Technology and Health Care 23 (2015) 373–379
DOI 10.3233/THC-150900
IOS Press

Letter to the Editor

Is the "$1000 Genome" really $1000? Understanding the full benefits and costs of genomic sequencing

Kathryn A. Phillips[a,*], Mark J. Pletcher[b] and Uri Ladabaum[c]
[a]*Center for Translational and Policy Research on Personalized Medicine, Department of Clinical Pharmacy, University of California at San Francisco, UCSF, San Francisco, CA, USA*
[b]*Department of Epidemiology and Biostatistics, University of California at San Francisco, San Francisco, CA, USA*
[c]*Department of Medicine, Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA, USA*

Received /Accepted: 12 December 2014

Keywords: Sequencing, economics, cost-effectiveness, price

Dear Editor,

New health technologies are often portrayed in the media as being low-cost innovations that will save health care costs. In the case of genomic sequencing – high-speed analysis of multiple genes in parallel fashion – there has been a great deal of media attention about the falling cost of sequencing, referred to as the "$1000 Genome" – with the implication that the full cost of testing is actually $1000. Genomic sequencing (herein called "sequencing") – is entering clinical care even though there are ongoing challenges of accuracy and reporting [1,2]. We examine how the full benefits and costs of sequencing will vary widely depending on how the technology is used – emphasizing that the net cost of sequencing will never simply be the cost of testing itself, even though sequencing may provide benefits in many scenarios. As providers and decision makers consider when sequencing might be useful clinically, we suggest a framework for evaluating sequencing's full benefits and costs so that the focus on the "$1000 price tag" for the sequencing technology *per se* does not obscure the complex decisions to be made about its effective and efficient use [3]. We also provide simulations of the possible economic impact of

*Corresponding author: Kathryn A. Phillips, 3333 California St, Room 420, Box 0613, San Francisco, CA 94143, USA. Tel.: +1 415 502 8271; Fax: +1 415 502 0792; E-mail: Kathryn.Phillips@ucsf.edu.

0928-7329/15/$35.00 © 2015 – IOS Press and the authors. All rights reserved

sequencing using a case study. (Note: We use the term "sequencing" throughout as a simplifying term but discuss how the term has various definitions depending on the context and use.)

In this brief report we focus only on the balance of economic factors within a clinical context – with an objective assessment of both benefits and costs – although many other issues will need to be considered before sequencing can be widely adopted and we do not examine issues such as test interpretation costs and issues with test concordance. However, regardless of whether one believes that sequencing should or should not be more widely applied at this time, it is important to begin to assess the true economic costs and benefits and to develop methods that can be used to evaluate sequencing as more evidence becomes available.

We specifically consider three issues and their impact on the full, "real world" benefits and costs of sequencing:

(1) The implications of "incidental findings" that are unrelated to the reason for ordering testing,
(2) Impacts on relatives, and
(3) Testing and therapies that occur after testing.

First, incidental findings may provide clinically useful information, but many findings will be of uncertain significance and not clinically useful [4] and they may lead to unwarranted testing or treatments that increase costs without improving outcomes. The impact of incidental findings will depend on which findings are returned to patients and their providers – a debate for which there is no consensus [5]. Second, identifying germline mutations in individuals has profound implications for potentially-affected relatives. Third, for both patients and families, the benefits and costs of sequencing will depend on the "downstream" effects – the additional testing and therapies after sequencing. It has been stated that the "cost of sequencing is expected to be recovered over a lifetime through the avoidance of unnecessary diagnostics and therapeutics" [6] – but, conversely, downstream effects and resulting costs could overwhelm the immediate direct costs of sequencing itself [7].

Lastly, of relevance to all three issues is that sequencing is likely to produce a large number of false positive results – either because the test is inaccurate or the results are a false indication of a condition. Although all medical tests have the potential for misinterpretation, this issue is particularly acute for sequencing given that the technologies are rapidly evolving and the ability to interpret sequencing results is at an early stage.

To illustrate how sequencing benefits and costs will vary depending on its use, we describe three scenarios capturing a range of potential applications of sequencing that provide a framework for such considerations. These scenarios are illustrative and thus by definition are simplifications, but they provide a means by which to consider the range of benefits and costs of sequencing.

