Review of economic assessments of emerging genomic technologies in oncology

Dr. Luís Quecedo Gutiérrez
Fundación Gaspar Casal, Madrid

Dr. Juan del Llano Señarís
Fundación Gaspar Casal, Madrid

Dra. Maria Luz Amador
Roche Farma España

Corresponding autor:
Luis Quecedo
General Díaz Porlier 78
28006 Madrid
Spain
+34 91 401 62 19
fgcasal@fgcasal.org
Summary

Introduction
A systematic review has been conducted of economic assessment studies of the application of genomics and proteomics in oncology. The aim is to assess the emerging diagnostic and therapeutic technologies whose cost-effectiveness ratio makes them socially suitable to be used in various health systems.

Methods
The relevant studies carried out in the last 10 years were retrieved from the Medline, Embase, Cancerlit, and Cochrane Library databases, and the results studied.

Results
Fourteen studies were analysed: 5 on breast cancer, 8 on colorectal neoplasm, and 1 on urologic disorders. Of the studies reviewed, 4 were cost-utility studies, 9 were cost-effectiveness studies, and 1 was a cost-minimisation study.

Discussion
In the context of breast cancer genetic counselling, BRCA 1 and 2 gene sequence analysis has resulted in a favourable cost-effectiveness. In the screening of patients with HER-2 protein overexpression, the use of the Hercep test followed by a FISH confirmation has shown a more favourable cost-effectiveness ratio than the use of FISH alone. The Oncotype Dx and MammaPrint microarray-based tests have great potential as tools for the analysis of the risk of recurrence and of gene expression profiles. In hereditary colorectal cancer, identification of the APC, MSI, and MLH1 and MSH2 genes through specific tests improves survival and the outcomes of family genetic counselling. In prostate cancers, test of DNA-ploidy is relatively inexpensive and provides a high QALY
Conclusion

There has been a significant increase in economic assessment studies of the applications of genomics. These have greatly contributed to the work of healthcare and medical decision-makers when assessing the suitability and pertinence of incorporating the contributions of genomics into oncology, and the ethical and social issues involved.

Keywords: genetic screening, pharmacogenomics, cost analysis, oncology, cancer.
Introduction

When assessing response to a therapeutic agent, the most outstanding observation made by physicians is the interindividual variation. This variability is associated with the genetic characteristics of each individual, which are modulated by physiological, pathological and environmental factors. The specific genetic makeup of an individual underlies both the pharmacogenomic factors that determine the drug concentration at its site of action, and the pharmacodynamic factors involved in the drug’s specific action and adverse reactions. In practice, this means designing personalised treatment strategies based on the specific genetic profile of each patient that could impact health policy decisions.

A basic concept in pharmacogenomics is that the therapeutic response to a drug is neither consistent nor predictable, largely due to individual genetic variability affecting either the receptor proteins for the drug, or cell transport mechanisms, or enzymes that participate in its metabolism. Thus, one of the main targets of pharmacogenomics is to yield a modality of individualised therapeutics that takes into account the risk/benefit ratio from different perspectives such as clinical, society, health policy, economics, that is, to determine the drug or technology of choice according to the specific manifestation of the patient’s condition, and the appropriate dose in order to achieve the sought therapeutical effect, minimising the risk of adverse reactions.

The National Cancer Institute estimates global health expenditure including direct medical costs, mortality associated cost and research investment as around 104 billion $ 1996 prices. Prompt screening has been for determined cases the most effective strategy of reducing costs in oncology. Pharmacogenomics has the potential of reducing medical
cost trough identifying those patients with respondant tumors of selected treatments. A large focus area of oncology research is the identification of the distinctive physiological characteristics of tumour cells. This information enables clinicians to decide whether or not a particular type of cancer requires a specific treatment, and to assess the effects of the treatments being used. The Human Genome Project has fostered the development of new healthcare technologies, which have brought to the conventional medical practice major technological advances such as screening and prevention for patients with genetic predisposition to certain conditions, development of therapies based on genetically engineered drugs or molecules, and establishment of individualised therapies based on the genetic information of the patient.

