Original Article

# Singapore Cancer Network (SCAN) Guidelines for Referral for Genetic Evaluation of Common Hereditary Cancer Syndromes

The Singapore Cancer Network (SCAN) Cancer Genetics Workgroup

## Abstract

**Introduction: The SCAN cancer genetics workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for referral for genetic evaluation of common hereditary cancer syndromes. Materials and Methods: The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. Results: To formulate referral guidelines for the 3 most commonly encountered hereditary cancer syndromes to guide healthcare providers in Singapore who care for cancer patients and/or their family members, 7, 5, and 3 sets of international guidelines respectively for hereditary breast and ovarian cancer (HBOC) syndrome, Lynch syndrome (LS), and familial adenomatous polyposis (FAP) were evaluated. For each syndrome, the most applicable one was selected, with modifications made such that they would be appropriate to the local context. Conclusion: These adapted guidelines form the SCAN Guidelines 2015 for referral for genetic evaluation of common hereditary cancer syndromes.**

**Ann Acad Med Singapore 2015;44:492-510**

**Key words: Familial breast cancer, Hereditary cancer syndromes, Referral guidelines**

## Introduction

Mutations in high penetrance genes account for approximately 3% to 5% of all cancers. In the last 2 decades, there has been better characterisation of an ever growing list of hereditary cancer syndromes, largely due to the identification of causative genes. Formal management guidelines, including testing, screening and preventive options, have been established for many of these syndromes.[1,2] Identification of these patients and families who are at extremely high risk of developing cancer for specialised management is crucial to reduce cancer occurrence and mortality. Formal cancer genetics programmes have been established in Singapore in both tertiary cancer centres in Singapore (National University Cancer Institute [NCIS], National Cancer Centre [NCCS]) since 2001.[3] However, there are no formal local guidelines providing guidance to general practitioners, physicians or surgeons on who should be referred for cancer genetic assessment.

## The SCAN Guidelines for Referral for Genetic Evaluation of Common Hereditary Cancer Syndromes

The SCAN Guidelines are clinical practice guidelines for referral for genetic evaluation of common hereditary cancer syndromes.

These first edition guidelines are intended to serve as recommendations by members of this working group reflecting their views on current existing international guidelines for the referral for genetic evaluation of common hereditary cancer syndromes. While it hopes to harmonise the management of such syndromes, it is not intended to serve as a standard or to replace good judgment and individualisation.

## Target Users of the Guidelines

The guidelines will be of interest to healthcare providers in Singapore who care for cancer patients and/or their family members.

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## Guideline Recommendations/Development

The SCAN Cancer Genetics Workgroup comprises a panel of 4 medical oncologists and 1 colorectal surgeon from Singapore with special interests in the management of hereditary cancer syndromes. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available.

The workgroup members shared a common view that referral guidelines represented a key issue that is both pressing and relevant to the medical community at large. In contrast, testing and management guidelines are less relevant as pre- and post-test genetic counselling, surveillance and preventive recommendations, test result interpretations, and the social and ethical implications of genetic testing would be most appropriately delivered by trained specialists, preferably in the setting of a specialised cancer genetics clinic in a tertiary cancer centre. Currently, only 2 such clinics exist in the 2 tertiary cancer centres in restructured hospitals in Singapore: NCIS and NCCS, to serve the entire Singapore population of ~5.5 million. Both clinics are led by medical oncologists trained in cancer genetics, assisted by a cancer genetics counsellor. In addition, there are a few specialists in private medical centres who are trained to provide cancer genetics evaluation and counselling.

The workgroup decided to focus on the following 3 hereditary cancer syndromes most commonly encountered in practice:

1. Hereditary Breast and Ovarian Cancer (HBOC) Syndrome,
2. Lynch Syndrome (LS), and
3. Familial Adenomatous Polyposis (FAP).

