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Correspondence on "Cost-effectiveness of exome and genome sequencing for children with rare and undiagnosed conditions" by Lavelle et al

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To the Editor

Lavelle et al[1] have published an important modeling assessment of exome sequencing (ES) and genome sequencing (GS) in 2 types of pediatric patients. They concluded that first-line rapid GS (rGS) is likely to be cost-effective for diagnosing critically ill babies with suspected genetic disorders relative to the standard of diagnostic care, defined as including other types of genetic and laboratory tests, which is consistent with other studies.[2,3] Lavelle et al[1] also concluded that first-line rGS dominates (costs less and is at least as effective) alternative testing strategies, including first-line rapid ES (rES). We believe that it is premature to conclude that rGS dominates rES for 2 primary reasons. First, the relative difference between rES and rGS testing costs may be substantially greater than the 14% differential assumed in their model (ie, $10,320 [±$3600] for trio rES vs $12,000 [±$3000] for trio rGS based on 2019 laboratory prices).[1] Second, the relative difference in diagnostic yield of rES and rGS may be less than the roughly 25% assumed in their model.[1] Based on published estimates, rES in critically ill babies may be, at least in some settings, similar in effectiveness while costing substantially less than rGS.[2]

In a commentary in this journal last year, we urged that published economic evaluations of GS distinguish between the price and cost (value of resources used) of sequencing and suggested that the use of microcosting data could improve the accuracy of cost-effectiveness analyses from either the societal or health care perspectives.[4,5] The health care perspective analysis by Lavelle et al[1] used "list prices adjusted to expected CMS (Centers for Medicare & Medicaid Services) reimbursement rate with a ratio of 0.96."[1] However, the "CMS reimbursement rate" only applies to Medicare Part B, which excludes inpatient care and Medicare Advantage, and is not relevant to pediatric practice. Medicaid payments, which *are* relevant to pediatric providers, are set by state programs and are lower than Medicare

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Conflict of Interest

The authors declare no conflict of interest.

payments.[6] In addition, although Medicare fees are often used as proxies for the costs of medical services,[7] it is uncertain that the Medicare Clinical Laboratory Fee Schedule is a good proxy for the cost of genetic sequencing.

The relative cost-effectiveness of rES and rGS should be informed by up-to-date evidence on costs and diagnostic performance and reflect specific clinical settings, meeting the needs of decision-makers in those settings. Our commentary cited recent estimates reporting substantially lower costs of rES than of rGS.[4] For example, in 2019, Brunelli et al[8] reported a cost of $6000 for a targeted rES gene panel in trios provided to Intermountain Primary Children's Hospital by the associated Regional and University Pathologists laboratory in Salt Lake City, Utah, which is roughly two-thirds lower than the published estimates of the cost of rGS available at the time. Similarly, Wang et al[9] reported that the cost of rES at Fudan University was one-third that of rGS in China. Both studies reported that the diagnostic yields of rES and rGS in trios were comparable in critically ill babies with suspected genetic diseases,[8,9] which suggests that the cost per diagnosis in those settings was considerably lower when using rES than rGS.

Notably, a recent review by Kingsmore and Cole[2] acknowledged that the typical cost of rES may be half that of rGS, $4000 to $5000 vs $8000 to $10,000, and the diagnostic yield for the two approaches among critically ill infants with suspected genetic disease "has been similar," which is consistent with a lower average cost per diagnosis for rES. However, technological change can alter the absolute and relative cost and diagnostic yields of testing strategies, emphasizing the importance of using up-to-date estimates that apply to the specific decision context. It should be noted that as direct analytical costs of sequencing decrease, informatics and related interpretation processes account for a growing share of the total cost of generating a clinical report. We previously reported that this trend reduced, but did not eliminate, the difference in costs between singleton ES and trio ES.[4]

Other considerations may also play an important role in decisions on optimal testing strategies. GS can identify pathogenic nonexonic variants not detectable by ES, but at the same time GS identifies greater numbers of variants of uncertain significance that can be problematic. Finally, a full economic evaluation should also consider how long it takes to report clinically actionable results. The average turnaround time for reporting results was 9.6 days for rES in the Intermountain study and 1 day in the Fudan study.[8,9] Faster turnaround times can potentially improve clinical outcomes as well as reduce overall costs by supporting earlier discharge from the neonatal intensive care unit.[10] All these issues require solid evidence to support sound decision making.

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