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Genetic testing and economic evaluations: a systematic review of the literature

Test genetici e valutazioni economiche: una revisione sistematica della letteratura

WORKSHOP 7
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Abstract

Objectives. To identify those studies in which economic analysis of predictive genetic and pharmacogenetic testing programs have been carried out. Since the Italian National Prevention Plan 2014-2018 foresees the implementation of genetic testing for inherited breast cancer, special attention was given to the cost-effectiveness of *BRCA1/2* testing programs.

Methods. A systematic review of primary economic evaluations (EEs) of predictive genetic and pharmacogenetic testing programs and an overview of previously published systematic reviews of economic evaluations (ERs) was performed.

Results. Overall 128 EEs and 11 ERs were identified. The methodological quality of both EEs and ERs was good on average. Both predictive genetic and pharmacogenetic testing programs were mainly concerned with oncological diseases. Seventeen percent of genetic testing programs are cost-saving, while a further 44% of cost/QALY ratios fall under the commonly used threshold of €37,000 per QALY. For *BRCA1/2* testing, only cascade genetic screening programs, targeted to close relatives of carriers, show clear evidence of cost-effectiveness.

Conclusion. Despite some limitations, EEs and ERs are powerful tools that provide indications to policy-makers on which genetic testing programs might be introduced into health care systems and public health practice.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 45-50)

Key words: genetic tests, pharmacogenetic tests, BRCA1/2, cost-effectiveness, systematic review

Riassunto

Obiettivi. Identificare le analisi economiche dei programmi sanitari dei test genetici predittivi e farmacogenetici. Particolare attenzione è stata data ai test genetici *BRCA1/2*, in quanto il Piano Nazionale della Prevenzione 2014-2018 prevede la realizzazione di programmi di prevenzione del carcinoma ereditario della mammella.

Metodi. E' stata svolta una revisione della letteratura economica di studi primari (valutazioni economiche, EE) e secondari (revisioni sistematiche, ER) finalizzata alla valutazione dei programmi sanitari genetici.

Risultati. Sono state identificate 128 EE e 11 ER. Sia gli studi primari sia i secondari hanno una buona qualità metodologica. I programmi genetici più frequentemente analizzati sono quelli relativi a patologie oncologiche. L'analisi dei rapporti costo-utilità ha evidenziato che il 17% dei programmi sono cost-saving e il 44% risulta sotto la soglia di €37.000 per QALY. Lo screening genetico *BRCA1/2* "a cascata" sui parenti dei portatori ha chiare evidenze di costo-efficacia.

Conclusione. Nonostante alcune limitazioni, EE e ER sono potenti strumenti di guida per l'implementazione di programmi di screening genetico.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 45-50)

Parole chiave: test genetici, test farmacogenetici, BRCA1/2, costo-efficacia, revisione sistematica

INTRODUCTION

As genomic technologies develop and groundbreaking research is translated into a better understanding of its implications for clinical practice, public and policy-makers' interest increases and effective genetic testing is carving out a thriving piece in health care systems and public health policies. For example, in Italy, the National Prevention Plan 2014-2018 has recently introduced genetic testing for *BRCA* as a preventive strategy aimed at reducing the incidence of inherited breast and ovarian cancer, delegating to Italian Regions the most appropriate

local planning of *BRCA* genetic testing programs.[1] Thus the promise of predictive medicine is gradually becoming a reality in public health care and this trend is likely to increase for the foreseeable future.

Despite the prominence of frontline research, the vast majority of potential genetic/genomic applications (tests or interventions) have not yet been implemented into clinical practice; indeed, it is estimated that not more than 3% of published research focuses on the translation from experimental genetic/genomic applications to evidence-based guidelines and health care practice.[2] Thus, this "implementation research" receives relatively little attention, with few genetic and genomic applications actively considered for introduction into clinical practice.[2,3] One barrier to such implementation is a lack of appreciation of the cost-benefit of new testing regimes, particularly pertinent nowadays, when health care systems are under financial pressure. Therefore, economic evaluations of candidate technologies should benefit clinicians and public health officials when deciding which genetic tests to introduce, how to manage carriers and non-carriers, and how to assess the impact of testing on health-related quality of life.[4] In fact, economic analysis allows one to collect and integrate all relevant factors linked to genetic testing (prevalence of disease and mutation, specificity and sensitivity of the test, association between genotype and phenotype, efficacy of interventions in preventing disease) and to estimate the benefits and costs of an entire health care program, beginning with the characteristics of a target population and continuing with preventive surveillance, prophylactic treatments and consequent follow-up.[4,5]

