The Cost-effectiveness of Germline BRCA testing in Prostate Cancer followed by Cascade Testing of First-Degree Relatives of Mutation Carriers

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Introduction

Background

Prostate Cancer (PCa) is the most diagnosed cancer and the 2nd leading cancer-related cause of mortality in Australian men with 3,901 deaths every year. The incidence of PCa is predicted to rise further in the next decade accompanied with a 42% increase in PCa related healthcare costs.

PCa is also highly heritable and 5-17% of PCa patients have pathogenic germline variants. Approximately one-half of these mutations are in the *BRCA* genes. Genetic testing is recommended in localised PCa patients with high-risk of mutations and all patients with metastatic PCa (mPCa) irrespective of risk.

We reviewed international guidelines for prostate cancer genetic testing and evaluated the economics of germline *BRCA* testing in all patients with mPCa and targeted populations with higher-than-average risk of mutations in localised PCa.

Aims

- To systematically review international guidelines for prostate cancer genetic testing and evaluate the consensus for implementation of genetic testing in Australia using a modified-Delphi technique of two rounds of surveys administered to healthcare providers, academics and consumers.
- To assess the cost-effectiveness of germline *BRCA* testing in PCa patients with:
  - metastatic castration-resistant prostate cancer (mCRPC)
  - mPCa
  - localised PCa patients with:
    - ➢ high/very high-risk PCa classification
    - ➢ family history of PCa (i.e., ≥1 first-degree/second-degree relative with PCa
    - ➢ Ashkenazi-Jewish ethnicity

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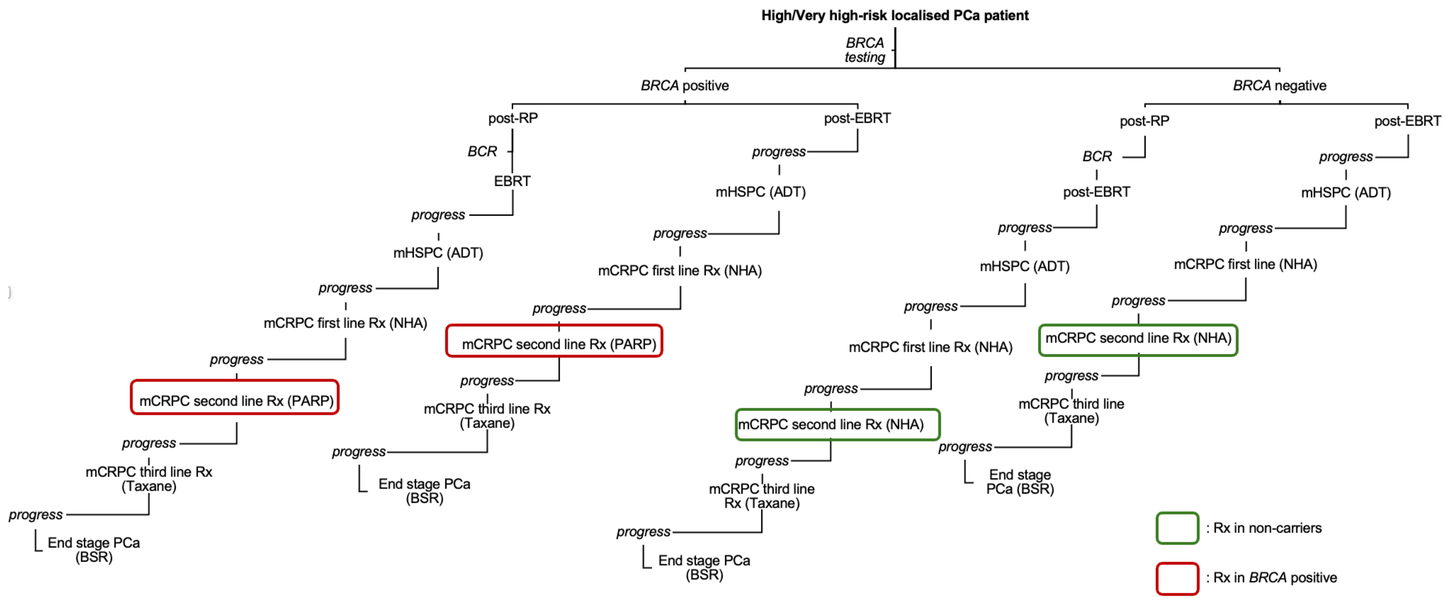
Methods

A modified-Delphi technique of two rounds of surveys was administered to healthcare providers, academics and consumers.

