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Unit No. 3

IT'S ALL IN YOUR GENES: WHAT PRIMARY CARE SHOULD KNOW ABOUT HEREDITARY CANCER SYNDROMES

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ABSTRACT

Primary care physicians are usually the first point of contact for patients with hereditary cancer syndromes. Though hereditary cancer syndromes are rare, accounting for roughly 5-10 percent of all cancers, a timely diagnosis is important, as not only do patients require long-term care from a young age, but their relatives also require management. In the past decades, enormous strides have been made to unravel the genetic basis of cancer, and this knowledge has been used to develop targeted treatments for hereditary forms of cancer. Germline genetic testing for patients and their families with suspected hereditary cancer syndromes is therefore a vital component of the practice of preventative oncology and must become routine clinical care. Here, we discuss the most common hereditary cancer syndromes and provide necessary information for primary care physicians regarding management of patients with Hereditary Breast and Ovarian Cancer syndrome and Lynch syndrome. We also highlight the importance of genetic testing, as well as barriers to testing globally and nationally. Addressing these barriers will bring us one step closer to implementing precision medicine in Singapore.

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Key words: cancer genetics, HBOC, Lynch, germline, genetic screening

INTRODUCTION

Cancer remains a leading cause of death in Singapore and globally.[1,2] Around 5-10 percent of cancers are hereditary in nature, caused by a pathogenic variant that runs in the family (refer to **Figure 1**).[3,4] Thanks to advances in genome sequencing, we have a much better understanding in identifying and understanding what genes are responsible for tumour formation. This has led to increased clinical utility and accessibility of genetic testing for patients and their family members, in whom results can guide cancer surveillance and treatment, improving long-term prognosis.

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OVERVIEW OF CANCER GENETICS

Cancer is the result of accumulative genetic alterations, also known as pathogenic variants or mutations, within a cell, leading to uncontrolled growth and ultimately tumour formation.[5] In most cases, these genetic changes happen sporadically in somatic cells and accumulate over many years.[6] Because somatic cells do not give rise to gametes, pathogenic variants are not passed on to future generations. However, pathogenic variants that occur in the germ line (egg or sperm cell) can be passed down to future generations.[7,8] Germline variants are present in every cell of the body, unlike somatic variants that are found within tumour cells, and may result in hereditary cancer syndromes.[6,9] As germline variants are present from birth, the pathway to the development of a tumour is shortened (refer to **Figure 2**). Therefore, carriers are generally diagnosed with hereditary cancer at younger ages and usually have a family history of cancer, in contrast to non-hereditary cancer where genetic changes accumulate throughout life and without a family history of cancer.[6]

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME IN A NUTSHELL

Hereditary breast and ovarian cancer syndrome (HBOC), which follows autosomal-dominant inheritance, is one of the most common hereditary cancer syndromes. It is associated with early-onset breast and ovarian cancer, but individuals with HBOC are also at higher risk of developing male breast cancer, prostate cancer, pancreatic cancer, and melanoma.[10] It accounts for around 5-10 percent of all breast cancer cases, 10-15 percent of ovarian cancer cases, and 3-5 percent of pancreatic and prostate cancers.[11-14] It is primarily caused by pathogenic variants in the *BRCA1* and *BRCA2* genes, which play a crucial role in repairing damaged DNA.[7,10,15,16]

Other genes associated with HBOC include but are not limited to *PALB2*, *TP53*, *PTEN*, and *RAD51C/D*.[10,17] These genes encode for components of multi-protein complexes (e.g., *PALB2* is a partner and localiser of *BRCA2*) and are vital in repairing DNA double-strand breaks.[18] Female *BRCA1* and *BRCA2* pathogenic carriers have a breast cancer risk of 65-79 percent and 61-77 percent by age 80, respectively, in comparison to around 13 percent for the general population.[19-27] Ovarian cancer risk ranges from 39-58 percent and 13-29 percent for *BRCA1* and *BRCA2* carriers by age 80, respectively, in comparison to <2 percent for the general population.[20,23-28] Male *BRCA1* pathogenic variant carriers are at risk of developing prostate (7-26 percent) and male breast cancer (0.2-1.2 percent) by age 70.[20,29-34] Notably, prostate and breast cancer risk are substantially increased in male *BRCA2* carriers with 19-61 percent and 1.8-7.1 percent respectively, by age 70.[20,29-35]

Certain ethnic groups, such as Ashkenazi Jews, have a high prevalence of *BRCA* mutations, which predisposes them to developing HBOC.[36,37] Moreover, studies have shown that type and location of the mutation can also affect one's cancer risk.[38-40] For example, mutations in the "ovarian cancer cluster region", the central portion of the gene in exon 11, are associated with a higher ratio of ovarian cancer than breast cancer cases. Individuals with mutations outside of this region are more likely to develop breast cancer than ovarian cancer.