This review aims to map which economic studies have been conducted concerning genetic and pharmacogenetic testing programs. Since the Italian National Prevention Plan 2014-2018 foresees the implementation of nationwide genetic testing for inherited breast cancer, special attention is given to full economic evaluations of *BRCA1/2* testing programs.

METHODS

We performed a systematic review of primary economic evaluations (EEs) of predictive genetic and pharmacogenetic testing programs and an overview of previously published systematic reviews of such economic evaluations (economic reviews, ERs).

Literature search and eligibility criteria

Two investigators independently searched Medline, Embase, NHS Health Economic Evaluations Database, the HTA database, the Cost-effectiveness Analysis (CEA) Registry, and the Cochrane database of systematic reviews from inception to the end of 2012 for EEs and ERs of genetic testing programs, using the following search terms: "genetic* OR pharmacogenetic*", "economic evaluation* OR cost-effectiveness OR cost-utility OR cost-benefit OR cost-minimization OR QALY* OR LYG*", "systematic review". A manual review of references from eligible EEs and ERs was also performed. Titles, abstracts and full texts of the resulting papers were examined in detail, and discrepancies were resolved by consensus. Articles were considered eligible if the authors had performed a full economic evaluation (for primary studies, EEs) or they had included only full economic evaluations (for systematic reviews, ERs) related to the implementation of genetic tests in health care programs.

Data extraction and quality assessment

For each EE, in addition to information on authors, journal, funding declaration and year of publication, the following data were recorded: type of economic evaluation (cost-utility, cost-effectiveness, cost-benefit, or cost-minimization analysis), analytical approach, outcome measures, study perspective, collection of cost and effectiveness data, time horizon, discounting, sensitivity analyses, setting, target population, gene and clinical condition, testing scope, health care pathways triggered by test results. The quality of the studies was assessed independently by two raters using the Quality of Health Economic Studies (QHES) scale.[6]

From each eligible ER, two investigators abstracted information independently on first author, year of publication, outcomes examined, number of included studies, and reported summary results (target population, gene and clinical condition, testing scope). Since no quality assessment checklists exist in the literature to evaluate ERs, the methodological quality of each ER was assessed with a tool developed from three available methodological handbooks that deal with the systematic review of economic evaluations.[7-9]

Data synthesis

Given the considerable heterogeneity of EEs, the combination of results by quantitative meta-analysis was not possible, and therefore a descriptive synthesis was performed. Due to the large quantities of data synthesized and results generated, we have reported here only those details of incremental cost-effectiveness ratios for *BRCA* testing strategies, which thus serve as an example and case study. A descriptive analysis of the ERs of genetic testing programs was also performed.

RESULTS

A total of 758 studies were retrieved from electronic databases; a further 45 articles were obtained from other sources, including a review of references cited in the 758 studies initially identified. After removing duplicates and screening for title/abstract, 190 and 23 full-text articles were assessed for eligibility as EEs and ERs, respectively. Double screening and review of these yielded 128 EEs and 11 ERs that met the inclusion criteria (for the PRISMA flow diagram, see the Appendix, available online).

Economic evaluations (EEs)

The 128 EEs included in this study (see the Appendix for references) mainly originated from the U.S. (62 EEs, 48%) and Europe (46 EEs, 36%) with only a few carried out in Asian countries (9 EEs), Canada (7 EEs), and Australia (4 EEs). Cost-utility analysis (CUA) was the methodology most frequently used (73, 57%), followed by cost-effectiveness analysis (CEA) (67%). Sixty-seven EEs (52%) adopted the health care system

perspective, 39 EEs (30%) the societal perspective and seven EEs performed the economical evaluation from the perspective of third-party payers; in 15 EEs the analytical perspective was not reported. The time horizon was lifetime in more than half of the studies (69 EEs, 54%); thirteen pharmacogenetic tests adopted a time horizon of less than one year. In terms of effectiveness, outcome measures were different according to the test category: for predictive genetic testing programs the results were mainly presented as LYGs, while for pharmacogenetic testing programs the outcomes most frequently used were QALYs (table 1).