Genomics contribute to clinical oncology in the following areas2,3,4:

- Elucidation of molecular and cellular mechanisms, and development and analysis of genomic and proteomic scanning techniques to characterise tumours
- Development and standardisation of protocols applicable to the epidemiology, diagnosis and prevention of familial and sporadic cancer
- Development and evaluation of new antitumour agents, with a special emphasis on the optimisation of active agents and the individualisation of pharmacological treatments, based on predictive factors

A comprehensive analysis of the potential benefits of pharmacogenomics should be conducted using formal economic assessment studies, including cost-effectiveness, cost-utility and cost-minimisation analyses, leading to better distribution of health system resources5,6. Recent systematic reviews of the use of genetic screenings in various medical specialities suggest that, in spite of the few assessment studies available, there is evidence to support the benefits of genetic screening in healthcare, not only for populations with high risk of developing certain diseases, but also for the general
population, and that the reduction of test costs would increase their utilisation\textsuperscript{7,8}. However, current economic studies evaluating pharmacogenomical interventions from a social point of view must be conducted based on the prevalence, severity and penetrance of the genetic alteration in question, the cost and availability of the diagnostic test, and the cost and severity of its implications\textsuperscript{9}.

The aim of the current work is to identify existing economic assessments on medical technologies in oncogenomics so as to evaluate the appropriateness of their use in clinical practice.
Materials and Methods

Data source and search strategies

The search for medical literature to be analysed was conducted in the major biomedical databases (Medline, Embase, Cancerlit), as well as publications by various healthcare technology assessment bodies, including INHATA, CCOHTA, NHSEED and the Cochrane Collaboration database of systematic reviews and clinical trials. The bibliographic search covered all the studies published between 1996 and 2007.

We have used specific MeSH descriptors, in both free and controlled language.

Table 1

Inclusion and Exclusion Criteria

Our review included all the scientific works available on the application of pharmacogenomics in oncology that covered clinical aspects such as screening and genetic counselling, therapeutic treatments and potential side effects. The methodology used in the studies selected for analysis had to meet some basic requirements, among them the inclusion of cost-effectiveness, cost-utility or cost minimisation economic assessment analyses. Studies with cost analyses that were merely descriptive or did not compare or estimate final outcomes, or calculate the life-years gained QALY, etc., were excluded. The studies selected had to include information about the screening tests used, the characteristics of the study population or the sources from which the data analysed was obtained, and the genetic mutations involved in the diseases studied.

The cost analyses selected had to include a sensitivity analysis, and information about the currency and discount rates used in the calculations.
Selection of Publications

Two independent reviewers not involved in the writing of this paper assessed the studies selected from the bibliographic search results. They were charged with coding the outcomes and resolving any discrepancies by discussion and mutual consensus.

Results

Of the 19 studies found, 14 met the inclusion criteria for our review. Five of them were related to screening and therapeutic aspects of breast cancer, 8 about genetic counselling and screening of hereditary colon cancer and familial polyposis, and 1 about prostate cancer. Table 2 summarises the studies reviewed.

The following aspects were taken into consideration when reviewing the reports: type of study, study population, type of mutation studied and test used, primary outcome and conclusions. We summarized the relevant details of the studies review in Table 3.

Discussion

Cancer is a major health concern in the developed world, with a particularly negative impact on the economically less favoured populations. Current survival rates for cancer have significantly increased, but still there is room for improvement in the work of both researchers and healthcare managers, regarding the prevention, diagnosis and treatment of the disease\textsuperscript{26}.

