One risk fits all?

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In Reply: When we initially proposed a special issue of *Journal of Clinical Oncology* devoted to the cost of cancer care to the editorial board, our objective was to inform and stimulate discussion regarding this complex and increasingly critical topic. In planning "Perspectives on the Cost of Cancer Care,"[1] we were struck by the dearth of empirical research that had been conducted on the economics of cancer care. Clearly, this situation is improving, as evidenced by recent publications in *JCO*[2-4] that stimulated the correspondence by Lopes and Gluck.

In their letter, the authors address the importance of perspective in cost-effectiveness (CE) analyses, which serves as the basis for interpreting and applying these studies. The greatest value of CE analysis is to inform decisions regarding allocation of resources from a finite pot.[5] A societal perspective takes into account productivity costs associated with cancer and its treatment. In most of the clinical literature, this perspective is not considered as (1) the empirical data are often shaped by social insurance policies within countries, (2) productivity costs have been found to vary little across treatment arms of a clinical trial (thus violating a parsimony objective of clinical research data collection), and (3) an important component of patient benefit, quality-adjusted survival, is already considered. From a theoretical perspective, these costs might be most important to consider when comparing treatments that offer different outcomes in terms of quantity and quality of life.

The CE analyses regarding trastuzumab therapy in breast cancer highlight several issues regarding the cost of cancer treatment. First, expensive drugs such as therapeutic antibodies will appear less so in adjuvant compared with metastatic settings. Furthermore, drugs for which a method exists to select patients most likely to benefit (eg, human epidermal growth factor receptor 2 expression) will have an advantage in the realm of economic analysis, especially if price was set before the characterization of the subpopulation was made. Finally, Lopes and Gluck offer several alternatives to address ethical concerns over disparities in cancer care, including governmental price controls, market-based approaches, and restructuring of current incentive structures for innovation. Space does not permit us to review the pros and cons of each of these proposals; however, we agree that as a society there is an urgent need to address the disparities in cancer care (and health care in general) that are likely to become increasingly acute as health care costs escalate.[6] The oncology community has an obligation to be informed and to participate in these discussions such that we may impact policy in service to our patients.

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One Risk Fits All?

To the Editor: In the April 10, 2007, issue of the *Journal of Clinical Oncology*, Chen and Parmigiani present a set of cancer risk estimates for counseling and management of *BRCA1* and *BRCA2* mutation carriers.[1] Based on 10 very different studies regarding the inclusion of patients, the authors calculated overall estimates for mean cumulative cancer risks at age 70. Though the authors observed significant between-study heterogeneity and discussed several possible sources, they could not explain it.

We have two concerns regarding the presented risk tables. First, the studied populations included in the meta-analysis are very heterogeneous indeed, comprising very high-risk research families (Breast Cancer Linkage Consortium) as well as high-risk families ascertained through familial cancer clinics and also cases

with Ashkenazi-based populations. In doing so, the obtained data will actually be applicable to neither of these groups nor to the population that attend family cancer clinics and are in need of tailored risk figures for counseling and management.

Second, ever since the first reports on cancer risks in *BRCA1* and *BRCA2* mutation carriers, the penetrance figures show an overall decreasing trend in subsequent studies. This is partly due to the fact that initial families that came for counseling were very strongly affected and to the fact that inclusion criteria for genetic testing have become less strict over the last decade. Indeed, in the manuscript it is mentioned that the three most recent familial cancer clinic–based studies on the penetrance of *BRCA1* and *BRCA2* mutations have lower risk estimates.[2-4] These studies seem to come closest to the current setting of familial cancer clinic counseling; therefore, we suggest that the included studies should not only be stratified by ascertainment, but also by year of publication.

Up-to-date cancer risk tables for *BRCA1* and *BRCA2* are definitely needed for counseling and management, but we suggest that we should further explore and not pool the sources of heterogeneity and variation in penetrance. By doing so, we can make cancer risk tables more population-specific with respect to sources of heterogeneity—such as ascertainment, ethnic background, family history, and possibly genotype—to facilitate tailored risk counseling.

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In Reply: We agree with De Bock et al that it is important to further explore whether and how penetrance may vary across clinical populations, and that reliable population-specific risk estimates would have a positive impact on counseling practice. Our study[1] is not to belittle the importance of this endeavor, but to provide reasonable compromises to be used in risk assessment while these questions are being addressed.

A possible source of study heterogeneity raised by De Bock et al is a decreasing temporal trend in the estimated penetrances. In Figure 1 in Chen et al,[1] we arranged studies chronologically so readers could form an opinion about this issue. The earliest study yielded higher estimates than the remainder in several age strata. Beyond this observation, however, we find it difficult to detect a clear temporal pattern. A recent population-based study by Risch et al[2] estimated breast cancer risk of BRCA1 mutation carriers by age 80 at 0.90 (95% CI, 0.77 to 0.97). This further questions the association between risk estimates and year of publication. Similar considerations apply to other sources of heterogeneity examined by the original article, which suggests that we are still at a time when a combined estimate is likely to be useful.

Estimates of the risk of breast cancer for BRCA1 by age 70 range from 0.36 to 0.71. What should a counselor do in the face of this variation? Select one of the estimates according to study characteristics, consider all studies, and present a range or risks, or rely on a compromise? Our software in BayesMendel supports all three options.[3] Selecting one of the estimates may open the door to improved tailoring, but may also be prone to errors and arbitrariness. Presenting all estimates has the advantage of being thorough about variation, but the challenge of communicating this variation and properly incorporating it into decision making can be daunting. This leaves a broad range of situations where one size, although it may not fit all, can be currently practical to many.

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