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Piloting a key and facilitated gene approach to health technology assessment of germline genetic testing for hereditary breast and ovarian cancer in Singapore

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Introduction

- Advancements in molecular genetics have expanded our understanding of hereditary breast and ovarian cancer susceptibility beyond *BRCA1* and *BRCA2*, to include genes such as *NF1* and *BARD1*. These additional genes, often included in the same multi-gene panels, typically have limited evidence on their clinical utility despite being shown to be clinically actionable.
- This necessitates an adaptive health technology assessment (HTA) approach for gene-related investigative technologies.
- ACE piloted a key and facilitated gene approach in a HTA evaluation on germline genetic testing for hereditary breast and ovarian cancer, anchored on a linked evidence approach.

Methods

- **Key genes** have well-defined pathogenic variant (PV) prevalence in the target population and an established evidence base supporting change in clinical management and health outcomes.

  The evaluation of clinical evidence on key genes will follow a linked evidence approach which encompasses linked evidence of test accuracy, change in management and health outcomes. Published economic evidence supporting germline genetic testing from Australia's Medical Services Advisory Committee (MSAC) and UK's National Institute for Health and Care Excellence (NICE) for key genes were reviewed.

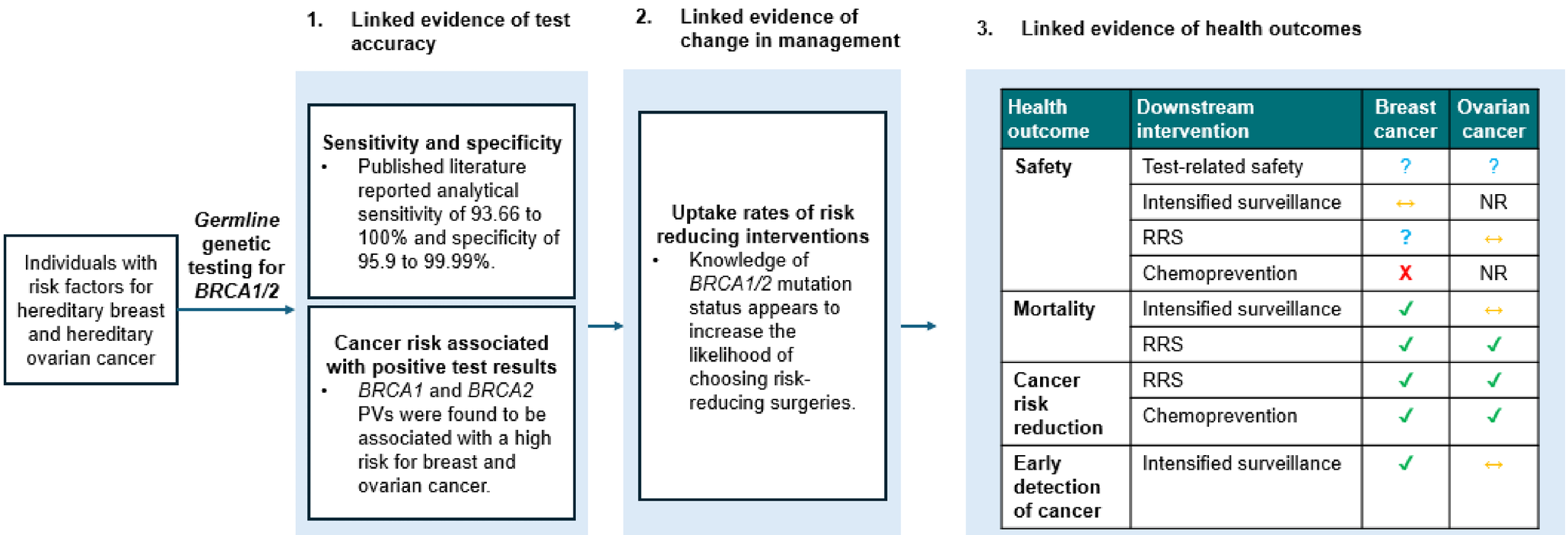
- **Facilitated genes** are other breast and ovarian cancer susceptibility genes identified by local clinicians, included in the same multi-gene panel, that have lower PV prevalence. Their inclusion should not increase unit cost of testing or adverse health outcomes.

  A simplified approach to the evaluation of facilitated genes was conducted through review of topline clinical evidence and a review of reimbursement status in overseas reference HTA jurisdictions.

Results

- ***BRCA1* and *BRCA2* genes were identified as key genes**
  - ~1 in 150 Singaporeans carry a PV for hereditary breast and ovarian cancer
  - The gene penetrance of *BRCA1* and *BRCA2* is >60% for breast cancer and up to 58% for ovarian cancer respectively.
  - Germline genetic testing for key genes is currently reimbursed in all reference overseas jurisdictions.

- **Clinical evidence synthesis via the linked evidence approach**



Health outcome	Downstream intervention	Breast cancer	Ovarian cancer
Safety	Test-related safety	?	?
	Intensified surveillance	↔	NR
	RRS	?	↔
	Chemoprevention	X	NR
Mortality	Intensified surveillance	✓	↔
	RRS	✓	✓
Cancer risk reduction	RRS	✓	✓
	Chemoprevention	✓	✓
Early detection of cancer	Intensified surveillance	✓	↔

Legend: ✓, statistically significant difference in favour of intervention; ↔, no statistical difference between intervention and comparator; ?, inconclusive results; X, statistically significant difference in favour of comparator; NR, not reported
Abbreviations: RRS, risk reducing surgery; PV pathogenic variant

- **17 facilitated genes were identified by local clinicians:**
  - Hereditary breast cancer: *ATM, BARD1, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53*
  - Hereditary ovarian cancer: *ATM, BRIP1, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, RAD51C, RAD51D*

  Clinical evidence supports germline genetic testing for these facilitated genes. Germline genetic testing of these facilitated genes is currently reimbursed in at least two overseas reference HTA jurisdictions.

Conclusion

- This pilot on the key and facilitated genes approach showed that this adaptive HTA approach can be fit-for-purpose for the evaluation of genetic testing in Singapore. Further use cases can help to refine the approach further.