Previous systematic reviews of economic assessments of the application of pharmacogenomics have shown that there is limited literature available on this subject\textsuperscript{7,8}. Most studies reviewed to date have focused mainly on rheumatology, haematology and oncology, and have primarily studied populations with high risk of developing or inheriting specific genetic mutations.
Current cancer pharmacogenomic studies focus on the diagnosis and screening aspects of high-prevalence hereditary tumours. Screening for the genetic mutations underlying certain malignant neoplasms, directly affects the follow-up of probands with positive genetic tests, as well as their first- and second-degree relatives, whose prognosis and quality of life may become considerably changed as a result. In this sense, it has been established that a significant number of women diagnosed with breast cancer receive unnecessary treatments with no benefit their health\textsuperscript{27}. The cost of overtreatment or of treating ineligible patients is significantly high, not only in economic terms, but also in connection with short- and long-term toxicity, and from a social perspective with its impact on quality of life and a resulting decrease in the resources available. Several genetic tests allow characterising breast cancer, and typifying the different genetic stages of its clinical course. Studies by Lawrence\textsuperscript{12} and Balmaña\textsuperscript{13} concluded that the cost-effectiveness ratio of BRCA 1 and 2 mutation analyses is acceptable in patients with high risk of hereditary breast cancer and their relatives. These tests are of particular value in the decision-making process in the context of genetic counselling to patients or their relatives. In spite of the fact that carrying out BRCA 1 and 2 gene analysis increases costs up to €4,294 per year of life saved, these assessments do not factor in the social and psychological impact of the disease on the quality of life of patients.

Overexpression of the HER-2 protein, the therapeutic target of trastuzumab, is found in 15-25% of patients with metastatic breast cancer. Combined treatment with trastuzumab and chemotherapy significantly increases the therapeutic response rate, the recurrence-free interval and survival.\textsuperscript{28,29} There are two genetic tests currently available in clinical practice: HercepTest\textsuperscript{TM} and FISH, with the former being the easier to use and the cheaper of the two. However, the FISH test is a better predictor of response to trastuzumab, so it can be used alone or to confirm a positive result with HercepTest.
Elkin\textsuperscript{11} analysed various strategies for the use of these tests, either alone or in combination, to assess therapeutic response in patients treated or not with trastuzumab.

This study highlights the importance of identifying those patients who are good candidates for treatment, and the considerable influence exerted on the cost-effectiveness ratio by both the high cost of treating false-positive cases, and the failure to treat false-negative patients— and this irrespective of the cost of the test. The difference between the two strategies (HercepTest and confirmatory FISH as opposed to FISH alone) is distributed in favour of the first one in a narrow range of up to $20,000 per QALY gained. This means that there is no dominant alternative to the combined use of HercepTest and confirmatory FISH; hence, choosing one over the other will essentially depend upon the budget available, after proper consideration of the pros and cons of each strategy.

The characterisation of genes controlling cell cycle, invasiveness, metastatic potential and angiogenesis – all of which influence the natural evolution of breast cancer – enables to identify those patients whose gene expression profiles or risk of recurrence make them good candidates for a particular treatment strategy. Conventional predictive factors, lymph node involvement and histological grade, often fail to identify patients with high risk of metastasis. Chemotherapy and hormonotherapy can reduce distant metastasis rate by up to 30%. However, 70-80% of lymph-node negative patients treated with chemotherapy do not really need it. Commercially available DNA microarray-based tests, which allow to analyze up to 70 genes involved in breast cancer (MammaPrint\textsuperscript{®}, Agendia), are able to predict survival and distant metastasis in patients with negative nodes. Using this test, Oestreicher et al.\textsuperscript{14} reported a 5% decrease in distant metastasis frequency, as compared with that obtained following traditional clinical criteria. However, the study found a reduction of 0.21 quality adjusted life-years,
with a cost savings of $2,882, therefore concluding that gene expression profile analyses have great potential, but still require validation prior to use in clinical practice. Another commercially available test, Oncotype Dx™, enables to analyse 21 genes by means of PCR techniques, in order to estimate the likelihood of recurrence of early breast cancer (lymph-node negative and oestrogen receptor positive). In their economic assessment of the use of Oncotype Dx™, Hornberger et al.15 reported a cost of €31,452 per quality-adjusted life-year gained, for re-staging a patient as medium-high risk of recurrence. Therefore, they concluded that in patients with early breast cancer, with negative lymph nodes and oestrogen receptor positive, the use of this test results in cost reduction and an increase in quality adjusted life-years gained.