Considering that at-risk patients may be referred from a diverse group of healthcare providers with different levels of knowledge on hereditary cancer syndromes, ranging from family physicians to specialists from different disciplines who may manage cancer patients or their families, it was decided that risk criteria chosen as referral guidelines should be clinical criteria that can be readily understood and assessed in the clinic. In addition, it was noted that while genetic evaluation and counselling is a health service that can be subsidised by the government, genetic tests are specialised tests that are self-paid by patients in Singapore and typically cost ~USD $1500 to $2000. High test cost has been cited as a barrier to genetic testing in Singapore.[4] Recognising this and the fact that medical resources are limited in Singapore with only 2 specialised cancer genetics clinics in the restructured hospitals serving the entire nation, it was decided to set the referral threshold at a sensitivity level equivalent to an a priori probability of diagnosing hereditary cancer syndrome of ≥10% to 20%, so as not to overwhelm the healthcare system.

Table 1 lists the guidelines that were reviewed, the details of which are summarised in Supplementary Tables 1-3. Guidelines were selected from various representative international professional bodies, excluding those that were published more than 10 years ago. Seven, 5, and 3 sets of international guidelines were reviewed for HBOC,[5-8] LS,[9-12] and FAP[10,12] respectively. The workgroup reviewed the guidelines and selected the most applicable one for each syndrome with modifications made for them to be appropriate to the local context (Table 2).

### 1. Hereditary Breast and Ovarian Cancer (HBOC)

International guidelines for HBOC typically divided the recommendations into 2 categories: for women with and without a personal history of cancer. All members elected to streamline the guidelines into a single category using the family as a unit and modify the wordings to include salient aspects of both personal and family histories. Most of the guidelines (NICE, Canadian Saskatchewan, USPTF, ASCO,

Table 1. International Guidelines Reviewed for Common Hereditary Cancer Syndromes by the SCAN Cancer Genetics Workgroup

| Hereditary Cancer Syndrome | International Guidelines Reviewed |
|---|---|
| Hereditary Breast and Ovarian Cancer Syndrome | National Comprehensive Cancer Network (NCCN, United States), 2014<br>United States Preventive Services Task Force (USPSTF), 2013[5]<br>National Institute for Health and Care Excellence (United Kingdom), 2013<br>American Society of Clinical Oncology (ASCO), 2012[6]<br>Saskatchewan Cancer Agency (Canada), 2012<br>European Society for Medical Oncology (ESMO) Guidelines Working Group, 2011[7]<br>The American College of Obstetricians and Gynaecologists (ACOG), 2011[8] |
| Lynch Syndrome | National Comprehensive Cancer Network (NCCN, United States), 2014<br>European revised guidelines for the management of Lynch syndrome, 2013[9]<br>American College of Medical Genetics (ACMG), 2013[10]<br>The Evaluation of Genomic Applications in Practice and Prevention working Group (EGAPP) Working Group, 2009[11]<br>American College of Gastroenterologists, 2008[12] |
| Familial Adenomatous Polyposis | National Comprehensive Cancer Network (NCCN, United States), 2014<br>American College of Medical Genetics (ACMG), 2013[10]<br>American College of Gastroenterologists, 2009[12] |

ESMO) were similar in recommending that women with young breast cancer, multiple family members with breast cancers, bilateral breast cancers, breast and ovarian cancers, male breast cancers, and multiple other related cancers (pancreatic, prostate, etc.) be included. In concordance with these recommendations, one local study showed that the highest risk group is families with breast and ovarian cancer.[13]

