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# Cost or price of sequencing? Implications for economic evaluations in genomic medicine

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Given the rapid expansion of genetic testing in clinical practice and evolving coverage decisions by payers, it is important that stakeholders understand basic aspects of economic assessments of the costs and value of genomic medicine. Cost-effectiveness analyses (CEAs) of genetic tests are appearing with increased frequency in the biomedical literature.[1–5] CEA is used to assess the balance of benefits and costs (i.e., value) of an intervention, e.g., a medical technology along with the associated clinical pathways.[6,7] The benefit is the net difference in outcomes of interest to stakeholders, e.g., quality-adjusted life-years or number of diagnoses. The other side of the value equation is the comparison of total costs between the new intervention and its alternative(s). If the reduction in costs of care relative to the standard of care exceeds the costs of the intervention, the intervention is cost saving for that comparison. CEAs that consider a range of feasible intervention strategies, some of which might yield similar outcomes at lower cost, could identify the most cost-effective approach in that setting.

Findings of CEAs can inform clinical implementation and insurance coverage decisions.[7,8] Accordingly, stakeholders have an incentive to understand how the assumptions made in economic analyses can influence estimates of cost-effectiveness. Because of gaps in available data and the large number of variables in most CEAs, modelers must make a variety of simplifying assumptions. Full documentation of these assumptions and discussion of study limitations can help readers appropriately interpret cost-effectiveness findings.[9]

The term "cost" has many meanings in health care.[10] It is standard practice in economics to define cost as the value of the resources or inputs, e.g., staff time, equipment, consumables, and space, and overhead costs, that are required to produce and deliver a service.[10,11] Two methods for estimating unit costs of services are microcosting and activity-based costing.[11] Activity-based cost accounting is sometimes used by health-care systems to estimate resource costs for all services. Microcosting involves primary data collection to measure use of resources such as staff time using direct observation, staff activity logs, or survey methods.[12,13] Microcosting studies may use administrative data to also estimate overhead costs. When well conducted, such studies can yield reliable estimates of resource costs of exome sequencing (ES) and gene sequencing (GS).[14–21]

In the absence of real-world cost estimates, analysts often use prices as proxies for costs. However, prices charged by clinical providers in the US health-care sector often bear a tenuous relation to costs.[22–25] The list price or billed charge for a service is what a vendor or provider charges a customer (payer). The paid price, i.e., total payment or allowable charge, is what providers get paid by payers, including reimbursements by health plans and out-of-pocket payments by patients. Although expenditures or payments are often referred to as costs, payments do not necessarily correspond to the amount of resources used. For example, the US Medicare fee schedule for physician services, which influences reimbursements for both public and private payers, reflects judgments of the *relative value* of different services, not the resources used.[12] Estimates of expected costs of care in CEAs are typically derived from administrative databases with patient-level information on use of services along with either payments or estimated costs based on charges multiplied by average hospital cost-to-charge ratios.

The perspective of an economic evaluation guides which outcomes and costs to include.[8] Most CEAs take the perspective of either a particular payer (e.g., Medicaid), the health-care sector as a whole (all payers and providers, regardless of who bears the cost), or society as a whole.[26,27] The perspective should reflect the needs of the decision-makers who are expected to use its results. Health-care and societal perspective analyses are expected to estimate costs independent of payer.[21,28] In contrast, use of payments or fee schedules is appropriate in CEAs from a payer perspective if the payments reflect the specified payer type. Use of US private insurance claims databases can overstate savings to public payers since private reimbursements typically exceed payments from public payers.[23,29,30]

Economic evaluations of diagnostic strategies that involve gene sequencing face specific costing challenges. Because of the rapid pace of technological progress in genomics, cost estimates can soon become outdated, and the appropriate comparator strategy may change with evolving standards of care. Consequently, CEA estimates may function as snapshots, and regular updating of estimates may be needed to take account of new technologies and changes in relative prices. Furthermore, cost (or price) estimates of sequencing can vary between laboratories for a variety of reasons. Testing costs may vary depending on which sequencing instrument is used,[16] and, for a given instrument, on staffing and utilization patterns.[19] Because of such variations, CEAs that combine cost estimates from different sources may mischaracterize relative costs.[31]

Pediatric gene sequencing poses an additional challenge in costing. Sequencing tests can be run on an individual patient (singleton) or, as is becoming more frequent, the patient (proband) together with the biological parents, a *trio*. Trio testing is more efficient at identifying de novo mutations, compound heterozygous variants, and newly published genes than singleton testing.[17] ES trios have the potential to reduce the cost of analysis and interpretation relative to singleton ES as well as increase diagnostic yield, accuracy, and turnaround time,[17,32] especially in more complex phenotypes.[33]

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As the laboratory costs of sequencing a specimen have decreased over time, the relative share of the costs of analysis and interpretation for sequencing including ES have increased, resulting in differences in costs for reportable results between singleton and trio ES to decrease.[21] The ratio of the cost of clinical trio to singleton ES or GS has fallen from roughly 2.5 in the past[18,19] to between 1.6 to 2.1 in three recent microcosting studies.[16,17,20] A laboratory in the Netherlands reported a ratio of 1.9 between the prices they charged for trio ES and singleton ES.[24] Consistent with these published cost and price ratios, several colleagues associated with US laboratories confidentially informed one of us (J.M.G.) that billed charges or estimated costs to produce results for trio ES varied from 1.4 to 2 times that of singleton ES.