In patients with hereditary colorectal cancer, the identification of APC gene mutations, microsatellite instability (MSI) or MLH1 and MSH2 (MMR) genes by means of genetic tests improves the survival of patients and their relatives. MSH2 and MLH1 mutation carriers have a 50-85% probability of developing colon and, to a lesser extent, ovarian (20-50%), and other organ (<10%) cancers.30,31 In clinical practice, detection of MSI and MMR gene mutations in patients with colorectal cancer serves mainly to optimise the genetic counselling to probands and their high-risk relatives, as tumours with high levels of MSI have better prognosis and derive little benefit from adjuvant therapy with 5-fluorouracil.32 The screening and subsequent genetic counselling of patients and their relatives make it possible to identify carriers of such defects. The economic assessments conducted by Ramsey,19 Reyes20 and Kievit21 showed a favourable cost-effectiveness ratio for the inclusion of these tests in different screening strategies. The ratio becomes more favourable when the relatives of probands with positive tests are included in the screening, and when combined strategies are used together with clinical criteria such as the Amsterdam test and/or modified guidelines.
Cromwell, Bapat and Chikhaoui found similar results when the identification of APC gene mutations was included in the screening and genetic counselling strategies of patients with familial adenomatous polyposis. All three groups found cost savings when this test is used, as compared to clinical screening. In addition, they stressed the importance of intangible costs such as avoiding unnecessary colonoscopies and their associated complications for patients.

Another genetic test used as a prognosis marker in oncological conditions is the DNA-ploidy analysis. This test is used to examine chromosomal balance, based on the hypothesis that loss of diploidy results in imbalanced expression of oncogenes and suppressor genes. Image-based autoanalyzers allow fast and reliable diagnosis by assessing ploidy in needle-biopsy samples. Calvert et al. examined the clinical application of autoanalyzers and developed a model for prostate cancer therapy using DNA-ploidy markers to select candidates for prostatectomy. In its economical and social assessment of this strategy and its impact on patient quality of life, this study found an incremental cost of £12,068 per quality-adjusted life-year gained, while in patients with localised, moderately graded tumours, prostatectomy seems to be relatively costly and adds little benefit to the patient quality of life. The recommendation is then to adopt the observation strategy, and base prostatectomy decisions upon prognosis marker results.

Conclusions

Most diagnostic tests developed and evaluated are used to either identify patients that are good candidates for a certain treatment, or make decisions about therapeutic interventions. These tests allow to select patients more accurately, and to individualise therapeutic interventions based on the particular genotype of each patient, thus avoiding unnecessary treatments. The studies reviewed show that the use of pharmacogenomics in clinical practice can reduce costs, when applied in the screening and genetic counselling
of patients with hereditary familial polyposis or nonpolyposis colorectal cancer. Genetic mutation analyses have shown a favourable cost-effectiveness ratio when used in the screening and genetic counselling of patients with hereditary breast and ovarian cancer. In patients with metastatic breast cancer, genetic screening of candidates for treatment with trastuzumab, has shown the suitability of the FISH test, alone or as confirmation of HER-2 positive cases, to reduce costs and improve the quality of life of eligible patients. This is also the case in patients with early breast cancer, since knowledge of the existing gene alterations optimises patient selection for adjuvant chemotherapy.

In recent years, an increasing number of economic studies have addressed, from a social point of view, the impact of pharmacogenomics on the health status of the population and on health economic resources. The efficiency threshold for adoption of a new healthcare technology in our current environment has been estimated at approximately €30,000 per life-year gained. The use of emerging technologies in oncology has ethical and moral implications that require careful consideration. Whilst there are currently few economic analyses available in this field, these studies provide invaluable help to healthcare decision makers and service providers, when considering the suitability and relevance of incorporating genomic and proteomic techniques into the arsenal of oncological diagnostic and therapeutic tools available in their portfolio of health services.

