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"Economic Evidence on Identifying Clinically Actionable Findings with Whole Genome Sequencing: A Scoping Review"

Michael P. Douglas, MS[1], **Uri Ladabaum, MD, MS**[2], **Mark J. Pletcher, MD, MPH**[3], **Deborah A. Marshall, PhD**[4], and **Kathryn A. Phillips, PhD**[5]

[1] Department of Clinical Pharmacy; Center for Translational and Policy Research on Personalized Medicine (TRANSPERS), University of California San Francisco

[2] Department of Medicine, Division of Gastroenterology and Hepatology, Stanford University School of Medicine

[3] Department of Epidemiology and Biostatistics, University of California San Francisco

[4] Department of Community Health Sciences, Cumming School of Medicine, O`Brien Institute for Public Health, University of Calgary

[5] Department of Clinical Pharmacy; Center for Translational and Policy Research on Personalized Medicine (TRANSPERS); UCSF Philip R. Lee Institute for Health Policy; and UCSF Helen Diller Family Comprehensive Cancer Center, University of California San Francisco 3333 California St, Room 420, Box 0613 San Francisco, CA 94143

Abstract

Background—The American College of Medical Genetics (ACMG) recommends that mutations in 56 genes for 24 conditions are clinically actionable, and should be reported as secondary findings after whole genome sequencing (WGS). Our aim was to identify published economic evaluations of detecting mutations in the general population or in targeted/high-risk populations in these genes and conditions and identify gaps in knowledge.

Methods—A targeted PUBMED search from 1994 through November 2014 was performed and we included original articles reporting cost-effectiveness or cost-utility ratio or net benefits/ benefit-cost focused on screening (not treatment) for ACMG listed conditions and genes in English. Articles were screened, classified as targeting a high-risk or general population, and abstracted by two reviewers. General population studies were evaluated for actual cost-effectiveness measures (e.g. ICER) while targeted populations studies were evaluated for whether at least one scenario proposed was cost-effective (e.g. ICER of ≤ $100,000 per life-year (LY) or quality-adjusted life-year (QALY) gained).

Results—A total of 607 studies were identified and 32 relevant studies were included. Identified studies addressed less than one third (7 of 24, 29%) of the AMCG conditions. The cost-effectiveness of screening in the general population was examined in only 2 of 24 (8%) conditions.

(corresponding author) Tel: (415) 502-8271 Fax: (415) 502-0792 PhillipsK@pharmacy.ucsf.edu.

Supplementary information is available at the Genetics in Medicine website

Conclusion—The cost-effectiveness of most genetic findings that the ACMG recommends for return has not been evaluated in economic studies or in the context of screening in the general population. The individual studies do not directly address the cost-effectiveness of WGS.

Keywords

Review; Economics; AMCG; Incidental Findings; “Whole Genome Sequencing”

INTRODUCTION

Whole genome sequencing (WGS) tests are being offered selectively in clinical care, and are expected to become more widely used in the future. The American College of Medical Genetics (ACMG) released recommendations that specify which secondary findings (SFs) from whole genome sequencing (WGS) should be returned to patients.[1] These recommendations identify 56 genes associated with 24 conditions in which mutations are considered clinically actionable (e.g. treatment or behavior modification that leads to improved health outcomes) (See definition box).

The ACMG made the recommendation to return certain SFs based on an established benefit of clinical utility, and all each of the genes included have clinically available tests.[1-4] However, when assessing the full implications of finding and reporting SFs found with WGS, the full range of benefits, risks and costs must be considered. The cost-effectiveness of returning SFs from WGS in the general population or in specific targeted/high-risk population clinical scenarios has not been assessed. Our aim was to identify published economic evaluations of detecting mutations in the general population or in targeted/high-risk populations in the 56 genes associated with the 24 conditions that are considered clinically actionable by the ACMG to identify available economic evidence and gaps in knowledge. Our results inform both the costs/benefits of genetic testing for these conditions in targeted populations and their costs/benefits in general populations, which may occur as WGS enters clinical care more broadly.