Economic evaluations of diagnostic pathways inclusive of ES and/or GS have estimated the cost of sequencing using microcosting estimates, list prices, or, in one study, both methods. For example, a study at the Rady Children's Institute of Genomic Medicine in San Diego, California, used microcosting methods to calculate the cost of rapid GS (rGS), mostly trios, for 42 critically ill infants.[20] Despite the high cost of trio rGS, Farnaes et al. calculated that 6 of 18 infants who received a diagnosis experienced significantly shorter hospitalizations relative to what would have been expected in the absence of next-generation sequencing, and the predicted reduction in costs, calculated using charge-based costing, exceeded the cost of rGS.[20,34] However, targeted rapid gene panels or trio rES might achieve similar outcomes at lower cost.[35,36]

A study conducted from the public payer perspective of the province of Ontario at Ontario Health (Quality) in Toronto calculated the incremental cost per molecular diagnosis in of genetic testing in children with unexplained developmental disabilities or multiple congenital anomalies.[2] Li et al. took unit costs of chromosomal microarray (CMA) and genome sequencing (GS) from a microcosting study conducted at the Hospital for Sick Children in Toronto,[16] which generated "precise costs associated with CMA, ES, and GS (proband and trio) in Ontario…in the target population."[2] However, for the cost of ES, Li et al. used the average *price* paid by the Ontario Out-of-Country Prior Approval Plan that, according to our calculations, was 20–50% higher than the weighted cost of ES in the Toronto microcosting study. The cost savings from using ES as a second-tier genetic test would have been even greater if local ES costs had been used instead of the average price charged by US commercial laboratories. The decision was presumably made in consultation with stakeholders, which is commendable. However, reimbursements to Ontario laboratories for ES will presumably be based on Ontario laboratory costs, not US prices. It is important for readers to realize that cost-effectiveness estimates from any single study may not apply to other settings.

Finally, Yeung et al. assessed the cost-effectiveness of ES relative to traditional genetic testing for children hospitalized in three pediatric hospitals in Melbourne, Australia with suspected genetic disorders that were considered life-threatening, disabling, or involved multiple organ systems.[1] The primary analysis compared costs and outcomes for a cohort of children who underwent singleton ES and a historical cohort with similar conditions who underwent clinical genetic assessments in previous years. The assumed cost of singleton ES was AU$3,100, the price charged by Victorian Clinical Genetic Services; the cost of variant segregation, if required, would be in addition to that amount. Schofield et al.[37] noted that the same laboratory had previously charged AU$2,000 for ES and that the subsequent increase to AU$3,100 was the highest price charged for singleton ES by any Australian laboratory, roughly twice the lowest price.[17] In a sensitivity analysis that modeled the use of trio ES in place of singleton ES, Yeung et al. assumed that trio ES would cost AU$3,500, the price charged by the genetics laboratory in New South Wales, which was just 13% more than the price of singleton ES in Victoria.

Yeung et al. state in the discussion, "Our current study further demonstrates that the implementation of trio sequencing in place of singleton sequencing involves only a small increase in mean costs."[21] In reality, the authors *assumed* a slight cost difference between trio and singleton ES. That assumption was in contrast to the Melbourne group's own microcosting finding of a 90% higher cost for trio sequencing.[19] The AU$3,100 price of singleton ES used by Yeung et al. was also 60% higher than the cost estimate of AU$1,939 per child reported by Tan et al.[12] Yeung et al. did not specify a study perspective. From the public payer perspective, the use of price data from the state laboratory would be justified, although not the price of trio ES from a different state. If the study was intended to generate generalizable cost-effectiveness results from the health-care perspective, the use of prices from two different laboratories rather than available local cost estimates would overstate the cost of ES relative to standard testing and understate the cost of trio ES relative to singleton ES.

In conclusion, we reinforce the importance of CEAs documenting their analytic perspectives and assessing the consistency of cost estimates with that perspective, per reporting guidelines.[9] Economic experts recommend that CEAs conducted from the societal or health-care perspectives use estimates of resource costs rather than prices wherever possible.[8,26,28] This is of particular importance for CEAs of sequencing since, as the National Human Genome Research Institute reminds us, "a given price may be either higher or lower than the actual cost."[38] Accordingly, it behooves consumers of economic studies to be aware of these issues when using results of economic studies to inform decision making.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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