The SG10K_Health study by PRECISE, which aims to improve patient outcomes by identifying genetic factors predisposing Singaporeans to prevalent disease conditions, revealed a high prevalence of HBOC in Singapore. Roughly 1 in 150 Singaporeans carry a pathogenic variant of HBOC in comparison to an estimated prevalence of 1 in 400-500 outside of Singapore, dependent on the population (refer to **Figure 3A**).[41-43] Of those at risk in the Singapore population, the most common pathogenic variants were *BRCA2* and *BRCA1* carriers followed by *PALB2* carriers (refer to **Figure 3A**).[41] Notably, the study observed that the genetic risk profile for HBOC is variable by genetic ancestry, with Malays having a slightly higher prevalence than Indians or Chinese (refer to **Figure 3B**). Individuals at risk require earlier and more frequent surveillance throughout their lives to prevent cancer. For example, asymptomatic *BRCA1/2* carriers are recommended to commence annual breast mammograms and/or MRI from age 25 (or 5-10 years prior to the earliest diagnosis in family, whichever comes first) as opposed to biannual mammograms from age 50 for the general population. **Figure 4**, which illustrates the estimated absolute risk of breast cancer associated with known pathogenic variants, strongly supports this change in practice.[44] Depending on the pathogenic variant, the modified graph shows that individuals with a positive test result are at a much higher risk of developing cancer at age 50 than the general population, e.g. *BRCA1* carriers already have an almost 30 percent risk of cancer at age 50 in comparison to <5 percent for the general population.[44] Whilst these carriers have a higher lifetime risk of developing cancers, the screening and risk-reducing measures recommended have been proven that it does not affect survival rates, e.g., breast cancer patients with a *BRCA1/2* pathogenic variant have similar overall survival as non-carriers.[45]

LYNCH SYNDROME IN A NUTSHELL

Another common hereditary cancer syndrome, following autosomal-dominant inheritance, is Lynch Syndrome, which is associated with early age onset colorectal cancer without polyposis, endometrial, ovarian, gastric, small-bowel, renal pelvis, pancreatic, bladder cancers, and other cancers.[46] It accounts for around 3 percent of all colorectal cancer diagnosis.

It is caused by pathogenic variants in the mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*, as well as the epigenetic regulator *EPCAM*.[47,48] MMR is a system that recognises and repairs errors that occur during DNA replication and plays a crucial role in maintaining genomic stability.[49] *EPCAM* pathogenic variants result in silencing of the MMR gene *MSH2*, thereby disturbing the MMR system.[50] In Singapore, around 1 in 530 individuals have a pathogenic variant of Lynch syndrome (refer to **Figure 5A**) in comparison to around 1 in 300 outside of Singapore, depending on the population.[41,51] Of those at risk in the Singapore population, the most common pathogenic variants were *MSH6* and *PMS2* carriers followed by *MLH1* carriers.[41] The genetic risk profile for Lynch syndrome is variable by genetic ancestry, with Chinese having a higher prevalence than Indians or Malays (refer to **Figure 5B**).

The lifetime risk for the development of cancer will depend on the pathogenic variant, as well as the individual's biological sex. At present, it is estimated that the colorectal cancer risk for *MLH1* through age 80 is between 46-61 percent, *MSH2/EPCAM* between 33-52 percent, *MSH6* between 10-44 percent, and *PMS2* at around 8.7-20 percent, in comparison to 4.1 percent for the general population.[52-58] *MLH1* risk for endometrial cancer through age 80 is between 34-54 percent, 21-57 percent for *MSH2/EPCAM*, 16-49 percent for *MSH6*, and 13-26 percent for *PMS2* in comparison to 3.1 percent for the general population.[52-58] These differences in cancer risk support the use of gene-specific screening and surveillance recommendations for Lynch syndrome. For example, individuals with an *MLH1* pathogenic variant should be offered earlier and more frequent colonoscopies than a *PMS2* carrier who can start screening later.

Most institutions usually perform clinical testing on all colorectal and endometrial tumours before proceeding with multigene testing to determine whether Lynch syndrome is likely. This includes microsatellite instability (MSI) testing and immunohistochemistry (IHC) for mismatch repair deficiency (dMMR) on the tumour sample.[59,60] Loss of MMR gene function results in microsatellite instability (MSI), which can be defined by an abnormal number of tandem repeats in the DNA of a tumour in comparison to normal tissue. This is a distinct feature of these tumours. IHC on the other hand involves staining of the MMR genes to detect the presence or absence of the MMR protein products. The absence of staining in one of the MMR proteins indicates a mutation in the gene. Therefore, microsatellite instability testing on both normal and tumour tissue, in parallel with immunohistochemistry testing of the MMR genes on tumour tissue, is highly informative and increasingly embedded into clinical practice before genetic testing.[59,60]

OVERVIEW OF OTHER HEREDITARY CANCER SYNDROMES

There are more than 400 hereditary cancer syndromes described such as Li Fraumeni, Cowden syndrome, Peutz-Jeghers syndrome, Hereditary Diffuse Gastric Cancer, Neurofibromatosis type 1 (NF1), and Familial adenomatous polyposis (FAP).[7,8] They are all passed on in an autosomal dominant fashion but are caused by pathogenic variants in different genes.