MATERIALS AND METHODS

Search Strategy

We identified economic evaluations for screening for all conditions and respective genes defined on the ACMG list of returnable results.[1] We conducted a targeted search of PubMed from 1994 through November 2014 for English language articles of cost-effectiveness, cost-utility or cost-benefit analyses that specifically addressed the conditions and genes of interest. We chose to limit the search to the last 20 years since the majority of all economic analysis of genetic testing has been done during this timeframe, and used MeSH and keywords to limit the studies to economic analyses and the disease or condition found in the ACMG list of returnable results.[1] The search strategy used the following terms:

- Disease or Condition –MeSH terms and keywords for each. The MeSH term was limited further using the genetics or diagnosis subheading for selected conditions (see Appendix A for specific terms used).

- Cost-Effectiveness – “Cost-Benefit Analysis” [MeSH] and “Cost-effectiveness” (keyword)

For conditions (e.g. Lynch Syndrome and hereditary breast ovarian cancer [HBOC] syndrome) that returned a large number of results, we limited the search by the addition of the specific terms for the relevant gene(s) – using MeSH terms when available, or keywords (e.g. MSH1, BRCA1 or BRCA2). We combined the results of these searches and validated our search as described below. We augmented our search strategies for economic evaluations related to genetic screening for the disease/conditions and genes on the ACMG list by reviewing references in the Tufts Center for the Evaluation of Value and Risk in Health CEA Registry database[5,6] and in recently published cost-effectiveness and cost-utility studies[7]

Article Selection

Titles and abstracts were screened by two independent reviewers according to pre-specified inclusion and exclusion criteria, and relevant full texts of articles were retrieved. Disagreements were resolved through discussion and referral to a third reviewer if necessary. The Article Inclusion criteria were: original articles only, focus on one of the conditions and genes listed in the ACMG article, English only, provide a measure of relative economic value defined as a cost-effectiveness or cost-utility ratio or net benefits/benefit-cost, and an economic evaluation screening for the gene, not a treatment. Article exclusion criteria were reviews, editorials, or methods articles, and studies solely of “costs”. We screened all full text articles to identify those that included at least one analysis of general population screening (or opportunistic screening of a general population) and those that included only analyses of targeted/high-risk population screening.

Data Extraction

For each included study, two reviewers independently extracted relevant data and study details. Basic article details including population demographics and cost-effectiveness data (specific *vs.* general population studied, incremental cost-effectiveness ratios [ICERs], and author conclusions) were abstracted (see Appendix C). Discrepancies were resolved through discussion.

We defined “cost-effective” as an ICER of ≤ $100,000 per life-year (LY) or quality-adjusted life-year (QALY) gained.[8,9] Using this definition, we determined whether at least one clinical scenario per targeted population study was “cost-effective” for screening for the condition of interest. We assumed testing in a general population scenario to mean the population tested was not limited by other risk factors (e.g. increased risk of condition due to family history) and a targeted population scenario to mean the population tested was limited by outside factors (e.g. family history of condition, other clinical factors suggestive of condition).

Evaluation of Methodological Quality

We used the "Quality Rating" assigned by trained coders from the Tufts Cost-Effectiveness Analysis Registry (CEAR) to examine the methodological quality of our included studies that were found in Tufts CEAR.[5]

RESULTS

Studies Identified

Our search yielded 607 candidate articles, of which 56 remained after title/abstract review, and 32 remained after full text review (figure 1) (a complete list of studies can be found in Appendix B).[10-41]