After reviewing the 7 sets of international guidelines, the committee decided to adopt the guidelines by the European Society for Medical Oncology (ESMO) Guidelines Working Group (2011) as the backbone guidelines,[7] as they were most encompassing, recommending 4 broad categories of patients to be referred: family history of breast or ovarian cancer, young onset cancer, male breast cancer, and multiple tumours. The workgroup built upon these general guidelines and added specific information to make the guidelines easy for referring physicians to follow. Of note, the age threshold for 'young onset cancer' was specified to be less than 40, while 'family history of breast or ovarian cancer' was further divided into 'family history of breast and ovarian cancer' and 'family history of 2 or more breast cancers, with at least one diagnosed below age 50' (adopted from the 2014 NCCN guidelines). In addition, members added a special note for clinicians to ask for a family history of young onset pancreatic and prostate cancer (diagnosed below age 50) in patients and/or families with breast cancer, and to consider referring these patients/families to a cancer genetics clinic for further evaluation (adopted from the 2014 NCCN guidelines). Recognising that patients with certain histological subtypes of breast and ovarian cancer have up to 10% to 20% chance of carrying a *BRCA1/2* mutation, patients with triple negative breast cancer diagnosed below age 50 (adopted from the 2014 NCCN guidelines with age threshold added to increase the specificity for referral)[14] and patients with epithelial ovarian cancer diagnosed at any age (adopted from the 2012 ASCO guidelines), in particular those with high-grade serous ovarian cancer,[15] were included in the referral criteria for HBOC.

The concept of population-based screening for *BRCA1/2* has been proposed recently.[16] However, given the high test cost that has to be borne by the patients as well as our currently limited medical resources to handle pre- and post-test genetic counselling and test interpretations required from large scale genetic testing, all members of the workgroup agreed not to include universal screening for HBOC syndrome in the guidelines, recognising that genetic testing administered without appropriate counselling may result in misinterpretation and harm.[17]

## 2. Lynch Syndrome (LS) or Hereditary Non-Polyposis Colorectal Cancer

Colorectal cancer (CRC) is a major public health problem, being the third most common cancer in men and women.[18] It is the second and third commonest cause of cancer-related deaths in men and women respectively and is largely preventable with recommended population screening.[18,19] It is estimated that approximately 3% of CRCs are attributable to LS.[20-22] This autosomal dominant genetic disorder is associated with greatly increased risks of developing colorectal, endometrial, gastric and other cancers.[20-23] Despite the increased risk of cancers seen in LS patients, long-term follow-up studies show that compliance with current surveillance recommendations is highly successful. LS patients show no increase in cancer-related mortality when compared to mutation-negative family members on long-term follow-up.[24] Unfortunately, unless

Table 2. Singapore Cancer Network (SCAN) Guidelines for the Referral for Genetic Evaluation of Common Hereditary Cancer Syndromes

| Suspected Hereditary Cancer Syndrome | Patients Who Should be Referred for Cancer Genetic Risk Assessment | Guidelines Adapted From |
|---|---|---|
| Hereditary Breast and Ovarian Cancer Syndrome | • Personal or family history of breast cancer diagnosed <40 years of age;<br>• Personal or family history of male breast cancer, any age;<br>• Personal or family history of epithelial ovarian cancer, any age;<br>• Personal or family history of triple negative breast cancer diagnosed <50 years of age<br>• Family with 2 or more breast cancers, at least one aged <50 years of age;<br>• Family with both breast and epithelial ovarian cancers;<br>• Two or more tumours in the same patient (bilateral breast cancer; multiple breast cancers; breast and ovarian cancer);<br>• Known *BRCA1/2* mutation in family. An a priori ≥10% probability of finding a mutation based on predictive models such as BRCAPRO, BOADICEA or Manchester Score*<br><br>(Special note: *BRCA1/2* mutation carriers are also at risk for pancreatic and prostate cancer and clinicians should additionally ask for these cancers in taking the family history. Physicians should consider referring families with breast cancer and young onset pancreatic or prostate cancer diagnosed before age 50.) | European Society for Medical Oncology (ESMO) Guidelines Working Group (2011) |
| Lynch Syndrome (LS) | Tumour microsatellite instability (MSI) and/or immunohistochemical (IHC) staining for mismatch repair (MMR) proteins should be considered in:†<br>1. Patient with CRC diagnosed <50;<br>2. Patient with synchronous or metachronous CRC or other LS-related tumours,‡ regardless of age;<br>3. Patient with CRC diagnosed <60 years of age with the MSI-H histology (presence of tumour infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern);<br>4. Patient with CRC diagnosed at any age, and who has at least 1 first-degree relative diagnosed with CRC or LS-related tumour diagnosed <50 years;<br>5. Patient with CRC at any age, and who has 2 or more first- or second-degree relatives with CRC or LS-related tumour at any age.<br><br>(Special note: If an MSI unstable tumour harbours the BRAF gene *p.V600E* mutation, it is most likely sporadic and germ line testing for mismatch repair genes is not necessary.)<br><br>When referral for clinical germline testing for mismatch repair genes should be considered:<br>1. Meets Amsterdam criteria§ or any of the above 5 listed criteria for tumour MSI or IHC testing for MMR proteins;<br>2. Endometrial cancer <50 years;<br>3. Known LS mutation in family;<br>(Special note: Consider testing individuals with ≥10% risk of LS on any mutation model[39-42] (e.g., MMRpro, PREMM, MMRpredict)* | National Comprehensive Cancer Network Guidelines - Genetic/Familial High Risk Assessment Colorectal (2014) |
| Familial Adenomatosis Polyposis (FAP) | 1. Patients with classic FAP (>100 adenomas) should be advised to pursue genetic counselling and genetic testing, particularly if they have siblings or children who could potentially benefit from predictive testing.<br>2. Patients with classic FAP, in whom APC genetic testing is negative, should undergo genetic testing for bi-allelic MYH mutations.<br>3. Patients with 10 – 100 adenomas can be considered for genetic testing for attenuated FAP and if negative, for MYH-associated polyposis.<br><br>(Special note: It should be highlighted that the number of adenomas is the cumulative number of adenomas seen in a patient's lifetime.) | American College of Gastroenterology - Medical Specialty Society 2009 |