Li Fraumeni syndrome increases the risk of multiple tumours such as soft tissue sarcoma and breast cancer and is caused by a germline pathogenic variant in *TP53*.[7,8,61]

Cowden syndrome is caused by pathogenic variants in the cell cycle control gene, *PTEN*.[62-64] Whilst relatively rare, it is characterised by both benign and malignant neoplasms and increases the risk for breast cancer, endometrial cancer, colon cancer, and thyroid cancer amongst others.[7,8,61,62]

Peutz-Jeghers syndrome is caused by germline mutations in the tumour suppressor gene *STK11*, which increases the risk for breast cancer, ovarian sex cord stromal cancer, and many others.[7,61]

Hereditary Diffuse Gastric Cancer is associated with germline mutations in the tumour suppressor gene *CDH1* and is characterised by an increased risk of diffuse gastric (stomach) cancer, lobular breast cancer, and colorectal cancer.[8,61,65]

NF1, caused by an *NF1* pathogenic variant, is known to increase the risk of multiple benign and malignant tumours such as sarcomas, ovarian cancer, and melanoma.[66]

Lastly, FAP is caused by germline pathogenic variants in the *APC* gene and is characterised by the presence of hundreds to thousands of adenomatous polyps in the colon and rectum, which increases the risk for colorectal cancer to almost 100 percent.[7]

GENETIC TESTING FOR CANCER RISK

Genetic testing has clinical utility in identifying carriers at increased risk of cancer and providing a genetic diagnosis of a hereditary cancer syndrome. Genetic testing options usually include single or multigene panels depending on the personal and family history of cancer, and usually includes clinically actionable genes.

Genetic testing offers multiple benefits. Identification of a germline pathogenic variant can guide life-saving treatment decisions and gene-directed therapy.[6] Family members are strongly encouraged to also undergo genetic testing once a carrier is identified within a family[6]; this is called cascade testing. In healthy individuals, this will help to understand their carrier status, clarifying their risk of developing cancer, which can guide their screening and prophylactic options to reduce and prevent cancer.[6] Non-carriers can then avoid unnecessary checkups and screening and provide peace of mind for those with strong family histories of cancer. Due to the clinical, psychosocial, ethical, and legal implications associated with genetic testing, patients considering genetic testing should receive pre-test and post-test genetic counselling from a genetics specialist/genetic counsellor.[61,62,67] Genetic counselling aims to simplify complex genetic information, explain the implications of a genetic test result, address concerns, and discuss test results whilst promoting informed decision-making.[61]

WHEN PRIMARY CARE PHYSICIANS SHOULD SUSPECT HEREDITARY CANCER AND REFER FOR GENETIC TESTING

Though hereditary cancer syndromes account for only 5-10 percent of all cancers, it is important for primary care physicians to identify them as not only do patients require long-term care from a young age, their relatives also require management.[68] Primary care physicians should suspect a hereditary cancer syndrome when a patient presents with the following characteristics[7,69]:

- A strong family history of cancer (≥2 relatives with similar types or patterns of cancer on one side of the family)
- Younger ages of cancer diagnosis to what is usually seen for that cancer type (aged under 60)
- Individuals with multiple primary cancers over their lifetime
- Rare tumours and/or non-malignant conditions

Primary care physicians should consult NCCN and eviQ guidelines on when to refer individuals for genetic testing – suggested criteria on when to refer for HBOC or Lynch syndrome testing are listed in **Figure 6**.[20,52,70]

HOW PRIMARY CARE PHYSICIANS SHOULD MANAGE INDIVIDUALS WITH HBOC AND LYNCH SYNDROME

Once a hereditary cancer diagnosis is made, these individuals require earlier and more frequent surveillance throughout their lives and may benefit from prophylactic surgery to prevent cancer. **Figures 7 and 8** depict suggested recommendations on how to manage individuals with HBOC and Lynch syndrome.

GENETIC TESTING CHALLENGES AROUND THE WORLD

Despite the increased clinical utility of genetic testing in guiding treatment options of cancer patients and surveillance strategies of at-risk family members, there remain several barriers to genetic testing. For instance, access to genetic testing remains inadequate and is often unavailable or prohibitively expensive in low-income and middle-income countries.[71] Disparities in genetic testing should be considered an urgent unmet need and failure to integrate preventative risk management plans for people with hereditary cancer syndromes represents a missed opportunity in global and population health.[71] The road to introducing genetic testing in low- and middle-income countries is long, with roadblocks being the lack of infrastructure and trust issues between the public and industry on genomic data sharing. Meanwhile, fear of employment and insurance discrimination of carriers is a barrier to the uptake of genetic testing. With the known benefits of genetic testing and reducing costs, there needs

to be a global effort to improve access and uptake of genetic testing.

We are currently in the process of testing acceptability and effectiveness of a digital pathway for genetic testing to make the process less clinician intensive, allowing for more patients to be able to access genetic testing in the future. Digital alternatives to current appointment-based counselling may extend and improve access to healthcare, making this a focus in many healthcare systems.[72-74]

GENOMIC EFFORTS AND CHALLENGES IN SINGAPORE

High-income countries have invested large sums in national genomic-medicine initiatives in the last decade (e.g., UK, Genomics England[75]; US, All of Us[76]; China, China Precision Medicine Initiative) in the hope that their discoveries will have immediate clinical benefit.[77]

Similarly, Singapore has embarked on a mission to generate precision medicine data in the form of large-scale genomic-phenotypic databases as part of its 10-year National Precision Medicine programme.[78,79] This will be Asia's leading reference genome database thanks to Singapore's ethnic diversity made up of around 80 percent of Asia's diversity. During Phase I, whole genome sequencing of 10,000 healthy Singaporeans was performed; this was known as the SG10K_Health study by PRECISE. In Phase II, five clinical implementation pilots (CIPs) that are cost-effective, sustainable, and relevant to Singapore communities were identified. One of them aims to improve access to clinical hereditary cancer genetic testing in cancer patients and their families in Singapore. Studies have shown that, even when genetic testing is available, uptake among family members is often poor, especially in Asian countries.[80-82] In Singapore, cascade testing is low, averaging at 10-15 percent, much lower than the 30 percent rate in the global community.[81-83] This is due to several factors such as non-systematic referral of patients, poor understanding of the benefits of genetic testing among patients and family members, and cost.[84] Recent modelling by Li et al[85] showed that if cascade testing uptake can be increased to 36 percent, subsidising testing would not only save lives but also allow healthcare cost savings.[86] Currently only the cost of diagnosis and treatment of cancers are being subsidised in Singapore; the cost of diagnostic testing for patients and their family members are not.[83] This CIP seeks to identify strategies on how cascade testing can be increased in a safe and cost-efficient manner in Singapore.