**Conflict of interests:** For the preparation of this paper we have received a partial unconditional donation from the Roche Institute.
Table 1. Search strategy

Table 2. Economic assessment studies of the use of genomics in oncology

<table>
<thead>
<tr>
<th>Studies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost-utility</td>
<td>4</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>9</td>
</tr>
<tr>
<td>Cost-minimisation</td>
<td>1</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>5</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>8</td>
</tr>
<tr>
<td>Other tumours</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 3 Summarized of the relevant studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Elkin\textsuperscript{11} 2004</th>
<th>Lawrence\textsuperscript{13} 2001</th>
<th>Balmaña\textsuperscript{13} 2004</th>
<th>Oestreicher\textsuperscript{14} 2005</th>
<th>Hornberger\textsuperscript{15} 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Condition</strong></td>
<td>Metastatic breast cancer</td>
<td>Hereditary breast and ovarian cancer</td>
<td>Hereditary breast and ovarian cancer</td>
<td>Early stage breast cancer</td>
<td>Early stage breast cancer</td>
</tr>
<tr>
<td><strong>Type of study</strong></td>
<td>Cost-utility, with a Markov decision analysis model</td>
<td>Cost-effectiveness</td>
<td>Cost-effectiveness</td>
<td>Cost-utility, with a Markov decision analysis model</td>
<td>Cost-utility, with a Markov decision analysis model</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>&gt;65 years metastatic breast cancer</td>
<td>121 patients with breast or ovarian cancer from the CARE (Cancer Assessment Risk Evaluation) program</td>
<td>143 families, 858 patients</td>
<td>Netherlands Cancer Institute Early Breast Cancer Trialist Collaborative Group</td>
<td>668 patients from the National Surgical Adjuvant Breast Cancer Project data base 1982-1988</td>
</tr>
<tr>
<td><strong>Type of mutation</strong></td>
<td>HER-2 Acquired</td>
<td>BRCA 1/2</td>
<td>BRCA 1/2</td>
<td>70 genes GENE expression profile</td>
<td>21 genes RT-PCR recurrent score</td>
</tr>
<tr>
<td><strong>Test</strong></td>
<td>HercepTest IHC assay (DAKO) and FISH (Pathvysion, Vysis, Downers Grove)</td>
<td>Gene sequencing of BRCA 1/2 (Myriad Genetics, Inc SALT lake City, UT)</td>
<td>PTT (protein truncation test) and SSCP (single strand conformation polymorphism)</td>
<td>MammaPrint\textsuperscript{8}, Agendia</td>
<td>Oncotype Dx\textsuperscript{TM} Breast Cancer Assay, Genomic Health, Inc, Redwood City, Calif (RT-PCR)</td>
</tr>
<tr>
<td><strong>Drug /health technology</strong></td>
<td>Treatment strategies with trastuzumab based on positive HERCP and/or FISH tests</td>
<td>Genetic counselling + genetic screening versus breast cancer patients not selected</td>
<td>Genetic counselling</td>
<td>Identify patients with high risk of recurrence, for adjuvant chemotherapy</td>
<td>Risk of recurrence of the disease, recurrence score for adjuvant chemotherapy</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>ICFER: Hercep+FISH: $125,000/QALY versus FISH: $145,000 Costs: No test $79,181 FISH $54,738 FISH+Hercep: $53,702</td>
<td>Cost for genetic mutation detected: - $8,034 test + genetic counselling - $79,104 breast cancer non selected population</td>
<td>Cost year of life gained $4,294</td>
<td>5% decrease of recurrences vs. a standard strategy Decrease of 0.21 QALY and cost reduction of $2,882</td>
<td>Cost of re-staging patients as mid-high risk with RT-PCR $31,452 per QALY Cost $13,768 per LYG</td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td>The most cost-effective strategy is screening with FISH alone or confirmatory FISH only in Hercep test positive</td>
<td>Screening programs + genetic tests in patients with high risk of breast cancer have an acceptable cost-effectiveness ratio</td>
<td>Although gene expression profiling analyses have great potential, they require further validation and refinement prior to clinical use.</td>
<td>The appropriate application of genetic tests predicts more accurately the risk of recurrence in lymph-node negative, oestrogen receptor positive patients in early breast cancer, increasing quality adjusted life-years and saving costs</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Condition</td>