APC: Adenomatous polyposis coli; CRC: Colorectal cancer; MSI-H: Microsatellite instability (high)
*This assessment should be made by a trained cancer genetics specialist.
†Alternatively, patients fulfilling these criteria may be referred to a cancer genetics clinic for genetic evaluation and workup.
‡LS-related cancers include cancers of the endometrium, stomach, pancreas, small intestine, ovary, kidney, brain, ureters, or bile duct.
§Amsterdam criteria: At least 3 family members affected with cancer, spanning 2 generations, with at least 1 affected family member diagnosed below age 50 years; the 3 affected family members have to be first-degree relatives of each other. In the Amsterdam I criteria, all 3 affected family members must have colorectal cancer; in Amsterdam II criteria, the affected family members may have colorectal, uterine, small bowel, ureteric or renal pelvis cancer.

there is strong clinical suspicion, many cases of LS are missed.[23] Furthermore, standard population CRC screening guidelines fail to provide early detection or prevention for most LS colon cancers as they tend to occur at young ages.[20-23] There is hence a clear need for better ways to detect patients at risk of LS.

The challenge in diagnosing LS, in contrast to FAP, is that it does not have pathognomonic clinical features of polyposis that distinguish it from a sporadic cancer. Guidelines for LS testing comprise one for screening of resected tumour specimens and another that targets germline genetic testing (usually blood) of at-risk individuals. Germline genetic testing by sequencing with or without multiplex ligation-dependent probe amplification is cost-effective in individuals who are of sufficient risk.[25]

Unfortunately, a high proportion of patients are missed when clinicians rely only on high risk clinical and/or pathological features.[21,26] Indeed, the revised Bethesda guidelines are now known to be inadequate for LS screening when family cancer history is not available. A universal screening paradigm greatly increased the rate of LS detection,[27] and the approach of universal screening for mismatch repair defect (MMR), the hallmark feature in LS,[20,26] in all colorectal cancer specimens, with either tumour microsatellite instability (MSI) testing with or without BRAF testing, or immunohistochemistry (IHC) staining of MMR proteins, has been proposed.[28] For screening, IHC is thought to be almost equally sensitive as MSI but more readily available.[26] Either MSI and/or MMR IHC as a screening tool to identify candidate LS cases for further workup are available in both tertiary cancer centres (NCIS and NCCS). However, while universal screening has been shown to be cost-effective,[29-32] infrastructure comprising trained medical staff, pathologists and workflows is required for effective implementation.[33-35] As such, there is disagreement within the workgroup with regard to universal screening, with 4 of 5 members voting not to include it in the current SCAN guidelines, given the lack of clear data and untested assumption in cost-effectiveness analysis studies that multiple family members will be tested following the identification of gene mutation in the proband in the local context.