The mean quality assessment score of all 128 EEs was 78, indicating good average quality. Almost 40% of studies were published after 2009 and these were assigned an average score slightly higher than those published prior to that year (81 *vs* 74). No significant differences in quality were detected between EEs of predictive genetic and pharmacogenetic tests (table 1).

Predictive genetic testing programs (66, 52%) were more often studied than pharmacogenetic testing programs (62, 48%). Predictive genetic testing programs were mainly concerned with prevention of oncological diseases (40%), in particular hereditary colorectal syndromes (Lynch syndrome and familial adenomatous polyposis) and hereditary breast and ovarian cancer syndrome. Less studied were genetic tests for some inherited disorders such as hereditary haemochromatosis, cystic fibrosis, chromosomal abnormalities, and thrombophilia. Other disorders such as familial hypercholesterolemia, fragile X syndrome, long QT syndrome, and hypertrophic cardiomyopathy were evaluated in only a few studies (table 1).

Most EEs of pharmacogenetic testing programs were concerned with the analysis of genetic information from patients with neoplastic disorders (breast, colorectal, and lung cancer) to target specific drug therapies (23, 37%). Genetic variations associated with anticoagulation treatment for venous thromboembolism were evaluated in nine EEs (14%). Pharmacogenetic tests for chronic viral diseases such as AIDS and hepatitis C were studied in 11 EEs (18%). Six studies assessed pharmacogenetic tests for the detection of thiopurine methyltransferase (TPMT) mutation carriers before therapy with thiopurine drugs; this allowed optimal dosage to be determined and toxicity to be minimized in patients with inflammatory bowel disease, rheumatic conditions, or acute lymphoblastic leukemia. A small number of studies also evaluated pharmacogenetic tests for depression and chronic kidney disease (table 1).

CUA is the most recommended method of economic evaluation according to widely accepted guidelines, because it incorporates quality of life measures and enables standardized comparisons across studies.[10] A total of 73 CUAs were retrieved in this study, of which 66 are also included in the CEA Registry, which is the most comprehensive and recent source of CEAs available.[11] From these 66 CUAs, a total of 138 incremental cost-effectiveness ratios were extracted and expressed as 2013 Euros per QALY gained. The majority (68%) of cost/QALY ratios indicate that genetic testing programs provide better health outcomes although at higher cost, with almost half the ratios falling below €37,000 per QALY, a commonly used threshold. Seventeen percent of genetic testing programs are cost-saving. Pharmacogenetic testing programs are more likely to be cost-saving, but predictive genetic tests more frequently result in cost-effectiveness ratios below the threshold of €37,000 per QALY (figure 1).

Economic reviews (ERs)

The 11 ERs included in this study were performed in Canada,[12-15] the US[16-18] and Europe (Netherlands, UK, and Germany),[19-22] from 2003 to 2012.[15,20] Two ERs focused on predictive genetic testing programs,[15,19] five on pharmacogenetic tests,[13,17,18,21,22] and three investigated both genetic testing programs.[12,14,16] The majority of these ERs were conducted to assess the methodological quality of EEs of genetic tests,[12-16,21] or to simply identify those economic studies conducted in the field,[17,18,21] since they included a wide range of genetic tests. Only two ERs focused on a specific genetic test.[20,22]

Almost all ERs evaluated the methodological quality of the primary studies using different standardized tools.[12-14,16,18-22] The most common limitations of primary studies found by the ERs were: lack of a defined analytical perspective;[12,14,16,19,21] lack of coherence between perspective of analysis and costs;[19] inappropriate sensitivity analyses;[12,19,21] no discussion of potential bias.[12,14,16] Other methodological deficiencies were the absence of definitions of time horizon and discount rate.[13,14,19,21]

The ERs themselves were of good or moderate quality. Almost all ERs formulated a clear research question and used appropriate eligibility criteria for the inclusion of primary studies, but the methodology for the identification and selection of primary studies was judged appropriate in only half of the ERs (data not shown).

