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Epidemiology matters: peering inside the "black box" in economic evaluations of genetic testing

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Cost-effectiveness analyses (CEAs) of genetic testing are increasing in frequency. Such analyses can inform providers, policy makers, and payers' coverage decisions.[1] CEAs usually measure improved health outcomes in terms of either life-years gained (LYG) or quality-adjusted life-years saved (QALYs). If the cost of purchasing a LYG or QALY through the use of a new intervention ("incremental cost-effectiveness ratio"; ICER) is favorable relative to established interventions, the new intervention is considered cost-effective (i.e., good value for money). Because cost-effectiveness estimates are dependent on assumptions, it is recommended that analysts conduct sensitivity analyses to determine how sensitive cost-effectiveness conclusions are to uncertainty in the model parameters.

It can be challenging to produce reliable cost-effectiveness estimates. One reason is that the choice of a comparison intervention can significantly alter results and the inference from such analyses. For example, universal screening may appear cost-effective relative to no testing but not when compared with targeted screening strategies. Also, costs may vary greatly between countries or health systems and depend on the methods used to estimate costs. In addition, the ICER threshold below which interventions are considered cost-effective varies between and within countries. Not surprisingly, published cost-effectiveness findings for the same application often vary from cost-saving (negative total costs) to not cost-effective.[2] Although most published CEAs in clinical genetics conclude that the genomic applications being evaluated are cost-effective[3] because most of those genomic applications lack evidence-based guidelines, it is not clear whether the genomic applications are necessarily effective or cost-effective.[4] Even for a testing application with good evidence of effectiveness, cost-effectiveness is context-dependent.

In the past year, *Genetics in Medicine* has published two original articles reporting CEAs of routine tumor testing for Lynch syndrome (LS) in patients with newly diagnosed colorectal cancer (CRC),[5,6] as well as a letter[7] that updated a previously published CEA.[8] Routine LS

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DISCLOSURE

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testing for CRC patients has been recommended by multiple bodies since 2009, beginning with the Evaluation of Genomic Applications in Practice and Prevention Working Group,[9] and it is considered a tier 1 application that warrants population- level implementation.[10] However, effective interventions are not necessarily *cost*-effective. Severin et al.[5] constructed a detailed Markov CEA model and used it to evaluate several testing strategies for LS in the German health-care context. They concluded that routine testing was very unlikely to be cost-effective relative to family history–based testing using the Revised Bethesda Guidelines (RBG) and that even RBG-based testing was unlikely to be cost-effective. In this issue of *Genetics in Medicine*, Leenen et al.[6] modeled a similar range of testing strategies in the Dutch health-care context and concluded that testing of all CRC patients 70 years of age or younger is likely to be cost-effective relative to testing younger patients only and possibly cost-effective relative to RBG-based testing. Both studies included RBG-based testing as a comparison, unlike some CEAs that compared routine testing with no testing.

Rather than create their own epidemiologic model of disease incidence and the effectiveness of surveillance in preventing cancer and death, Leenen et al.[6] borrowed estimates of health gains per proband and per relative identified with LS from the literature and applied them to empirical estimates of testing costs and uptake in the Netherlands. That modeling approach has the advantage of simplicity and can facilitate comparisons with findings of previous CEA studies. However, it leaves the epidemiologic assumptions that underpin estimates of effectiveness and cost-effectiveness inside an unexamined “black box.” Key parameters that can influence estimates of health gains resulting from identification of LS carriers include the following:

- Number of relatives tested per index case
- Uptake and adherence to intensive colonoscopic surveillance by relatives
- Age-specific incidence of CRC among carriers and the general population
- Efficacy of surveillance in reducing risk of CRC among carriers
- Distribution of CRC cases by disease stage with and without surveillance

Leenen et al. conducted sensitivity analyses that revealed that the most influential parameter in their cost-effectiveness model is the gain in life expectancy per mutation-carrying relative detected. They varied this parameter within the range of published estimates and concluded that in most cases, the ICER is less than €40,000 per LYG, which they considered a measure of cost-effectiveness in the Netherlands.

