with a particular decision or action. In our A1555G testing study, for example, we considered the adverse consequences of avoiding aminoglycosides in the presence of bacterial infections for CF patients with a positive test result for the A1556G point mutation. We also considered the possibility of mitigating aminoglycoside-induced hearing loss with hearing aids and cochlear implants.

The results of CEA can be displayed in a simple and easy to digest format, facilitating their use by decision-makers of varying levels of research sophistication. We summarized our complex CEA for A1555G testing in the one number that has become the standard in most studies (including all 14 cost-utility studies in our literature review): the incremental cost-effectiveness ratio (ICER) per QALY. In addition to its simplicity within a single study, the ICER can be compared across studies, allowing decision-makers to rationalize resource allocation broadly among different kinds of interventions that affect QALYs.

Thus, CEA is an attractive analytical model, as evidenced by the endorsement of the U.S. Panel on Cost-Effectiveness in Medicine (Carlson et al., 2005) and its widespread use in evaluating genetic technologies.

### Weaknesses

As articulated by Caruso (2008), the biggest strength of cost comparative studies—the condensing of complex processes into simplified economic terms—is also their biggest weakness. Caruso writes, “Even when conducted with the best of intentions, the method is still problematic, because it substitutes calculation for informed and considered judgment” (page 2). If the support for CEA arises from the supposition that judgment is well informed and thus well replaced by calculation, the dilemma is that the very uncertainty that renders judgment of the decision-maker ill informed most often applies equally to the researcher. The danger is that the data inadequacies and uncertainties that face the researcher can be masked in the calculation of the ICER. Because Caruso’s focus is on the use of cost-benefit analysis in the politically-

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<sup>1</sup> When QALYs rather than LYs are used, the studies are often termed “cost utility” analyses (Carlson et al., 2005).

charged regulatory arena, she outlines the many purposeful ways that inputs into cost-benefit analyses can be manipulated within a range of reasonableness to achieve a specific desired output.

But as the quote above illustrates, even for the researcher who aspires to be bias-free, there are data minefields at every turn.<sup>2</sup> In our CEA of the A1555G test, many of the most important parameters in the model, including variant prevalence and incidence and aminoglycoside-induced hearing loss severity and timing, had to be based on a paucity of data. Often even poor data for critical variables do not exist. In these cases, researchers must either omit them from the calculus or make assumptions about their value. These omissions and assumptions *necessarily* change the results. While sensitivity analyses (changing the assumptions and assessing how the changes affect the results) can offer some indication of the importance of the assumption, it does not help the researcher choose a course of action in the case where the centrality of the assumption is confirmed. Further, when data gaps suggest multiple sensitivity analyses to account for the many possibilities (in our CEA of A1555G testing, we tested multiple values for 22 variables), the study outcome becomes a matrix rather than a single number, thus obviating the virtues of simplicity and clarity.<sup>3</sup>

Even in those rare areas where the necessary data are both complete and vetted, there are still challenges. We stated earlier that the choice of CEA over cost-benefit is made to eliminate the need to place a monetary value on life in the case of medical interventions. However, for CEA to be useful as a decision-making tool, defining the outcome as cost per QALY does not escape what is essentially the same value judgment. The central value of ICER in our CEA was \$79,300. Is that too high? There is no strictly *empirical* answer. In comparison to the most commonly cited threshold of \$50,000, the answer is “yes” (Neumann et al., 2000). However, in comparison to the second most commonly cited threshold of \$100,000, it is not (Ibid). Awkwardly, there are many such benchmarks, most of which are arbitrary and without basis in theory *because they are inherently a-theoretical* (Grosse, in press). The World Health Organization proposed a threshold of \$120,300 for the U.S. in 2005 based on a multiple of GDP per capita (WHO, 2002; Eichler et al., 2004). Thresholds based on values implied by federal regulatory decision making range from \$200,000 to \$300,000 per LY (Grosse, in press; Ubel et al., 2003; Braithwaite et al., in press). Maciosek et al. report that nearly 20 percent of the clinical preventive services recommended by the U.S. Preventive Services Task Force cost more than \$165,000 (in 2000 dollars) per QALY (2006).

Finally, cost comparative studies that report an outcome as a single composite number, either a purely monetary cost-benefit ratio or an ICER per QALY, do not provide important information about the distribution of the costs and benefits across various subpopulations. That is, two interventions, both of which cost \$50,000 per QALY, may be viewed very differently by society if the benefits accrue primarily to low income children in the first intervention and high income elderly in the second. Again, there are no theoretical or empirical means of accounting for what are pure value judgments on the part of decision makers.

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<sup>2</sup> Nearly 35 percent of the 63 articles we reviewed failed to report the direction and magnitude of potential bias.

<sup>3</sup> We have not discussed the discounting of costs and benefits to account for the differential timing of each. The appropriate discount rate to use to bring all costs and benefits to present value to allow comparison of apples to apples is the subject of an entire body of literature in itself.

## Discussion

Does CEA provide any value to decision makers? Most certainly. In the words of Russell et al. (1996), “Although CEA does not reflect every element of importance in health care decisions, the information it provides is critical to informing decisions about the allocation of health care resources” (page 1177). However, this form of quantitative analysis might best be used as part of what the Committee on Risk Characterization terms an “analytic deliberative process” that elevates qualitative logic to an equal role (Caruso, 2008). Caruso describes the process as an iterative one in which “participants question value judgments and assumptions from a fresh perspective. They challenge one another’s biases and data. “They use values and judgment as a positive force to give context and authority to traditional analysis” (page 5).

There are a number of venues in which such analytic deliberation can and does take place. The deliberation is most often among technical experts—those who have knowledge about the quantitative values and/or the modeling process. However, the expertise of the medical and economic technicians does not extend to social values. Gold et al. (2007) note that decisions based solely on quantitative analysis and technical expertise are at risk of being at odds with public notions of distributive justice and equity. They argue that the public is ready (at last) to abandon the notion that health care can be consumed without limit and to engage in prioritizing what will and will not be paid for with collective dollars.

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