Cost-effectiveness of *BRCA* genetic testing programs

BRCA1/2 mutations account for about 5-10% of all breast cancers and for around 15% of ovarian cancers overall.[23] Harmful mutations in *BRCA1* and *BRCA2* have high penetrance, dramatically increasing lifetime risk of developing breast and ovarian cancers (45-65% breast and 11-39% ovarian cancer).[24] *BRCA* genetic testing is a powerful tool for reducing the incidence of these inherited cancers. Nine EEs that compared different strategies for determining the most efficient use of such tests were retrieved after a systematic search (updated to Jan 2015). Three main programs were analyzed in these EEs: population-based genetic screening,[25-27] family history (FH)-based screening and,[28-30] and cascade genetic screening.[31,32]

Population-based genetic screening was assessed for the Ashkenazi Jewish community in three EEs in which *BRCA1/2* tests were offered to all women regardless of their individual or familial risk.[25-27] Cost-effectiveness results were more favourable if women underwent prophylactic surgery (mastectomy and salpingo-oophorectomy), varying from cost-saving to $8,300 per QALY. Three EEs described a FH-based screening program in which only high risk women were tested, with the risk assessment based principally on the family history.[28-30] This ap-

Table 1. Main characteristics of full economic evaluations (EEs) of predictive genetic and pharmacogenetic tests.
Tabella 1. Principali caratteristiche delle valutazioni economiche complete dei test genetici e farmacogenetici.

	Predictive genetic test	Pharmacogenetic test	Total
	EEs (%)	EEs (%)	EEs (%)
Type of economic evaluation			
CUA	20 (30.3)	37 (59.7)	57 (44.5)
CEA	34 (51.5)	16 (25.8)	50 (39.1)
CEA & CUA	9 (13.6)	7 (11.3)	16 (12.5)
CBA	2 (3.1)	1 (1.6)	3 (2.3)
CBA & CEA	1 (1.5)	--	1 (0.8)
CMA	--	1 (1.6)	1 (0.8)
Analytical perspective			
health care system	28 (42.4)	39 (62.9)	67 (52.3)
societal	22 (33.3)	17 (27.4)	39 (30.5)
third-party payer	5 (7.6)	2 (3.2)	7 (5.5)
n.r.	11 (16.7)	4 (6.5)	15 (11.7)
Time horizon			
lifetime	39 (59.1)	30 (48.4)	69 (53.9)
>1 year	7 (10.6)	13 (21.0)	20 (15.6)
≤1 year	4 (6.1)	13 (21.0)	17 (13.3)
n.r.	16 (24.2)	6 (9.6)	22 (17.2)
Outcome measures of effectiveness			
LYGs	24 (36.4)	2 (3.2)	26 (20.3)
QALYs	21 (31.8)	37 (59.7)	58 (45.3)
LYGs & QALYs	7 (10.6)	5 (8.1)	12 (9.4)
cases detected	8 (12.2)	1 (1.6)	9 (7.0)
disease-free newborns	2 (3.0)	--	2 (1.6)
cancer-free years	1 (1.5)	--	1 (0.8)
adverse effects avoided	1 (1.5)	8 (13.0)	9 (7.0)
monetary units	1 (1.5)	1 (1.6)	2 (1.6)
patients cured	--	1 (1.6)	1 (0.8)
others	--	4 (6.4)	4 (3.1)
n.r.	1 (1.5)	3 (4.8)	4 (3.1)
Quality score (QHES scale)			
0-25	--	--	--
26-50	4 (6.1)	4 (6.4)	8 (6.3)
50-75	27 (40.9)	19 (30.6)	46 (35.9)
76-100	35 (53.0)	39 (63.0)	74 (57.8)
type of disease			
hereditary colorectal cancer	17 (25.7)	--	17 (13.3)
hereditary breast/ovarian cancer	9 (13.6)	--	9 (7.0)
hereditary haemochromatosis	6 (9.1)	--	6 (4.7)
cystic fibrosis	6 (9.1)	--	6 (4.7)
chromosomal abnormalities	6 (9.1)	--	6 (4.7)
thrombophilia	5 (7.6)	--	5 (3.9)
familial hypercholesterolemia	3 (4.5)	--	3 (2.3)
fragile X syndrome	2 (3.0)	--	2 (1.6)
long QT syndrome	2 (3.0)	--	2 (1.6)
hypertrophic cardiomyopathy	2 (3.0)	--	2 (1.6)
breast cancer	--	15 (24.3)	15 (11.7)
venous thromboembolism	--	9 (14.5)	9 (7.0)
AIDS	--	8 (12.9)	8 (6.3)
colorectal cancer	--	5 (8.1)	5 (3.9)
inflammatory bowel disease	--	4 (6.5)	4 (3.1)
chronic hepatitis C	--	3 (4.8)	3 (2.3)
lung cancer	--	3 (4.8)	3 (2.3)
major depressive disorder	--	3 (4.8)	3 (2.3)
chronic kidney disease	--	2 (3.2)	2 (1.6)
acute lymphoblastic laeukemia	--	2 (3.2)	2 (1.6)
rheumatic diseases	--	2 (3.2)	2 (1.6)
others	8 (12.3)	6 (9.7)	14 (10.9)
Total	**66 (100)**	**62 (100)**	**128 (100)**