CONCLUSION

Understanding our genetic make-up has the potential to be one of the most significant developments in clinical medicine. Genetic testing results allow patients and at-risk family members to make proactive decisions about their health, enabling early intervention and gene-directed preventive measures. It is therefore imperative for primary care physicians to be able to identify and manage patients with hereditary cancers. Through Singapore's recent efforts on implementing precision medicine, there is hope for creating a healthier Singapore, whilst also easing the burden on the healthcare system.

Figure 1. Distribution of Cancer. Adapted from Genetic Counseling Aids "Greenwood Flipbook", Greenwood Genetic Center.

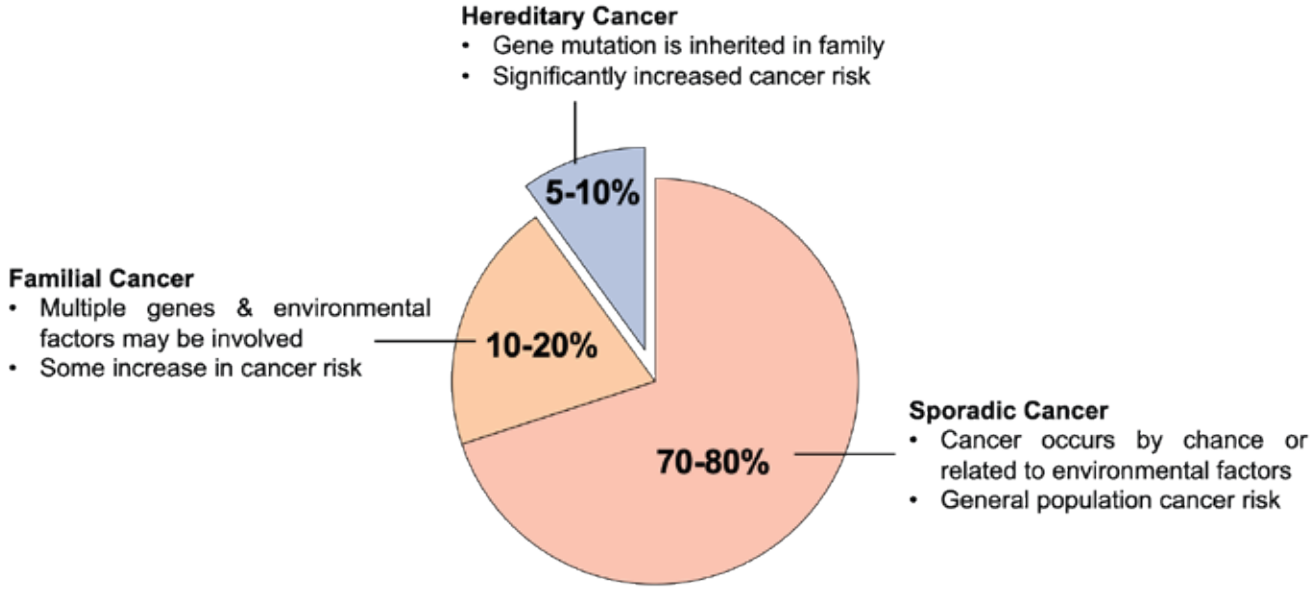
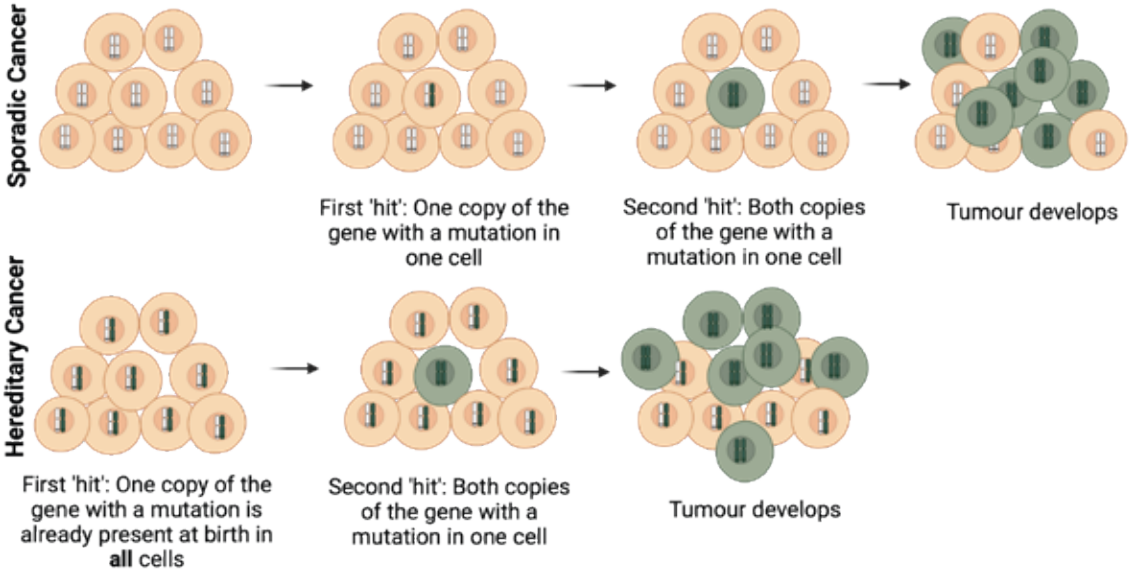