The guidelines for LS were divided into criteria for tumour screening for MSI or IHC for MMR proteins, and criteria for referral for germline genetic testing. The 2013 American College of Medical Genetics (ACMG) guidelines[10] and the 2014 NCCN guidelines were adopted as the backbone guidelines for tumour screening and germline genetic testing respectively. Tumour screening guidelines were largely based on the revised Bethesda criteria,[36] and were included as there are specialists who have access to tumour screening and sufficient expertise to interpret results in at-risk individuals. However, the workgroup acknowledged that not all physicians are willing or able to order tumour screening tests, and added a special note that physicians may refer patients who fulfill criteria for tumour screening to a cancer genetics clinic for further workup, rather than arrange tumour testing themselves.

### 3. Familial Adenomatous Polyposis (FAP)

Classic FAP with its carpeting of adenomatous polyps throughout the colon and rectum is an easily recognisable phenotype and should prompt clinicians to initiate confirmatory genetic testing. More challenging would be the recognition of attenuated FAP or MYH-associated polyposis which has a less florid polyposis phenotype. The workgroup felt that an addendum to existing guidelines should be made to highlight that the number of adenomas (10-100) that would trigger consideration for attenuated FAP or MYH-associated polyposis refers to the cumulative incidence of adenomas over a patient's lifetime.

### Pre-test Genetic Counselling and Test Interpretation by Trained Specialists

All members in the committee agreed that genetic counselling and informed consent is required before genetic testing.[37] In our local setting, this is provided by trained specialists with the recognition that erroneous interpretation of genetic tests results can cause harm.[17] Moreover, many primary care physicians may be unprepared or unable to interpret genetic tests information.[38]

### Conclusion

The systematic development of guidelines will be helpful in the development of cancer genetics in Singapore. Inevitably, the increasing availability of genetic testing will allow greater opportunities for detecting patients with inherited disorders, while also increasing risks from indiscriminate utilisation. These adapted guidelines constitute best practice recommendations on the evaluation of at-risk individuals based on consensus and experience of trained clinical cancer geneticists familiar with the Singapore setting and its unique healthcare system. These guidelines also allow for dissemination of experience and education in Singapore for improving referral and interpretation of genetic tests results.

Of note, the workgroup eventually selected recommendations from multiple source guidelines developed by a variety of organisations, with additional calibration based on local data and experience. This bears testimony to the unique practice setting in Singapore, while also indicating that no single international organisation's

guidelines may be transplanted here as ideal practice. There was general consensus in the selection of relevant recommendations, with only one dissenting opinion in the development of LS guidelines, suggesting that there is a common view of how cancer genetics may be best developed in Singapore.

In conclusion, we have developed best practice recommendations surrounding referral for patients at risk of common hereditary cancer syndromes in Singapore. These recommendations are aimed at improving the identification and evaluation of such patients, and would be relevant to all physicians involved in caring for patients who may have or are at risk for cancer.