CUA: cost-utility analysis; CEA: cost-effectiveness analysis; CBA: cost-benefit analysis; CMA: cost-minimization analysis; EE: economic evaluation; n.r.: not reported; LYGs: life years gained; QALYs: quality-adjusted life years gained

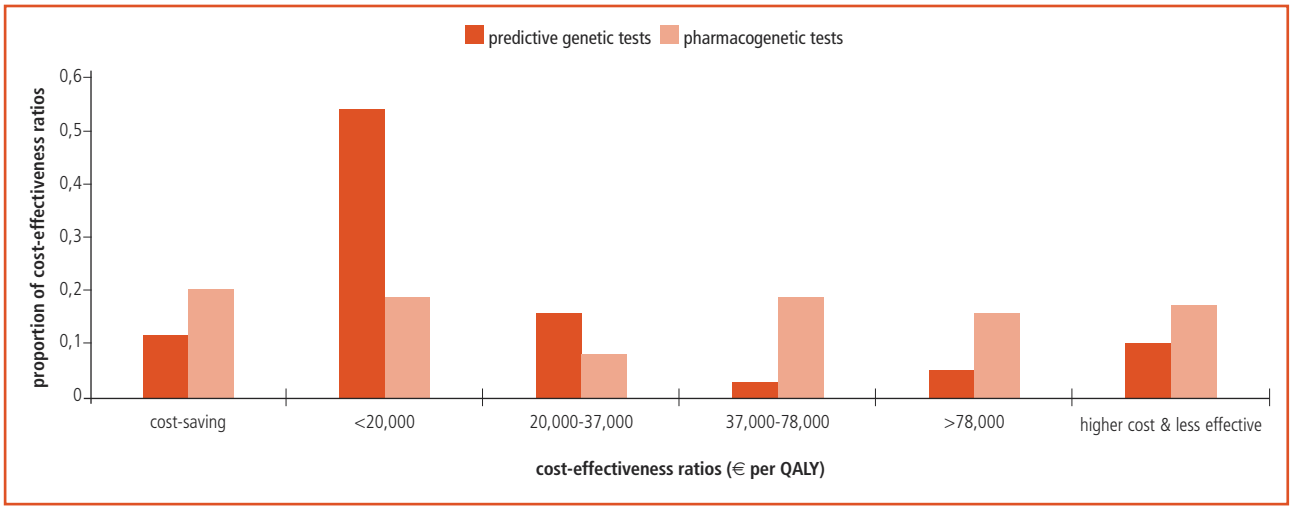

Figure 1. Distribution of cost-effectiveness ratios (€ per QALY gained) for genetic and pharmacogenetic tests (N=138 ratios).
Figura 1. Distribuzione dei rapporti di costo-efficacia (€ per QALY guadagnato) per i test genetici e farmacogenetici (N=138 rapporti).