Figure 2. Development of sporadic cancer vs hereditary cancer. Adapted from Genetic Counseling Aids "Greenwood Flipbook", Greenwood Genetic Center. Created with BioRender.com



Figures 3A & 3B. Prevalence of HBOC in the Singapore population (A) and genetic risk profile for HBOC by genetic ancestry (B).[41] Actual percentages for pathogenic variant carriers may change as more data gets collected in the future.

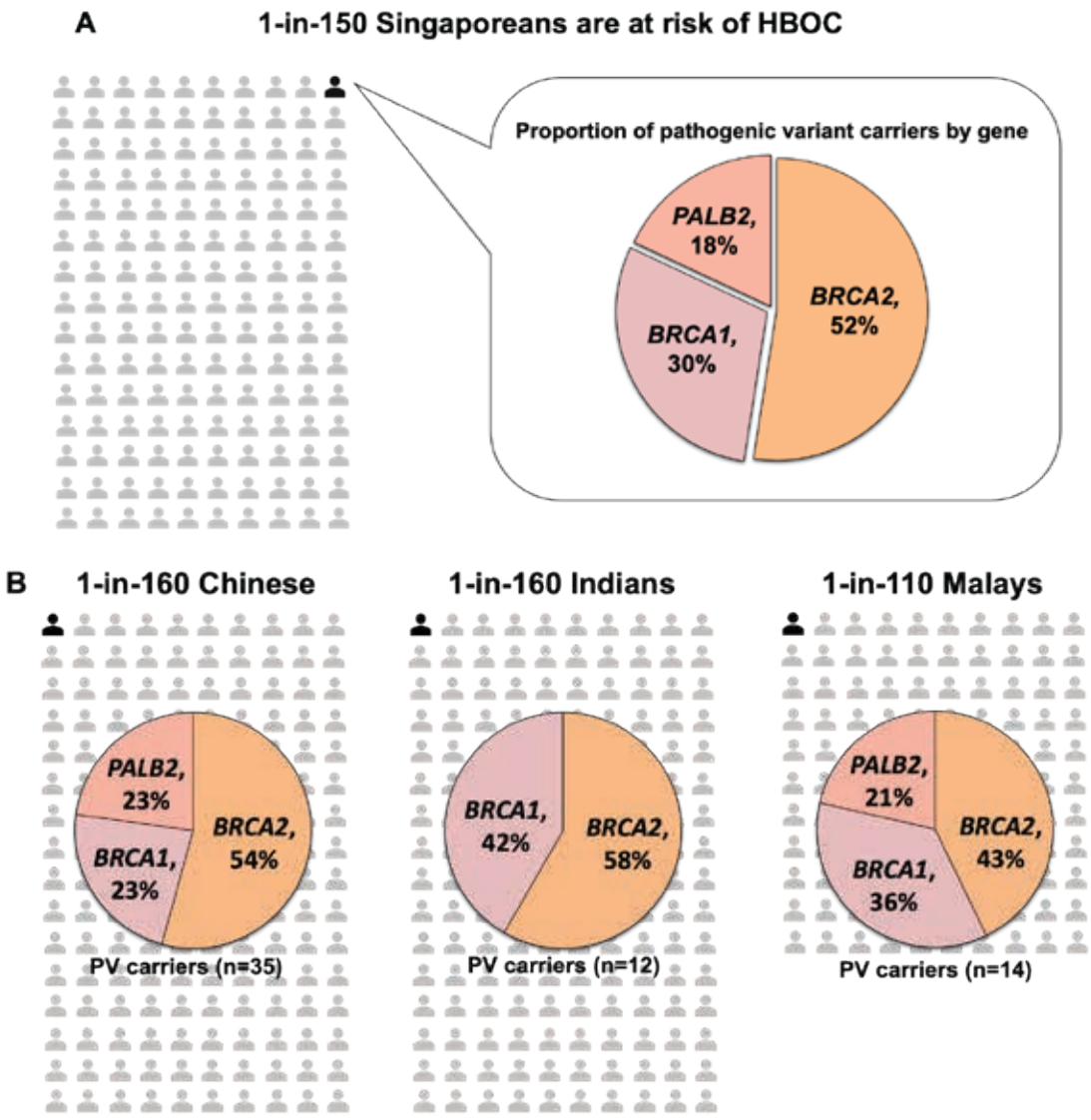
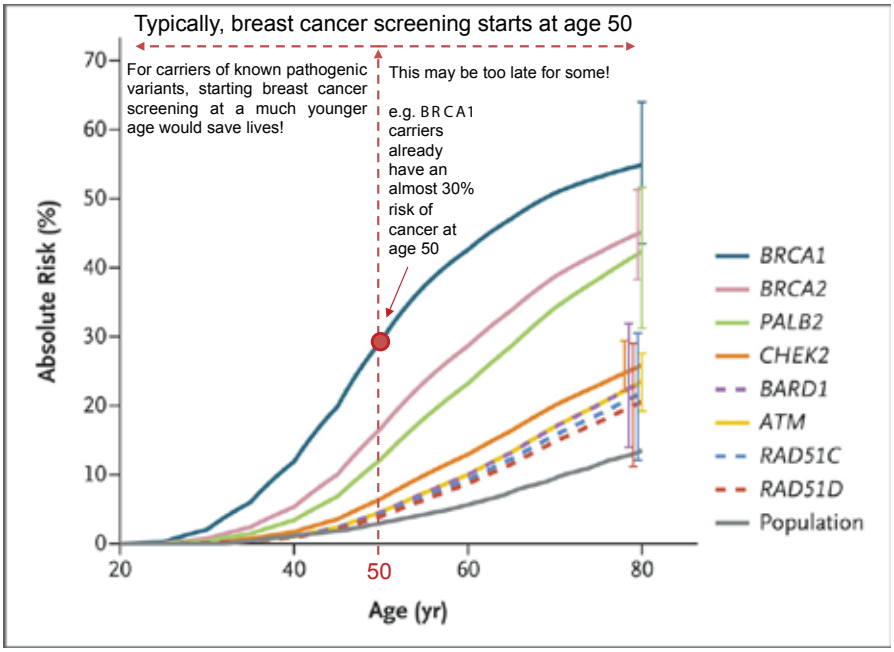