***Conflicts of Interest***

*Dr Ang reports receiving lecture fees from Myriad Genetics; Dr Tan reports receiving grant support from Pfizer, and holding the following pending patents: "A Multigene Assay for Prognosis and Drug Response Prediction in Clear-Cell Renal Cell Carcinoma Patients that Identifies Distinct Biological Subtypes", "Method for Predicting Clinical Toxicities and Outcomes in Patients Receiving Sunitinib Using Gene Polymorphisms", "Self-Assembled Micellar Nanocomplexes Comprising Polyethylene Glycol-Epigallocatechin-3-Gallate Conjugates and Anticancer Drugs", "Antibody Specific for Parafibromin, a New Marker of Parathyroid Carcinoma", licensed to Santa Cruz Biotechnology, and "Method for Determining Mutation Status in Colorectal Cancer Patients Using Allele-Specific PCR", licensed to AIT Biotech; Dr Ngeow, Dr Koh and Dr Lee have nothing to disclose.*

***Acknowledgements***

*The workgroup members are grateful to Ms Pearlyn Lee (Workgroup Member–Non-Voting) for providing administrative assistance.*

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***Reviewers***

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Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome

| Guideline Title | Genetic/Familial High Risk Assessment: Breast and Ovarian | Familial Breast Cancer. Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer | Breast Cancer Treatment Guidelines | BRCA in Breast Cancer: ESMO Clinical Recommendations | Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility | Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update | Breast Cancer Screening |
|---|---|---|---|---|---|---|---|
| Date Released | 2014 Version 1 | June 2013 | March 2012 | January 2011 | December 2013 | November 2012 | August 2011 |
| Guideline Developer | NCCN: National Comprehensive Cancer Network (US) | NICE: National Institute for Health and Care Excellence (UK) | Saskatchewan Cancer Agency (Canada) | European Society for Medical Oncology (ESMO) Guidelines Working Group | US Preventive Services Task Force (USPSTF) | American Society of Clinical Oncology (ASCO) | The American College of Obstetricians and Gynecologists (ACOG) |
| Reference | NCCN: National Comprehensive Cancer Network (US) Guidelines. Genetic/ Familial High-Risk Assessment: Breast and Ovarian. 2015 Version 1. Page 8. | NICE: National Institute for Health and Care Excellence (UK) Guideline 164. June 2013. Pages 24 – 28. | Saskatchewan Cancer Agency (Canada). Breast Cancer Treatment Guidelines. Page 2. | Annals of Oncology 22 (Supplement 6): vi31-vi34, 2011. | Ann Intern Med 2014; 160 (4):271-281. | Journal of Clinical Oncology 31.7 (2013):961-965. | Obstetrics and Gynecology (2011) Vol 118: Issue 2 – Part 1. Pages 372 – 382. |
| Who to Refer: Breast Cancer BRCA Screening for Women Without Personal History of Breast or Ovarian Cancer | • A known mutation in a breast cancer susceptibility gene within the family<br>• ≥2 breast primaries in a single individual<br>• ≥2 individuals with breast primaries on the same side of the family<br>• ≥1 ovarian cancer primary from the same side of the family<br>• First- or second-degree relative with breast cancer ≤45 years | People who should be offered a referral to a specialist genetic clinic:<br>• At least the following female breast cancers only in the family:<br>- Two first- or second-degree relatives diagnosed with breast cancer at younger than an average age of 50 years (at least 1 must be a first-degree relative) or<br>- Three first- or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years (at least 1 must be a first-degree relative) or | • Age greater than 60<br>• A history of lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS), or atypical proliferative lesion of the breast (atypical ductal or lobular hyperplasia)<br>• Women between 35 and 59 years of age with an estimated risk of breast cancer of 1.66% or higher over 5 years from the Gail model<br>• Individuals with *BRCA 1* and *BRCA2* mutations | • Family history of breast or ovarian cancer<br>• Young age at onset<br>• Male breast cancer<br>• Multiple tumours (bilateral breast cancer or breast and ovarian cancer in the same patient) | Family history factors associated with increased likelihood of potentially harmful BRCA mutations include<br>• Breast cancer diagnosis <50 years<br>• Bilateral breast cancer, family history of breast and ovarian cancer<br>• Presence of breast cancer in ≥1 male family member<br>• Multiple cases of breast cancer in the family | Women at high risk for familial breast cancer syndromes should be referred for genetic counselling in accordance with clinical guidelines recommended by the US Preventive Services Task Force. Criteria to recommend referral include the following:<br>• Ashkenazi Jewish heritage<br>• History of ovarian cancer at any age in the patient or any first- or second-degree relatives<br>• Any first-degree relative with a history of breast cancer diagnosed before the age of 50 | <u>Relative risk >4.0</u><br>• Female<br>• Age (65+ vs <65 years, although risk increases across all ages until age 80)<br>• Certain inherited genetic mutations for breast cancer (*BRCA1* and/or *BRCA2*)<br>• Two or more first-degree relatives with breast cancer diagnosed at an early age |