It is important to take a close look at the plausibility of the epidemiologic assumptions that underlie the published estimates of health gains from intensive surveillance of carriers. Leenen et al. cite published estimates from 11 studies ranging from 0.50 to 32.76 LYG per relative. Part of that range is explained by mixing together discounted and undiscounted life expectancy; when a 3% discount rate is applied, the range is from 0.50 to 20.97. The higher estimates come from studies that were published before much was known about the epidemiology of LS. Among studies published since 2011, the highest estimate of 8.20 LYG per relative (reported in the text as 6.9–7.2 LYG per relative) came from a Dutch modeling

study.[11] That study assumed 3.5% annual incidence of CRC among mutation carriers, which is much higher than is consistent with epidemiologic estimates of age-specific CRC annual incidence among mutation carriers (0.3 to 1.5%).[5,12] Consequently, that study may not be a reasonable basis for comparison of the cost-effectiveness of testing for LS.

The three other recent estimates cited by Leenen et al. ranged from 0.50 to 0.68 LYG per relative. Ladabaum et al.[13] and Severin et al.[5] projected that routine testing relative to no testing would add 0.50 and 0.52 discounted LYG per mutation-carrying relative, respectively. Despite the similarity of those estimates, the two studies adopted different assumptions, including the choice of discount rates (3.5 and 3.0%, respectively).[2] The cumulative incidence of CRC until age 70 was assumed by Severin et al. to be 35% and by Ladabaum et al. to be 50%; other authors have concluded that a cumulative incidence of 35% appears to be the best estimate.[14] Snowsill et al. argued that the study used by Ladabaum et al. to estimate cumulative CRC risk was subject to ascertainment bias. Conversely, Severin et al. assumed lower effectiveness of surveillance than did Ladabaum et al. (52 vs. 58%); others suggest that surveillance may have 61% effectiveness.[14]

Grosse et al. reported an estimate of 0.80 LYG per carrier detected after adjusting the model of Mvundura et al. using information consistent with the study by Severin et al.[7] One potential explanation for the difference in estimates of health impact is that Mvundura et al. used a static model instead of the Markov state-transition models used by recent studies.[5,13] An important implication is that the most informative cost-effectiveness estimates are likely to be based on fully specified state-transition models of disease incidence and progression informed by epidemiologic estimates from studies in which various sources of bias have been minimized.

Leenen et al. contend that their results are “very conservative” because their assumption of health gains is at the low end of the range of published estimates. However, the likely range of estimates of health gains from routine LS testing based on state-transition models is 0.5–0.6 LYG per mutation-carrying relative identified. Higher estimates of health gains from identifying LS mutation carriers may not be consistent with the best available epidemiologic evidence or based on recommended modeling techniques. Consequently, although the point estimates reported by Leenen et al. appear reasonable, uncertainty regarding those estimates remains. Consequently, whether testing meets the €40,000 per LYG criterion of cost-effectiveness may still be questioned and it is still unclear what cost-effectiveness criterion, if any, is used by decision makers in the Netherlands.

In addition, whether LS testing is considered cost-effective in a particular setting depends on additional factors such as the number of relatives per index case and the proportion of relatives who are tested, as well as the costs of genetic counseling.

Leenen et al. made an important contribution by integrating cost-effectiveness estimates with a population-based cohort study of routine LS testing that included empirical data regarding both the numbers of relatives tested and detected with mutations and the costs associated with such testing.[6] Routine LS testing in CRC patients up to age 70 years is probably cost-effective relative to no screening, at least in some settings, and may even be cost-effective

relative to RBG-based testing. Definitive conclusions about the cost-effectiveness of genetic tests for LS and other diseases in a given setting require a fully specified model of health outcomes resulting from the detection of carriers that is based on the best available epidemiologic estimates.

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