Scenario 1: Sequencing of tumors for planning cancer treatment

The most rapidly advancing use of sequencing is tumor sequencing to plan cancer treatment [8]. In this scenario, the purpose of sequencing is to detect specific variants to tailor treatments, and thus the benefits and costs of sequencing will be driven largely by the cost of testing itself and the impact of those specific findings. However, incidental findings that impact benefits and costs may still occur, since cancer patients may also have germline sequencing in order to characterize the cancer and therefore both patients and families may be impacted by these findings.

Treatment for colorectal and lung cancers illustrates the use of tumor sequencing. Many patients with these tumors are tested for several mutations using single gene tests (e.g., EGFR, KRAS, BRAF, ALK).

However, since the cost of each test is $200–$1400, the use of tumor sequencing may provide additional information that can better characterize the cancer for treatment options at possibly lower cost.

In sum, it is possible that tumor sequencing could provide more clinically useful information at the same (or lower) cost than multiple single gene tests. However, the net impact of replacing single gene tests with tumor sequencing will depend not only on testing costs, but also on the impact of incidental findings and on downstream treatments, which may include off-label use of therapies based upon unvalidated incidental findings.

Scenario 2: Sequencing for individuals with risk factors

Another rapidly advancing use of sequencing is in individuals at risk for inherited conditions, where single gene tests have traditionally been performed [9]. It's been predicted that whole genome sequencing will replace single gene tests or even gene panels as the price of sequencing drops [10]. As with Scenario 1, while the primary purpose of sequencing in this scenario is to detect variants in specific genes, incidental findings in other genes can be expected. However, when performing screening for hereditary risk instead of tumor profiling, there may be more to gain – but also more costs and secondary risk to accrue – from identifying incidental findings.

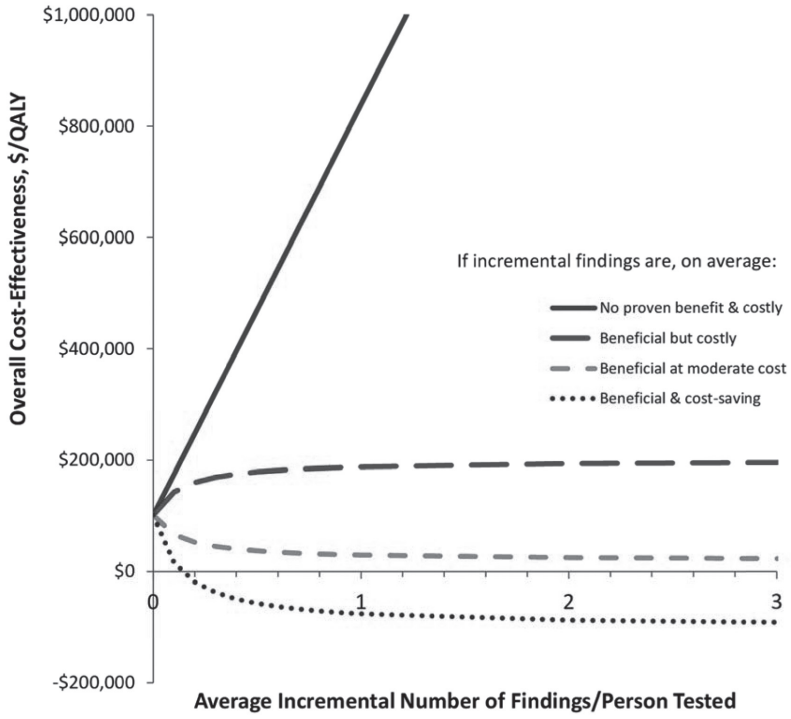
Sequencing of inherited variants for breast and ovarian cancer – *BRCA1/2* – illustrates the use of sequencing to replace single gene tests. *BRCA* testing has typically cost $3000–$4000. However, it can cost less to detect *BRCA* using gene panels or even whole genome sequencing – and such testing also provides more information than only *BRCA* status [11].

In sum, replacing single gene tests with sequencing is likely to yield both vastly more information but the downstream consequences of this information – both positive and negative – will determine the full benefits and costs of sequencing. The downstream impact of incidental findings is expected to be substantially more important when testing persons for future risk than for tumor sequencing (as described in Scenario 1).