proach proved cost-effective ($4,294 per LYG, $3,500-5,000 per QALY), but the costs of the identification of high-risk women were not considered. In both of the two EEs that focused on cascade genetic screening, BRCA tests were offered to close relatives of previously identified carriers (known familial mutation) and were cost-effective ($32,670 per QALY, €832 per LYG).[31-32] Finally, one EE investigated genetic screening among women with breast cancer to prevent both ipsilateral (if they were treated with breast-conserving therapy) and contralateral cancer recurrence, in addition to ovarian cancer.[33] This strategy was cost-effective only for particular conditions.

DISCUSSION

The results of the exercise conducted in this study clearly show that genetic testing is a major theme in health economics, with many examples in the literature of full EEs and ERs covering a wide range of diseases. Nevertheless, a remarkable number of genetic tests have not yet been evaluated, including some with demonstrated clinical utility that are related to diseases with high health burden and/or high expenditure (e.g., melanoma, congenital disorders assessed using a newborn screening panel, epilepsy, trigeminal neuralgia, chronic gout, Huntington's disease).[34] However, since the economic health literature was only searched for papers published up to the end of 2012, it is possible that many emerging tests and currently available tests are not included in the present review. By contrast, most genetic tests assessed by EEs have not been evaluated for clinical effectiveness;[35,36] this could prematurely move genetic testing toward practice with potentially adverse effects for patients and the health care system.[37]

Only 12% of predictive genetic tests and 21% of pharmacogenetic tests are cost-saving. The majority of the cost-utility ratios indicate that these tests provide better health care, but at higher cost. These results are consistent with the findings of a previous review of EEs of personalized medicine tests,[35] indicating that genetic testing can save money only in a small minority of cases. However, these results are in line with those from other fields, where it was shown that less than 20% of preventive measures and treatments for existing conditions are cost-saving.[38] Of more concern is the absence of demonstrated clinical utility for a significant proportion of genetic tests. Therefore, some genetic tests may not be cost-effective because of a lack of demonstrated clinical utility.[35,36] On the other hand, more reassuring is the methodological quality of the economic evaluations retrieved, which is good on average and may be improving over time.

The principal limitations of conducting a systematic review of economic evaluations derive from their high degree of heterogeneity, meaning that results cannot be pooled across studies and are difficult to investigate with current statistical methods.[13,14,16,17] Nevertheless, even using descriptive approach only, exhaustive reviews of economic evaluations may usefully inform stakeholders and policy-makers of the potential for cost-effectiveness interventions.[14,15,18] Thus, in the example we used, *BRCA1/2* genetic testing, a systematic review of cost-effectiveness analyses clearly illustrates that there is evidence of cost-effectiveness only for genetic testing targeted to populations at high risk, such as the close relatives of carriers (cascade genetic screening programs). Despite these findings, FH-based screening programs are very promising, but the published EEs did not include the costs of the selection process of high-risk women through a familial risk assessment. Therefore, at least in Italy, only cascade genetic screening programs can be considered ready at present for a full implementation in health care.

In conclusion, full EEs of genetic tests and ERs are potentially very useful for providing indications to policy-makers by which genetic applications could be introduced into general health care and public health practice. However, many genetic tests have not yet been subjected to formal EE and, perhaps most importantly, many genetic tests have not been demonstrated to have clinical utility. EEs, particularly those using rigorous modelling exercises, could also be useful for the selection of genetic/genomic applications that are most promising in terms of value for money and may thus direct and prioritize research efforts.

Conflicts of interest: part of the work described in this paper is connected to the project «L'impatto economico dei test genetici sul Servizio Sanitario Nazionale (SSN): valutazione dei percorsi diagnostico-assistenziali, stime di costi-efficacia e costi-utilità e analisi delle politiche sanitarie a livello europeo» (The economic impact of genetic testing on the National Health Service: evaluation of diagnostic care pathways, estimates of cost-effectiveness and cost-utility and investigation of health policies at European level), funded by the Italian Ministry of Health.

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