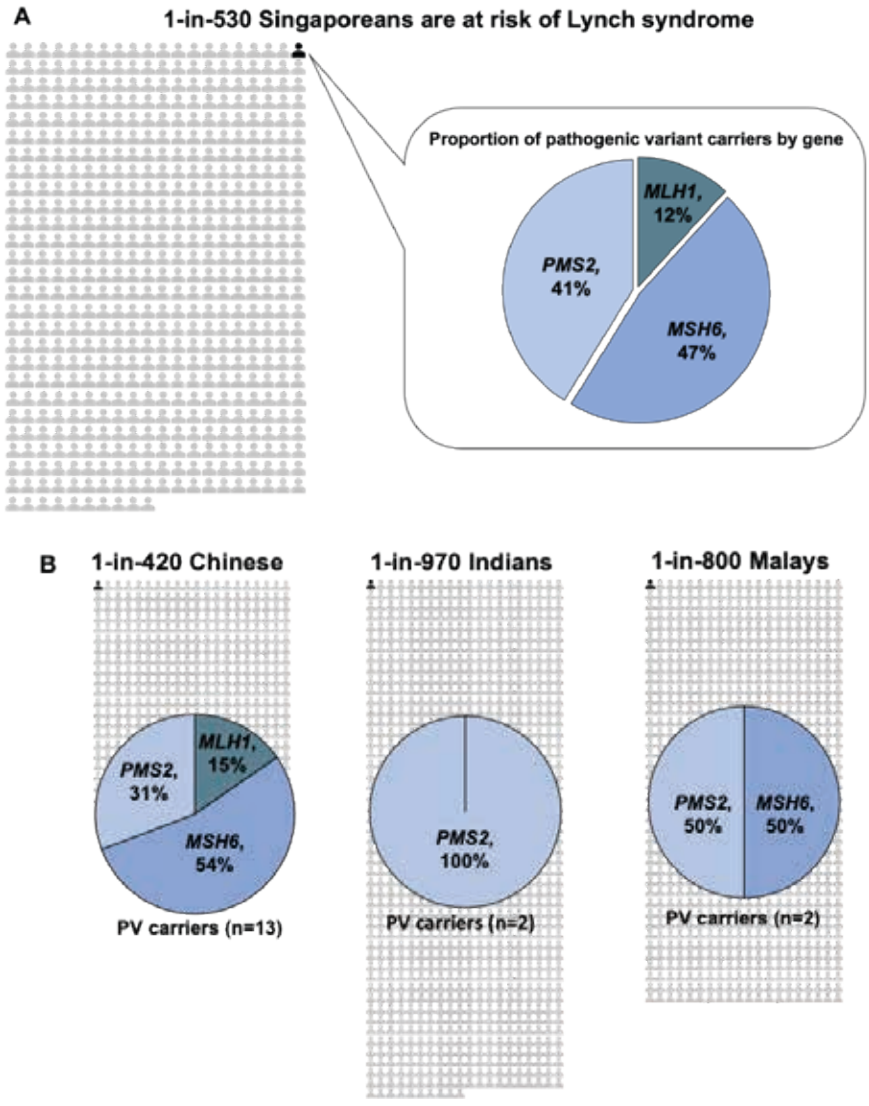


Figure 4. Estimated absolute risk of Breast Cancer associated with known pathogenic variants.[44] Graph from Breast Cancer Association Consortium[44] was modified.



Figures 5A & 5B. Prevalence of Lynch syndrome in the Singapore population (A) and genetic risk profile for Lynch syndrome by genetic ancestry (B).[41] Actual percentages for pathogenic variant carriers may change as more data gets collected in the future.