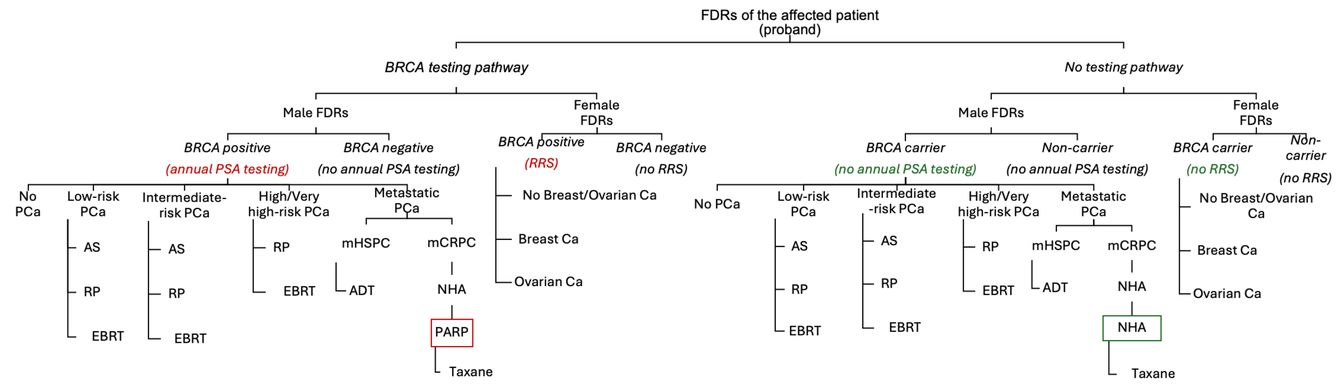
Cost-utility analysis of germline *BRCA* testing was performed in five populations of patients that reached consensus for genetic testing or where there are clinical practice-based recommendations for testing. These groups include PCa patients with 1) mCRPC 2) mPCa 3) localised PCa with high/very high-risk classification; 4) localised PCa with a family history of PCa; 3) localised PCa with Ashkenazi-Jewish ancestry. Analyses were performed from an Australian payer perspective using semi-Markov models over a lifetime time horizon using TreeAge Pro Healthcare; quality-adjusted life years (QALYs) were the health outcomes. Decision uncertainty was characterized using one-way and probabilistic sensitivity analyses.

Model Description



(Abbreviations: ADT: androgen deprivation therapy; BCR: biochemical recurrence; BSR: basic supportive care; EBRT: external-beam radiotherapy; mCRPC: metastatic castration resistant prostate cancer; mHSPC: metastatic hormone sensitive prostate cancer; NHA: novel hormonal agent; PARP: poly-ADP ribose polymerase inhibitor; PCa: prostate cancer; RP: radical prostatectomy)

Figure 1. Decision tree with stage-specific treatments in the *BRCA* testing of high/very high-risk localised PCa



(Abbreviations: AS: active surveillance; ADT: androgen deprivation therapy; Ca: cancer; EBRT: external-beam radiotherapy; FDRs: first-degree relatives; mCRPC: metastatic castration resistant prostate cancer; mHSPC: metastatic hormone sensitive prostate cancer; mPCa: metastatic prostate cancer; NHA: novel hormonal agent; PARP: poly-ADP ribose polymerase inhibitor; PCa: prostate cancer; PSA: prostate-specific antigen; RP: radical prostatectomy; RRS: risk reduction surgeries)

Figure 2. Decision tree with stage-specific treatments in the *BRCA* testing of first-degree relatives of the affected patient in the cascade testing model

Results

Table 1. Results of the cost-effectiveness analysis

Intervention	Testing patients alone without cascade testing: Costs	QALYs	Incremental costs	Incremental QALYs	ICER (% cost-effective in PA)	Testing patients followed by cascade testing of FDRs: Costs	QALYs	Incremental costs	Incremental QALYs	ICER (% cost-effective in PA)
Scenario 1: Testing mCRPC patients										
No testing	AU$103,335	0.90	comparator	comparator	comparator (98%)	-	-	-	-	-
BRCA testing	AU$111,177	0.96	AU$7,841	0.06	AU$143,613/QALY (2%)	-	-	-	-	-
Scenario 2: Testing mPCa patients										
No testing	AU$156,312	2.286	comparator	comparator	comparator (100%)	AU$158,471	9.191	comparator	comparator	comparator (0%)
BRCA testing	AU$160,043	2.300	AU$3,731	0.014	AU$265,942/QALY (0%)	AU$162,299	9.425	AU$3,828	0.234	AU$16,392/QALY (100%)
Scenario 3: Testing localized PCa patients with high/very high-risk classification										
No testing	AU$62,041	11.042	comparator	comparator	comparator (100%)	AU$62,874	13.706	comparator	comparator	comparator (0%)
BRCA testing	AU$63,654	11.045	AU$1,612	0.003	AU$591,408/QALY (0%)	AU$64,524	13.794	AU$1,650	0.087	AU$18,872/QALY (100%)
Scenario 4: Testing localized PCa patients with a family history of PCa (≥1 FDR/SDR with PCa)										
No testing	AU$35,126	19.081	comparator	comparator	comparator (100%)	AU$35,404	19.970	comparator	comparator	comparator (4%)
BRCA testing	AU$36,465	19.082	AU$1,339	0.0003	AU$3.9 million/QALY (0%)	AU$36,755	19.998	AU$1,351	0.029	AU$47,294/QALY (96%)
Scenario 5: Testing localized PCa patients with Ashkenazi-Jewish ancestry										
No testing	AU$44,935	17.307	comparator	comparator	comparator (100%)	AU$46,011	20.748	comparator	comparator	comparator (0%)
BRCA testing	AU$46,523	17.310	AU$1,588	0.002	AU$650,098/QALY (0%)	AU$47,648	20.860	AU$1,637	0.112	AU$14,637/QALY (100%)

FDRs: first-degree relatives; ICER: incremental cost-effectiveness ratio; PA: probabilistic sensitivity analysis of cost-effectiveness at a willingness-to-pay of AU$75,000/QALY; PCa: prostate cancer; QALYs: quality-adjusted life years; SDR: second-degree relatives

Conclusion

Germline *BRCA* testing is not cost-effective in patients diagnosed with PCa. The poor yield in this setting is influenced by low prevalence of pathogenic *BRCA* variants, personalised treatment introduced late in PCa disease progression pathway (i.e., during mCRPC) and the high costs of germline testing and personalised treatment (i.e., olaparib). Germline *BRCA* testing, however, provides high value for money after cascade testing cancer-free FDRs of PCa patients with pathogenic variants.