Identifying Persons with Lynch Syndrome: Why and How?

Uri Ladabaum

Published online: 26 October 2014
© Springer Science+Business Media New York 2014

The promise of personalized medicine rests on individualized management with emphasis on the twin goals of prevention when possible, and treatment when necessary. In the case of Lynch syndrome (LS), the paradigm of identifying persons at high risk for serious disease, and intervening to improve outcomes, can be realized.

LS, one of the most common inherited cancer predisposition syndromes, is caused by germline mutations that affect DNA mismatch repair (MMR) genes [1]. Persons with LS are at much higher risk for colorectal, endometrial, gastric, ovarian and other cancers than is the general population. Since most people with LS are unaware of their condition, the initial diagnosis is often based on analysis of preventable cancers. In persons diagnosed with LS, close colonoscopic surveillance [2] and prophylactic hysterectomy–oophorectomy once child-bearing is completed [3] can substantially decrease cancer incidence and mortality; furthermore, chemoprevention with aspirin may reduce the overall risk of cancer [4]. When an individual with LS is identified, testing at-risk relatives can determine who also carries the family's LS-causing mutation and should be offered intensive management. Unaffected relatives can follow average-risk screening recommendations.

In this issue of *Digestive Diseases and Sciences*, Gould-Suarez et al. [5] use decision analytic modeling to compare the cost-effectiveness of several strategies to diagnose LS among patients presenting with colorectal cancer. The

strategies considered rely on first applying the revised Bethesda guidelines (RBG), or first testing colorectal cancers for features suggestive of LS [abnormal immunohistochemistry (IHC) or microsatellite instability (MSI)], or proceeding directly to germline testing for mutations in the DNA MMR genes. The primary clinical effectiveness measure in the study was the number of true LS cases detected. The primary economic outcome was the mean cost to detect one case of LS with each strategy.

Decision analytic modeling can address questions that cannot be answered directly with a definitive, controlled clinical trial—although a prospective randomized controlled trial of competing strategies to identify LS, with long enough follow-up to ascertain relevant clinical outcomes, is unlikely to ever be performed, such a trial can be simulated based on best estimates for probabilities and costs derived from the literature.

Key features of a decision analysis include the time horizon and the degree to which downstream clinical and economic consequences are considered. The analysis by Gould-Suarez et al. focuses on the number of LS cases detected; it does not attempt to estimate the downstream consequences of detecting these cases. This short-term analysis has the advantage of needing a simpler model that requires fewer assumptions and model inputs than would be needed for a longer-term analysis. It has the limitation that the measure of cost-effectiveness (cost per case detected) can be difficult to interpret.

Deciding what is “cost-effective” usually requires a judgment about willingness to pay for an incremental improvement in clinical outcome. When one strategy is more effective and less costly than another (that is, it is dominant), then the choice between strategies is straightforward. But when one strategy is more effective and more costly than another one, then the acceptability of the more

U. Ladabaum (✉)
Gastrointestinal Cancer Prevention Program, and Clinical
Cancer Genetics Program, Division of Gastroenterology and
Hepatology, Department of Medicine, Stanford University
School of Medicine, 300 Pasteur Drive, Alway Bldg Rm M211,
Stanford, CA 94305-5187, USA
e-mail: uri.ladabaum@stanford.edu

Fig. 1 Graphical representation of the effectiveness and cost for each strategy depicted in Table 1, based on the study by Gould-Suarez et al. [5]. Each point represents an individual strategy, numbered as in Table 1. The slope connecting two points on the “efficiency frontier” (dashed lines) provides a visual equivalent of the incremental cost-effectiveness ratio (ICER) between strategies. Note that the dominated strategies (those that are less effective and more costly than alternatives) all lie above the efficiency frontier

effective strategy hinges on the willingness to pay for the greater effectiveness. There is some consensus, based on the estimated costs and outcomes of accepted medical practices, that an incremental cost-effectiveness ratio (ICER) of \$50,000–100,000 per life-year or quality-adjusted life-year (QALY) gained is acceptable in the US. It is more difficult to judge how much we should be willing to pay per incremental case of LS detected without knowing the downstream outcomes and costs.