Figures 6A & 6B. Suggested criteria on when primary care physicians should refer individuals for HBOC (A) and Lynch syndrome (B) testing.[20,52,70] Created with Biorender.com.

A

Suggested Criteria On When Primary Care Physicians Should Refer Individuals For Genetic Testing For HBOC

- Breast cancer diagnosed at or under 45 years of age
- Breast cancer diagnosed at any age in an individual of Ashkenazi Jewish ancestry
- Male breast cancer
- Multiple primary breast cancers either in one or both breasts
- Ovarian cancer
- Triple-negative breast cancer before age 60 years
- Combination of breast and ovarian cancer
- Pancreatic cancer
- Metastatic or high grade prostate cancer
- Two or more relatives on the same side of a family with breast cancer, one under age 50
- Three or more relatives on the same side of a family with breast cancer at any age
- A previously identified faulty BRCA1 or BRCA2 gene in the family

B

Suggested Criteria On When Primary Care Physicians Should Refer Individuals For Genetic Testing For Lynch Syndrome

- A previously identified Lynch Syndrome pathogenic variant in the family
- Identification of a tumour with MMR deficiency determined by PCR, NGS or IHC diagnosed at any age
- Colorectal or endometrial cancer and any of the following:

1.) Diagnosis < 50 years

2.) A synchronous or metachronous LS-related cancer at any age

3.) One first-degree or second-degree relative with an LS-related cancer diagnosed <50 years

4.) ≥2 first-degree or second-degree relatives with an LS-related cancer at any age

- Family history of any of the following:

1.) ≥1 first-degree relative with a colorectal or endometrial cancer diagnosed <50 years

2.) ≥1 first-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer at any age

3.) ≥2 first-degree or second-degree relatives with LS-related cancer including ³1 diagnosed <50 years

4.) ≥3 first-degree or second-degree relatives with LS-related cancer at any age

- Increased model-predicted risk (e.g. PREMM5, MMRpro, MMR predict) for Lynch syndrome

Figure 7. Summary of suggested HBOC management guidelines. Adapted from NCCN and eviQ guidelines.[20,70] Created with Biorender.com.