Populations, Conditions and Genes Examined

We found CEAs for only a fraction (7 of 24, 29%) of all conditions and genes on the ACMG list (Table 1). Only four of 32 studies contained analyses for genetic screening in a general population: Familial Hypercholesterolemia and Lynch Syndrome (2 of 24 conditions on the ACMG list, or 8%) (Table 1), whereas all studies included analyses of high-risk or targeted populations (Table 1). Most articles focused on Lynch Syndrome (genes *MLH1*, *MSH2*, *MSH6*, *PMS2*) (n=14), HBOC syndrome (genes *BRCA1*, *BRCA2*) (n=6), and Familial Hypercholesterolemia (genes *LDLR*, *APOB*, *PCSK9*) (n=6) (Table 1). The remaining (n=6) studies addressed MYH-Associated Polyposis (gene *MUTYH*) Multiple Endocrine Neoplasia Type 2 (gene *RET*), Hypertrophic Cardiomyopathy and Dilated cardiomyopathy (genes MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA), and Romano-Ward Long QT Syndromes Types 1, 2, and 3, Brugada Syndrome (genes *KCNQ1*, *KCNH2*, *SCN5A*) (Table 1).

Cost-effectiveness of Screening in the General Population

The four CEAs that examined general population screening included several different analyses for Familial Hypercholesterolemia (six analyses) and Lynch Syndrome (three analyses examining no risk stratification prior to genetic testing)[11,22,23,40] (Table 2).

Two analyses by Marks (2000, 2002) found screening for Familial Hypercholesterolemia at 16 years of age to be cost-effective in the general population (i.e. mutation prevalence assumed to reflect general population prevalence) (Table 2).[22,23] Furthermore, these same studies found screening for Familial Hypercholesterolemia between the ages of 16 and 55 in the general population, or opportunistically in primary care, borderline cost-effective ($104,502 - $125,200 / QALY gained) (Table 2).[22,23]

Both Dinh (2011) and Snowskill (2014) found that general population screening with up-front germline testing for Lynch Syndrome was not found to be cost-effective (ICER values ranged from nearly $129,852 to over $7 million per LY or QALY gained) (Table 2).[11,40] However, Dinh found that as the risk thresholds for genetic testing were set to 5% and 10% (a targeted/high-risk population evaluation), the ICERs fell below $50,000 per QALY gained.[11]

Cost-effectiveness of Screening in Targeted/High-Risk Populations

For seven conditions, the cost-effectiveness of genetic testing was examined in at least one high-risk or targeted clinical scenario. All of these CEAs found genetic testing to be cost-effective in at least one high-risk or targeted clinical scenario (Table 1) (Appendix B).

Evaluation of Methodological Quality

Although sample sizes were too small to examine the quality of the methods used in detail, we were able to estimate the methodological quality of seven of the included studies using data from the Tufts CEAR. We calculated a mean quality score of 4.5 for the included studies (range 3.5 - 6, scale of 1-7) which was equivalent to the mean score for all studies in the CEAR (4.5, N=4007).

DISCUSSION

We found very few (7 of 24, 29%) published health economic evaluations of screening for clinically actionable gene variants in the conditions and genes for which the ACMG recommends returning secondary findings to patients. In the conditions and genes that have been formally evaluated, most studies have focused on Targeted/high-risk populations or high prevalence (i.e. <1:1,500) populations (Table1). Our findings suggest that substantial additional data and analyses are required in order to evaluate fully the benefits, risks and costs of return of these secondary findings to patients.

The few CEAs that addressed testing for specific genes in the general population suggest that such testing in low-prevalence populations may not be cost-effective (Table2). However, it must be appreciated that with WGS, a relatively low testing cost may be incurred to obtain information for multiple conditions. If most of the cost incurred from screening is from the test itself rather than the follow up treatment and healthcare utilization, then WGS-enabled screening may improve cost-effectiveness. To illustrate, several models have found that screening for Familial Hypercholesterolemia in some general populations (i.e. at 16 years), but not in others, may be cost-effective.[22,23] Testing for this condition in high risk populations (family members of persons with clinical diagnosis or genetic mutations) using a case finding/cascade screening approach is usually found to represent the most cost-effective (lowest ICER) application of the screening technology.[22,23,25,34,37,41] Furthermore, in the case of general population screening for Familial Hypercholesterolemia, the clinical utility of the genetic test compared to a standard cholesterol test to evaluate individual patient's possible need for lipid lowering drugs (e.g. statins) may be the more cost-effective approach considering the clinical care pathway would certainly require a cholesterol test prior to statin use anyway. In Lynch syndrome, models demonstrate that general population screening of non-risk stratified individuals with traditional gene sequencing methods is not cost-effective.[11,40] When a risk threshold for genetic testing was set to 5% and 10% (non-universal screening), the ICER values fell below the common benchmark threshold of $50,000 per QALY gained.[11] We found no CEAs of BRCA1/2 screening in the general population.