Scenario 3: Sequencing for general population screening

Some have proposed that sequencing be used in populations without any known risk factors [4,12]. In the absence of any disease-specific pre-test focus of interest, the results will be comprised entirely of "incidental" findings. Although the immediate downstream costs were not excessive in a recent exploratory study of whole genome sequencing [1], there was little agreement among physicians about which findings should be acted on, long-term downstream costs were not included, and it was noted that sequencing could produce a "cascade of interventions of unclear costs" [13].

Sequencing with the aim of identifying future health risks, such as Lynch syndrome, in a population without known risk factors provides an example of how sequencing in healthy populations needs to consider downstream consequences. Most individuals with Lynch syndrome are unaware that they are carriers and thus there is an unmet need, but Lynch syndrome screening in the general population is currently associated with unacceptably high costs [14]. However, if affordable whole exome/genome sequencing were deployed widely, more individuals could benefit from learning that they have Lynch syndrome. Detecting Lynch syndrome and pursuing "cascade testing" in relatives results in improved clinical outcomes, but given the substantial costs incurred by screening and preventive interventions,



Notes:

- Assumptions: Cost of sequencing = $1000 and prevalence of Lynch syndrome = 3%

-The lifetime discounted consequences of identifying a patient with Lynch among colorectal cancer patients is additional costs of $12,400 and 0.45 additional QALYs (derived from Ladabaum, 2011).

Legend definitions:

- No proven benefit & costly: average cost = $10,000 and average QALY benefit = 0
- Beneficial but costly: average cost = $20,000 and average QALY benefit = 0.1
- Beneficial at moderate cost: average cost = $2,000 and average QALY benefit = 0.1
- Beneficial and cost-saving: average cost = (-)$10,000 and average QALY benefit = 0.1

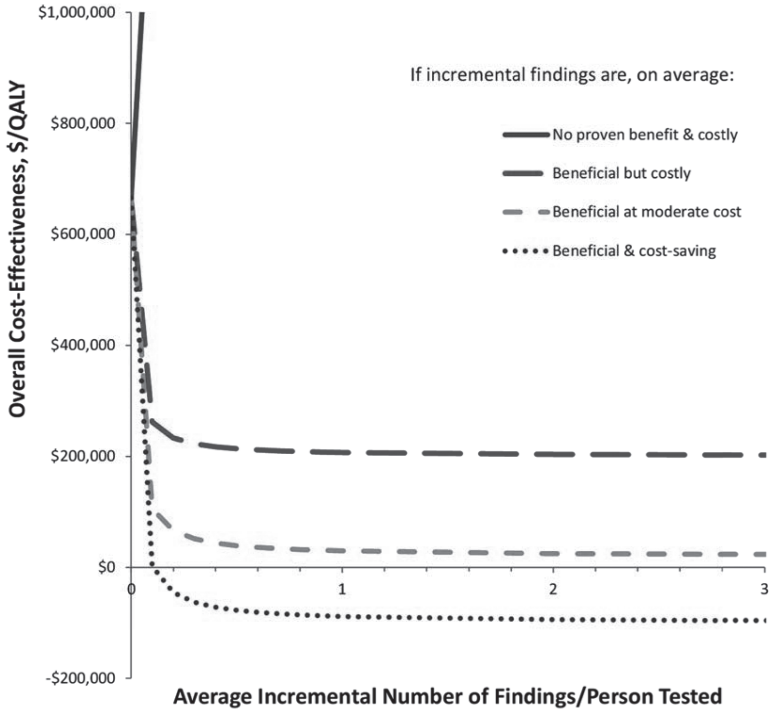
Fig. 1. How cost-effectiveness of genomic sequencing for lynch syndrome in colorectal cancer patients will vary based on number and type of incremental findings.

this results in net costs, not net savings [15]. Thus, the balance of benefits/costs of general population sequencing to detect Lynch syndrome have to be weighed against more targeted approaches.

In sum, the net impact of sequencing as a general population screening test extends far beyond the cost of testing itself. The ultimate balance of benefits and costs will be determined in large part by the number and handling of findings and their downstream consequences. Thus, the benefit/costs of general population sequencing will have to be compared against those for more targeted use of sequencing technologies, such as using panels of genes known to have clinical utility. In general, screening of general populations has been shown to be less cost-effective than targeted screening.