Figure 1 displays graphically the clinical (LS cases detected) and economic (total cost) outcomes for each

strategy presented in Table 1 of the study by Gould-Suarez et al. [5]. The slope connecting two points reflects the value of the ICER as the incremental cost per additional LS case detected by the more effective versus the less effective strategy. The efficiency frontier (dashed line) links those strategies that are not dominated. Strategies above the efficiency frontier are less effective and more costly than other strategies (they are excluded by simple dominance), or their ICER is higher than the ICER of a more effective strategy when both are compared against a less effective strategy (they are excluded by extended dominance). Table 1 shows the ICERs of the strategies on the efficiency frontier, identifying the excluded (dominated) strategies. Note that the ICERs shown here differ from the values presented by Gould-Suarez et al., as Gould-Suarez et al. compare each strategy to a common baseline based on the mean cost per case detected. The ICERs shown here reflect the incremental cost per additional case detected as one moves from the least to the most effective non-dominated strategy.

The base case results considered in Fig. 1 and Table 1 stem directly from how the specific testing sequences were modeled by Gould-Suarez et al., and the authors’ assumptions about test performance characteristics. For this reason, they may not be directly comparable to the results of previous studies. Modeling results must always be interpreted with caution. That RBG followed by germline testing are more effective than MSI followed by germline testing in the base case of Gould-Suarez et al. results directly from the assumption that RBG are more sensitive than MSI for identifying LS—which is not supported by all studies. Also, germline testing is assumed to detect almost all cases of LS, with no consideration of “Lynch-like” cases without a germline mutation as

Table 1 Incremental cost-effectiveness of strategies analyzed by Gould-Suarez et al. (adapted from [5])

Strategy number	Testing sequence	LS cases identified	Total cost per 150,000 patients	Incremental cost per additional LS case identified
3	RBG/MSI/IHC4	3,605	\$78,423,107	[Cost/case detected = \$21,754]
4	RBG/MSI/MMR4	3,626	\$96,634,077	Dominated (simple)
6	MSI/IHC4	3,963	\$286,255,416	Dominated (simple)
2	RBG/IHC4	3,974	\$93,297,780	\$40,311
7	MSI/MMR	3,986	\$303,583,506	Dominated (simple)
1	RBG/MMR4	4,074	\$210,267,288	Dominated (extended)
9	IHC4/MSI 1	4,368	\$352,947,504	\$659,009
8	IHC4/MSI/MMR	4,370	\$375,257,030	Dominated (extended)
10	IHC4/MSI 2	4,392	\$389,732,904	\$1,532,725
5	MMR4	4,478	\$929,999,138	\$6,282,166

The strategies are ordered from least to most effective, with the number of cases identified and total costs as reported by Gould-Suarez et al. The rightmost column shows the incremental cost per additional case detected as one progresses through the non-dominated strategies

LS Lynch syndrome, RBG revised Bethesda guidelines, MSI microsatellite instability testing, IHC immunohistochemistry, MMR mismatch repair

detected by currently available technology. For such reasons, definitive conclusions about the ranking of specific strategies should not generally be drawn from the base case results of a single modeling study. Other studies and the results of extensive sensitivity analyses must be considered carefully. Figure 1 and Table 1 illustrate progressively higher ICERs as increasingly more effective strategies diagnose incremental LS cases. Which ICER is the maximum acceptable is a judgment call, but there is exponential steepening of the slope as the strategies become more effective at disease detection.