In all of the CEAs included, we found at least one high-risk or targeted population screening scenario in which screening was suggested to be cost-effective.[10-41] It remains unclear whether substituting WGS (with its yield of SFs) instead of condition-specific targeted testing in these scenarios would improve clinical effectiveness and/or cost-effectiveness. However, it is important to consider the lowering of WGS costs may affect the cost-effectiveness of using single gene tests. For example, three of the four general population studies included in our study included sensitivity analyses on the test cost and in all three cases the cost-effectiveness was relatively more sensitive to test cost compared to other variables[11,22,40] and in one case a 50% decrease in test cost resulted in a 35% reduction of the ICER value for universal screening ($14400 vs. $22,154 cost/life year gained).[22] Furthermore, the proportion of the total cost/life year gained that was attributable to the test cost ranged from 0.7-6.7% ($3495/$490,315;[11] $2500/$129852;[40] $1492/$22154;[22] and $1603/23805[23]).

Limitations

We searched only PubMed and thus we may have missed articles not indexed in PubMed, but we expect that this would be rare and we also supplemented our search findings with other databases and key articles. Because we found very few relevant CEAs addressing general population screening, these results should be considered only suggestive of what might be found with a larger sample. The individual analyses that we identified do not directly address the cost-effectiveness of WGS, and sequencing of multiple genes at once will have a different range of effects and a different ICER than screening for only one condition.

Conclusions and Future Research

It would be useful to have more economic analyses of the conditions and genes in the ACMG list in the general population or in high-risk populations. CEAs that examine WGS in populations at high risk for specific conditions, in which the primary aim is to examine the genes associated with this condition, but where SFs in other genes are also reported to patients, would be highly informative. Comparisons of WGS vs. existing methods, including the use of gene panels, would be of great interest. Furthermore, one must consider how to integrate the economic evaluation of multiple or all of these conditions, and the impact of considering these genes/conditions jointly on the cost-effectiveness of WGS.[42,43] For example, the use of existing CEA results (e.g. QALYs, ICERs) in the development of future CEA models for multiple conditions may not be appropriate data inputs. It is possible that WGS may be more cost-effective than screening for individual conditions/genes since one is screening for multiple diseases. However, WGS may result in a higher number of false positives that generate further tests/costs thus impacting the cost-effectiveness negatively.

In summary, the cost-effectiveness of screening for most of the conditions and genes on the ACGM actionable list remains undefined. Furthermore, the clinical and economic consequences that may follow ascertainment of findings in the ACGM list of conditions and genes have not been explored. When considering the full range of effects that WGS may have in the general population, it will be necessary to integrate the clinical and economic effects stemming from identifying clinically actionable findings, findings with unclear

implications for management, and findings of unknown significance across a large number of clinical conditions and associated genes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Defining Screening, Testing and Reporting on Clinically Actionable Conditions

"Screening" is the use of genetic methods, including sequencing, to determine the presence of a genetic-based condition/gene/variant in a general population (e.g. population screening and returning SFs – all returned results would be considered SFs).

"Testing" is the use of genetic methods, including sequencing, to determine the presence of a condition/gene/variant in when a clinical indication is present (e.g. Lynch Syndrome Testing in high-risk individuals and returning SFs).

"Condition" is the disease, syndrome or other known susceptibility (e.g. 24 conditions outlined in ACMG Recommendations; Lynch Syndrome).