<td>Type of study</td>
<td>Population/source of data</td>
<td>Type of mutation</td>
<td>Test</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------------------------</td>
<td>------------------------------------</td>
<td>---------------------------</td>
<td>------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Cromwell16, 1998</td>
<td>Familial adenomatous polyposis</td>
<td>Markov model with assessment of cost minimization</td>
<td>257 patients from the Gastrointestinal familial cancer Registry Hospital Mount Sinai</td>
<td>APC gene mutation</td>
<td>PTT (Protein truncation test)</td>
</tr>
<tr>
<td>Bapat17, 1999</td>
<td>Familial adenomatous polyposis</td>
<td>Decision analysis model with assessment of cost minimization</td>
<td></td>
<td>APC gene mutation</td>
<td>Heteroduplex analysis HDA and PTT Protein truncation test</td>
</tr>
<tr>
<td>Chikhaoui18, 2002</td>
<td>Familial adenomatous polyposis</td>
<td>Markov decision analysis model with assessment of cost minimization</td>
<td>Systematic review of the literature available</td>
<td>APC gene mutation</td>
<td>Heteroduplex analysis HDA and PTT Protein truncation test</td>
</tr>
<tr>
<td>Ramsey19, 2001</td>
<td>Hereditary non polyposis colorectal cancer</td>
<td>Decision analysis model with assessment of cost minimization</td>
<td>National colorectal cancer registry data, Creighton International Hereditary Colorectal Cancer Registry</td>
<td>MSH2, MLH1 and MSI</td>
<td>Colaris test Myriad Genetics</td>
</tr>
<tr>
<td>Reyes20, 2002</td>
<td>Hereditary non polyposis colorectal cancer</td>
<td>Markov decision analysis model with assessment of cost minimization</td>
<td>National colorectal cancer registry data, Creighton International Hereditary Colorectal Cancer Registry and Medicare claims records</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Kievit(^{21}) 2004</td>
<td>Brown(^{22}) 1995</td>
<td>Hagen(^{23}) 2008</td>
<td>Calvert(^{24}) 2003</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Hereditary non polyposis colorectal cancer</td>
<td>Hereditary non polyposis colorectal cancer</td>
<td>Hereditary non polyposis colorectal cancer</td>
<td>Prostate cancer</td>
<td></td>
</tr>
<tr>
<td>Type of study</td>
<td>Cost-effectiveness</td>
<td>Markov decision analysis model with effectiveness analysis</td>
<td>Markov decision analysis model with effectiveness analysis</td>
<td>Markov model with cost-utility analysis</td>
<td></td>
</tr>
<tr>
<td>Type of mutation</td>
<td>MSH2, MLH1 and MSI.</td>
<td>Not stated</td>
<td>MSI, direct genetic testing</td>
<td>Chromosome balance</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>MSI analysis DNA analysis</td>
<td>Not stated</td>
<td>Not stated</td>
<td>DNA-ploidy test</td>
<td></td>
</tr>
<tr>
<td>Drug/health technology</td>
<td>Increased endoscopic surveillance and colectomy in the presence of mutations</td>
<td>Screening with genetic tests vs. no screening</td>
<td>Four strategies: 1.-Family case +MSI 2.-Purely clinical diagnosis 3.-direct gene testing people at risk 4.-nationwide screening</td>
<td>Observation vs. surgery vs. surgery only in aneuploids selected with test</td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Cost per life-year gained for two strategies: Classic vs MSI testing in patients selected based on clinical criteria</td>
<td>Cost $11-330,000 per LYG, depending on prevalence of HNPCC</td>
<td>1.-cost 3.867€ per LYG 2.-4.397€ 3.- 6.208€ 4.- 15.705€</td>
<td>Incremental cost for QALY (ICER) £12,068</td>
<td></td>
</tr>
<tr>
<td>Result</td>
<td>Cost-effectiveness ratio of £2,184 per LYG</td>
<td>Genetic tests in large population groups are cost-effective only in certain circumstances</td>
<td>It’s necessary a reduction of 65% in the gene test cost in order for a cost effective nationwide gene screening for HNPCC</td>
<td>Radical prostatectomy in selected moderately graded tumours with DNA-ploidy as prognosis marker is less expensive and provides better QALY</td>
<td></td>
</tr>
</tbody>
</table>
References