Since modeling studies are essentially thought experiments whose validity depends directly on the model structure, assumptions, and inputs, it is valuable when a new model (constructed independently from previous models) is used to explore questions previously analyzed by other published models. The study of Gould-Suarez et al. illustrates, like previous studies [6, 7], that pathology-based strategies that can be implemented with greater reliability are likely to be preferred over strategies based on ascertaining clinical criteria such as RBG, and that direct germline testing could be the preferred strategy if testing costs decreased substantially. Previously considered models with longer time horizons and ICERs in terms of cost per life-years or QALYs gained have produced results suggesting that screening for LS among persons with colorectal cancer may be cost-effective when using traditional thresholds [6, 7], that the cost-effectiveness of such screening for LS depends on testing of at-risk relatives after probands with LS are identified [6, 7], and that risk assessment followed by germline testing in the general population could potentially be cost-effective [8].

“Universal” colorectal (and perhaps endometrial) tumor testing for LS in pathology laboratories appears to be emerging as a standard of care in the US [9]. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, the National Comprehensive Cancer Network (NCCN), and other groups have endorsed tumor testing to screen for LS. In a recently released guideline [10], the US Multi-Society Task Force on Colorectal Cancer stated: “Testing for MMR deficiency of newly diagnosed CRC should be performed.” There is discretion regarding the specific testing method. While IHC can narrow down the specific LS-associated genes of interest in a patient, it is an operator-dependent test. In some settings, MSI testing may be more readily available or reliable. For universal testing programs to be successful, close integration between clinical services, including cancer genetics, is essential. Informing unsuspecting patients with cancer about abnormal tumor screening results and inviting them for genetic counseling are delicate matters.

As laboratory techniques evolve, it is conceivable that gene “panel testing” or even some version of whole-

genome analysis could be preferred on a technical basis to focused studies of a single or a few genes associated with a specific syndrome. Already, panel tests have come into clinical use, especially in cases where the differential diagnosis includes several cancer predisposition syndromes. If we contemplate applying such methods to screen broadly for LS, we will need to devise protocols and policies to deal with the additional information that could be uncovered [11]. Which findings in other parts of the genome will be curated and interpreted? Which findings will be returned to patients? How will patient consent be managed? Or turning the perspective around: in persons found to have mutations in LS-associated genes in the course of “routine” genomic screening, in the absence of any family history of LS-associated cancers, is the risk of cancer different than in the more selected patients who have had germline testing in the past?

LS is a paradigm for personalized medicine at the dawn of a new era of genomics in medicine. Modeling studies like the one by Gould-Suarez et al. remind us of the potential of current and emerging methods to find many of the persons (and families) who are affected by LS and are not aware of it—and to offer them interventions that can decrease the risks of cancer-related morbidity and mortality.

References

1. Lynch HT, Lynch PM, Lanspa SJ, Snyder CL, Lynch JF, Boland CR. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. *Clin Genet*. 2009;76:1–18.
2. Jarvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology*. 2000;118:829–834.
3. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N Engl J Med*. 2006;354:261–269.
4. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet*. 2011;378:2081–2087.
5. Gould-Suarez M, El-Serag HB, Musher B, Franco LM, Chen GJ. Cost-effectiveness and diagnostic effectiveness analyses of multiple algorithms for the diagnosis of Lynch syndrome. *Dig Dis Sci*. (Epub ahead of print). doi:10.1007/s10620-014-3248-6.
6. Ladabaum U, Wang G, Terdiman J, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. *Ann Intern Med*. 2011;155:69–79.
7. Mvundura M, Grosse SD, Hampel H, Palomaki GE. The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. *Genet Med*. 2010;12:93–104.
8. Dinh TA, Rosner BI, Atwood JC, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. *Cancer Prev Res*. 2011;4:9–22.

9. Beamer LC, Grant ML, Espenschied CR, et al. Reflex immunohistochemistry and microsatellite instability testing of colorectal tumors for Lynch syndrome among US cancer programs and follow-up of abnormal results. *J Clin Oncol*. 2012;30:1058–1063.
10. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US multi-society task force on colorectal cancer. *Am J Gastroenterol*. 2014;109:1159–1179.
11. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013;15:565–574.