Simulations of the impact of incidental findings on cost-effectiveness of Lynch syndrome screening

Estimating the clinical and economic impact and cost-effectiveness of sequencing is unusually complex given the many factors and unknowns involved and conducting a detailed analysis is beyond the



Notes:
- Assumptions: Cost of sequencing = $1000 and prevalence of Lynch syndrome = 0.25%
-The lifetime discounted consequences of identifying a patient with Lynch among persons in the general population is additional costs of $8,500 and 0.61 additional QALYs (derived from Ladabaum, 2011).
Legend definitions:
- No proven benefit & costly: average cost = $10,000 and average QALY benefit = 0
- Beneficial but costly: average cost = $20,000 and average QALY benefit = 0.1
- Beneficial at moderate cost: average cost = $2,000 and average QALY benefit = 0.1
- Beneficial and cost-saving: average cost = (-)$10,000 and average QALY benefit = 0.1

Fig. 2. How cost-effectiveness of genomic sequencing for lynch syndrome in a general population will vary based on number and type of incremental findings.

scope of this article. However, to illustrate how incidental findings could have a large impact on the cost-effectiveness of screening, we conducted a series of simulations building from our previously published cost-effectiveness model of Lynch syndrome screening [15]. Although Lynch syndrome is just an illustrative example, by using a previously validated model we were able to ground our simulations in actual results.

Figures 1 and 2 show how the cost per QALY gained will vary depending on the number of incremental findings returned to each person tested (note that we use the term "incremental" to reflect that we did not separate findings into actionable or non-actionable findings given that this will vary depending on the population sequenced and the thresholds used for return of results). Overall, the results show that the cost per QALY gained for Lynch syndrome screening will vary dramatically based on whether incremental findings provide net benefits/savings or net harms/costs. If incremental findings are of unproven benefit and costly, the cost per QALY gained increases well beyond standard thresholds of acceptable cost-effectiveness – conversely, if such findings are clinically beneficial and cost-saving, screening becomes cost-saving.

Figure 2 shows that screening for Lynch syndrome in the general population, which is prohibitively expensive with current methods, remains prohibitively expensive unless there are clinically useful incremental findings that are only moderately costly. Further analyses of the cost per person tested (not shown) also reflect that incremental findings could have a variable impact – from highly costly to cost-saving. In addition, the total cost per person tested – and thus the budget impact in a population – could be substantial or there could instead be cost-savings as the number of findings per person increases, depending on the average long-term cost per finding. Although the expected number and type of incremental findings is not known with any certainty, it has been estimated that currently only a very small percentage of generally healthy individuals sequenced will receive clinically actionable incidental findings such as Lynch syndrome [1].

In conclusion, the true cost of sequencing extends beyond the test itself and thus the headline of the "$1000 Genome" is not an accurate portrayal of its cost. The full benefits and costs of sequencing will vary widely depending on how it is used, and decision makers should consider incidental findings, impacts on relatives, and time horizons that include downstream tests and therapies. At this time there is not enough evidence to indicate whether sequencing provides more benefits than costs. For the balance between the benefits/costs of sequencing to be favorable, several conditions will need to be present, e.g., when the incremental information provided beyond that of single gene tests is actionable, sequencing is less costly than the tests it is replacing, the results lead to treatment decisions that result in improved outcomes and/or reduced costs, relatives found to have genetic mutations follow proven preventive interventions, and incidental or uncertain findings do not lead to unproven interventions that may yield no benefit and may even cause harm.

Given that methods for assessing and comparing the net costs, benefits, and cost-effectiveness of sequencing strategies have yet to be developed and to our knowledge there have not been any published economic analyses of sequencing, this report should be considered only a first step in creating a framework for such analyses. Although the full economic impact of sequencing cannot be defined until more is known about its clinical benefits, it is important to develop methods and initial estimates of the balance of benefits/costs now in order to guide sequencing adoption [16–18]. Emerging evidence on the impact of sequencing and its benefits and costs should continue to guide the applications of this technology, and systematic, rigorous economic analyses – such as cost-effectiveness analyses and budget impact analyses – will be needed.

Acknowledgements

This study was funded by grants from the National Human Genome Research Institute (R01 HG007063) and the UCSF Mount Zion Health Fund and Helen Diller Family Comprehensive Cancer Center (5P30CA082013-15). We are grateful for contributions from Michael P. Douglas, UCSF; R. Kate Kelley, UCSF, and our collaborators at the UCSF Center for Translational and Policy Research on Personalized Medicine (TRANSPERS).