"Clinically Actionable" is the ability to administer treatment or behavior modification that leads to improved health outcomes (e.g. BRCA1/2 mutations are clinically actionable to reduce breast cancer risk).

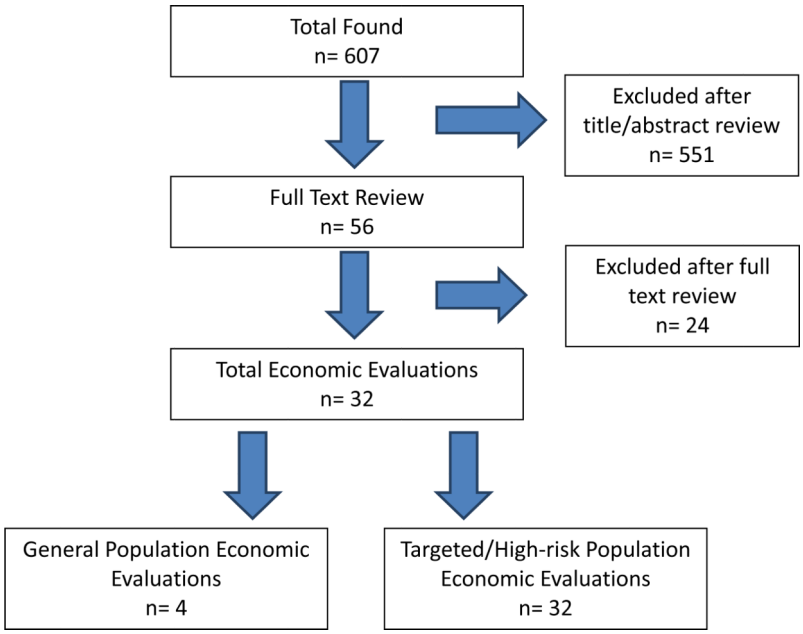

Figure 1.
PRISMA diagram of included and excluded studies

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Table 1

Summary of Articles found and CEAs identified for each condition defined on the ACMG list of secondary findings.

	Condition	Condition Prevalence*	Genes	TOTAL # of CEAs	Total # of CEAs including both High Risk and General Populations** (General population testing: # favorable*** (# total))	Total # of CEAs focused only on High Risk Population (High risk population testing: # favorable***/(# total))
1	Lynch Syndrome	Common	MLH1, MSH2, MSH6, PMS2	14	2 (0)	12 (12)
2	Hereditary Breast and Ovarian Cancers	Common	BRCA1, BRCA2	6	0	6 (6)
3	Familial hypercholesterolemia	Common	LDLR, APOB, PCSK9	6	2 (2)	4 (4)
4	Romano-Ward Long QT Syndromes Type 1, 2, (RWS) and 3, Brugada Syndrome (BS)	Rare (RWS) Rare (BS)	KCNQ1, KCNH2, SCN5A	2	0	2 (2)
5	Hypertrophic cardiomyopathy (HC), Dilated cardiomyopathy (DC)	Common (HC) Common (DC)	MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA	2	0	2 (2)
6	MYH-Associated Polyposis (MAP); Adenomas, multiple colorectal, FAP type 2; Colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas	Extremely Rare	MUTYH	1	0	1 (1)
7	Multiple Endocrine Neoplasia Type 2	Extremely Rare	RET	1	0	1 (1)
8	Catecholaminergic polymorphic ventricular tachycardia	Rare	RYR2	0	0	0
9	Familial adenomatous polyposis	Rare to Extremely Rare	APC	0	0	0
10	Von Hipel Lindau syndrome	Extremely Rare	VHL	0	0	0
11	Li-Fraumeni Syndrome	Rare	TP53	0	0	0
12	Peutz-Jeghers Syndrome	Extremely Rare	STK11	0	0	0
13	Multiple Endocrine Neoplasia Type 1	Extremely Rare	MEN1	0	0	0
14	Familial Medullary Thyroid Cancer (FMTC)	Rare	RET, NTRK1	0	0	0
15	PTEN Hamartoma Tumor syndrome	Extremely Rare	PTEN	0	0	0
16	Retinoblastoma	Rare	RB1	0	0	0
17	Hereditary Paraganglioma (PGL)-Pheochromocytoma (PCC) syndrome	Extremely Rare Extremely Rare	SDHD, SDHAF2, SDHC, SDHB	0	0	0
18	Tuberous Sclerosis Complex	Rare	TSC1, TSC2	0	0	0
19	WT1-related Wilms tumor	Rare	WT1	0	0	0