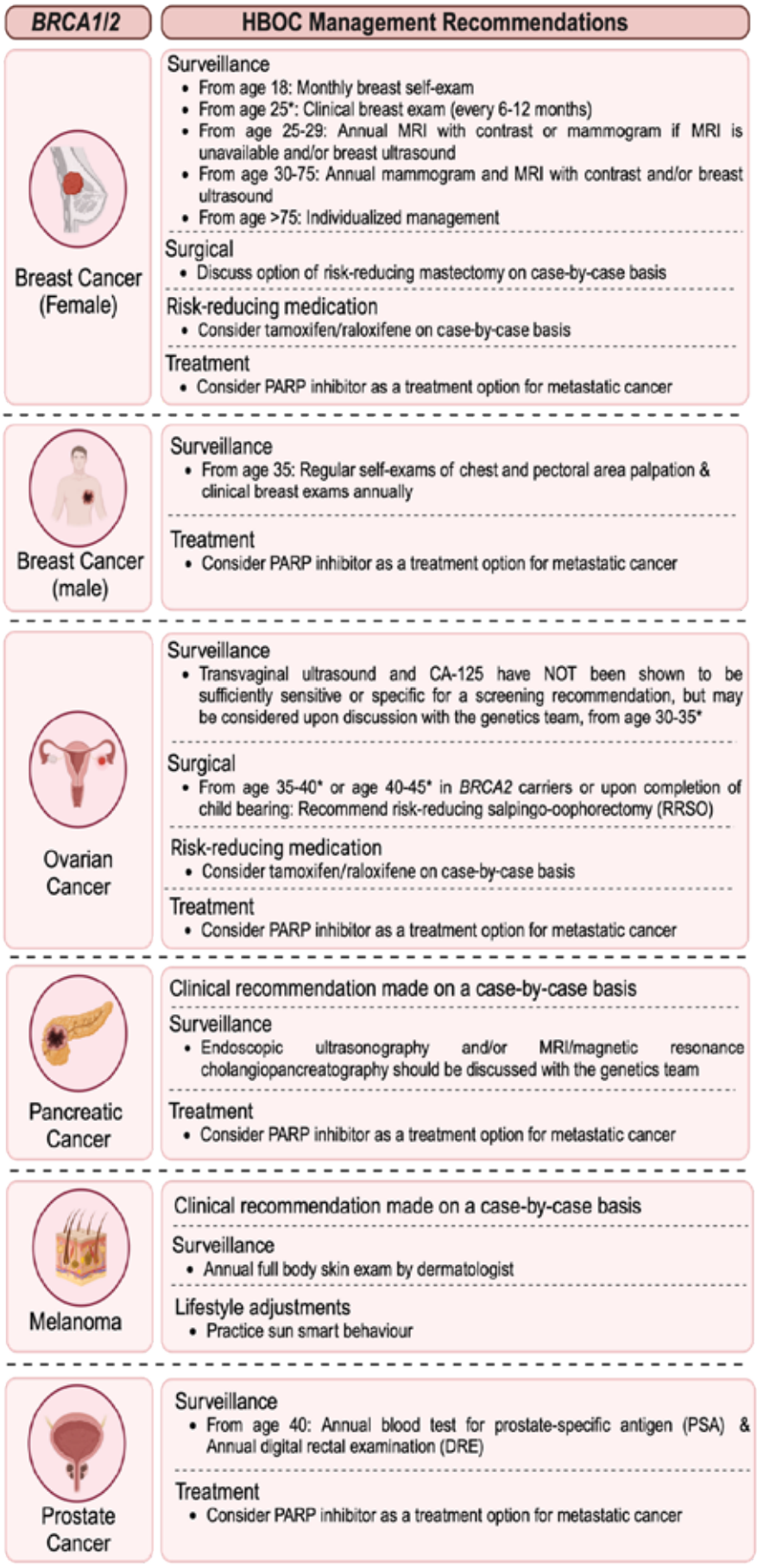
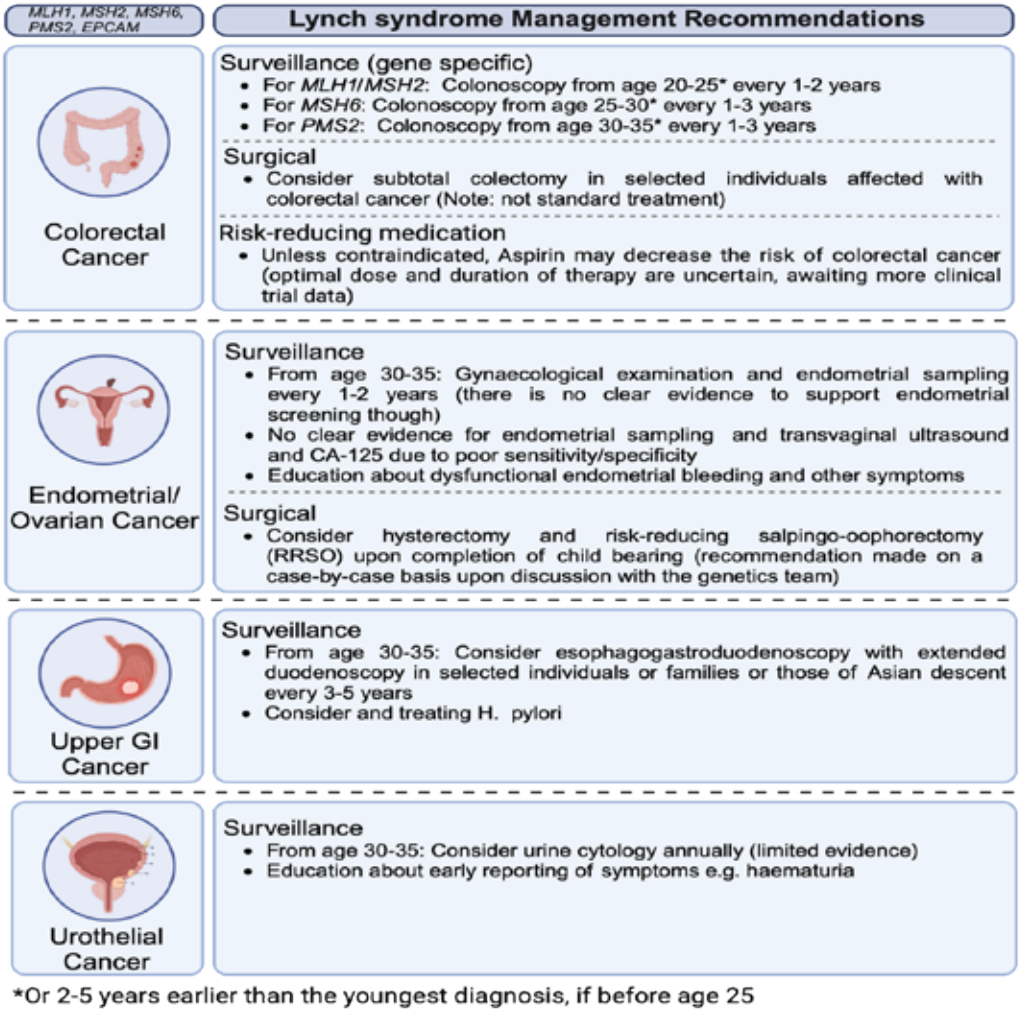


Figure 8. Summary of suggested Lynch syndrome management guidelines. Adapted from NCCN and eviQ guidelines.[52,70] Created with Biorender.com.



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LEARNING POINTS

- **Hereditary cancer syndromes account for roughly 5-10 percent of all cancers and are usually inherited in an autosomal dominant manner. It is caused by germline pathogenic variants in cancer genes such as *BRCA1/2*.**
- **The SG10K_Health study by PRECISE revealed a high prevalence of HBOC and Lynch syndrome pathogenic variant carriers in Singapore (1-in-150 and 1-in-530 Singaporeans, respectively).**
- **Genetic testing can help identify carriers and guide treatment, screening, and risk-reducing measures for cancer. At-risk family members can also access cascade testing to determine and decide on personalised cancer risk management plans.**
- **Most institutions perform microsatellite instability testing and immunohistochemistry for MMR proteins on tumour tissue, followed by genetic testing, to diagnose Lynch syndrome.**
- **Differences in cancer risk support the use of gene-specific screening and surveillance recommendations for HBOC and Lynch syndrome.**
- **Cascade screening uptake is poor in Asian countries, including Singapore, in comparison to the global community. A clinical implementation pilot in Singapore aims to address this issue by improving access to testing in cancer patients and their families.**