References

[1] Dewey FE, Grove ME, Pan C, Goldstein BA, Bernstein JA, Chaib H, et al. Clinical interpretation and implications of whole-genome sequencing. JAMA: the journal of the American Medical Association. 2014 Mar 12; 311(10): 1035-45. PubMed PMID: 24618965.

[2] McCarthy JJ, McLeod HL, Ginsburg GS. Genomic medicine: A decade of successes, challenges, and opportunities. Science translational medicine. 2013 Jun 12; 5(189): 189sr4. PubMed PMID: 23761042. Epub 2013/06/14. eng.
[3] Evans JP, Khoury MJ. The arrival of genomic medicine to the clinic is only the beginning of the journey. Genetics in medicine: official journal of the American College of Medical Genetics. 2013 Apr; 15(4): 268-9. PubMed PMID: 23306801.
[4] Berg JS, Khoury MJ, Evans JP. Deploying whole genome sequencing in clinical practice and public health: meeting the challenge one bin at a time. Genetics in medicine: official journal of the American College of Medical Genetics. 2011 Jun; 13(6): 499-504. PubMed PMID: 21558861.
[5] Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genetics in medicine: official journal of the American College of Medical Genetics. 2013 Jul; 15(7): 565-74. PubMed PMID: 23788249. Pubmed Central PMCID: 3727274. Epub 2013/06/22. eng.
[6] Church G. Improving genome understanding. Nature. 2013 Oct 10; 502(7470): 143. PubMed PMID: 24108012.
[7] The Road to the $1,000 Genome 2010 [cited 2014 January 16, 2014]. Available from: http://www.bio-itworld.com/2010/09/28/1Kgenome.html.
[8] Johansen Taber KA, Dickinson BD, Wilson M. The promise and challenges of next-generation genome sequencing for clinical care. JAMA internal medicine. 2014 Feb 1; 174(2): 275-80. PubMed PMID: 24217348.
[9] Park JY, Kricka LJ, Fortina P. Next-generation sequencing in the clinic. Nature biotechnology. 2013 Nov; 31(11): 990-2. PubMed PMID: 24213773.
[10] Biesecker LG, Burke W, Kohane I, Plon SE, Zimmern R. Next-generation sequencing in the clinic: Are we ready? Nature reviews Genetics. 2012 Nov; 13(11): 818-24. PubMed PMID: 23076269. Pubmed Central PMCID: 3891793.
[11] Clain E, Trosman JR, Douglas MP, Weldon CB, Phillips KA. Emergence of New BRCA1/2 Tests and Gene Panels: Availability & Payer Coverage Policies. UCSF: 2014.
[12] Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. The New England journal of medicine. 2014 Sep 18; 371(12): 1170. PubMed PMID: 25229935.
[13] Feero WG. Clinical application of whole-genome sequencing: proceed with care. JAMA: The journal of the American Medical Association. 2014 Mar 12; 311(10): 1017-9. PubMed PMID: 24618961.
[14] Dinh TA, Rosner BI, Atwood JC, Boland CR, Syngal S, Vasen HF, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer prevention research. 2011 Jan; 4(1): 9-22. PubMed PMID: 21088223. Pubmed Central PMCID: 3793254.
[15] Ladabaum U, Wang G, Terdiman J, Blanco A, Kuppermann M, Boland CR, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: A cost-effectiveness analysis. Annals of internal medicine. 2011 Jul 19; 155(2): 69-79. PubMed PMID: 21768580. Pubmed Central PMCID: 3793257.
[16] Towse A, Garrison LP, Jr. Economic incentives for evidence generation: promoting an efficient path to personalized medicine. Value in health: The journal of the International Society for Pharmacoeconomics and Outcomes Research. 2013 Sep-Oct; 16(6 Suppl): S39-43. PubMed PMID: 24034311. Epub 2013/09/27. eng.
[17] Buchanan J, Wordsworth S, Schuh A. Issues surrounding the health economic evaluation of genomic technologies. Pharmacogenomics. 2013 Nov; 14(15): 1833-47. PubMed PMID: 24236483. Pubmed Central PMCID: 3909837. Epub 2013/11/19. eng.
[18] Payne K, Shabaruddin FH. Cost-effectiveness analysis in pharmacogenomics. Pharmacogenomics. 2010 May; 11(5): 643-6. PubMed PMID: 20415553. Epub 2010/04/27. eng.