	Condition	Condition Prevalence*	Genes	TOTAL # of CEAs	Total # of CEAs including both High Risk and General Populations** (General population testing: # favorable*** (# total))	Total # of CEAs focused only on High Risk Population (High risk population testing: # favorable***/(# total))
20	Neurofibromatosis type 2	Extremely Rare	NF2	0	0	0
21	EDS - vascular type	Rare	COL3A1	0	0	0
22	Marfan Syndrome (MS), Loeys-Dietz Syndromes (LDS), and Familial Thoracic Aortic Aneursyms and Dissections (FTAAD)	Rare (MS) Unknown (LDS) Unknown (FTAAD)	FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYLK, MYH11	0	0	0
23	Arrhythmogenic right ventricular cardiomyopathy	Common	PKP2, DSP, DSC2 TMEM43, DSG2	0	0	0
24	Malignant hyperthermia susceptibility	Extremely Rare	RYR1, CACNA1S	0	0	0
Total				**32**	**4**	**28**

NOTES:

Shaded cells indicate conditions for which where Economic Evaluations were found.

* Prevalence categories are defined as: “common” – 1:1 to 1:1,499, “rare” – 1:1,500 to 1:19,999, and “extremely rare” – 1:20,000+

** No CEAs focused only on General Populations

*** Favorable = Study presented at least one scenario where at least one testing scenario was cost-effective (< $100,000/QALY or LY).

Table 2

Details of Economic Evaluations of General Population

Condition	Gene(s)	Population	ICER*	Key Conclusion from Articles
Familial Hypercholesterolemia	LDLR, APOB, PSCK9	General Population (at 16 years old)	$22,154 (cost/ life year gained) [22] $23,805 (cost/ life year gained) [23]	"When targeted on the young (16 year old school children), universal screening also appears relatively cost-effective. However, screening is less cost effective in 16-55 year olds with the least cost-effective in men aged over 35 years. This is because the gains in life expectancy for these individuals are small." [22] "Screening family members of people with familial hypercholesterolemia is the most cost effective option for detecting cases across the whole population." [23]
		Opportunistic screening (16-55 years who visit their GP)	$104,502 (cost/ life year gained) [22] $112,287 (cost/ life year gained) [23]	
		General Population (16-55yo)	$116,200 (cost/ life year gained) [22] $125,200 (cost/ life year gained) [23]	
Lynch Syndrome	MLH1, MSH2, MSH6, PMS2	General Population (20yo, no risk)	$490,315 (cost/ life year gained) [11]	"Universal screening offered the greatest benefit in clinical outcomes, although it did so at the least attractive cost-effectiveness ratios. However, as the risk threshold for genetic testing was set to 5.0% and 10% (non-universal screening), the cost-effectiveness values fell below the benchmark of $50,000 per QALY. [11] "Results suggest that reflex testing for LS in newly diagnosed CRC patients aged < 50 years is cost-effective. Such testing may also be cost-effective in newly diagnosed CRC patients aged < 60 or < 70 years." [40]
		General Population (25yo, no risk)	$7,008,872 (cost/life year gained) [11]	
		General Population (no risk)	$129,852 (cost/ life year gained)	

*ICERs from Marks 2000, 2002, and Snowsill 2014 were reported in GBP. They were converted to USD based on year end (Dec 31st) conversion rates: 0.66 (2000), 0.62 (2002), 0.64 (2014).