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

| Guideline Title | Genetic/Familial High Risk Assessment: Breast and Ovarian | Familial Breast Cancer. Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer | Breast Cancer Treatment Guidelines | BRCA in Breast Cancer: ESMO Clinical Recommendations | Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility | Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update | Breast Cancer Screening |
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| | • ≥1 family member on the same side of the family with a combination of breast cancer and ≥1 of the following (especially if early onset):<br>- Pancreatic cancer<br>- Prostate cancer (Gleason score ≥7)<br>- Sarcoma<br>- Adrenocortical carcinoma<br>- Brain tumours<br>- Endometrial cancer<br>- Leukaemia/ lymphoma<br>- Thyroid cancer<br>- Dermatologic manifestations and/or macrocephaly<br>- Hamartomatous polyps of GI tract<br>- Diffuse gastric cancer<br><br>• Male breast cancer | - Four relatives diagnosed with breast cancer at any age (at least 1 must be a first-degree relative) or<br><br>• Families containing 1 relative with ovarian cancer at any age and, on the same side of the family:<br>- One first-degree relative (including the relative with ovarian cancer) or second-degree relative diagnosed with breast cancer at younger than age 50 years or<br>- Two first- or second-degree relatives diagnosed with breast cancer younger than an average age of 60 years or<br>- Another ovarian cancer at any age or<br><br>• Families affected by bilateral cancer<br>- One first-degree relative with cancer diagnosed with cancer in both breasts at younger than an average age 50 years or<br>- One first- or second-degree relative diagnosed with bilateral cancer and one first- or | | | • ≥1 or more family member with 2 primary types of BRCA-related cancer<br><br>• Ashkenazi Jewish ethnicity<br><br>• Several familial risk stratification tools are available to determine the need for in-depth genetic counselling, such as the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and FHS-7 -Referral Screening Tool and FHS-7 are the simplest and quickest to administer | • Two or more first- or second-degree relatives diagnosed with breast cancer at any age<br><br>• Relative with diagnosis of bilateral breast cancer<br><br>• History of breast cancer in a male relative | • High breast tissue density<br><br>• Biopsy-confirmed atypical hyperplasia<br><br>2.1 – 4.0<br>• One first-degree relative with breast cancer<br><br>• High-dose radiation to chest<br><br>• High bone density (postmenopausal)<br><br>1.1 – 2.0 Factors That Affect Circulating Hormones<br>• Late age at first full-term pregnancy (>30 years)<br><br>• Early menarche (<12 years)<br><br>• Late menopause (>55 years)<br><br>• No full-term pregnancies<br><br>• Never breastfed a child<br><br>• Recent oral contraceptive use |

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

| Guideline Title | Genetic/Familial High Risk Assessment: Breast and Ovarian | Familial Breast Cancer. Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer | Breast Cancer Treatment Guidelines | BRCA in Breast Cancer: ESMO Clinical Recommendations | Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility | Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update | Breast Cancer Screening |
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| | | second-degree relative diagnosed with bilateral cancer and one first- or second-degree relative diagnosed with breast cancer at younger than an average age of 60 years or<br><br>• Families containing male breast cancer at any age and, on the same side of the family, at least:<br>- One first- or second-degree relative diagnosed with breast cancer at younger than 50 years or<br>- Two first- or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years.<br><br>• If their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more and an affected relative is unavailable for testing<br><br>• A formal risk assessment has given risk estimates of: | | | | | • Recent and long-term use of estrogen and progestin<br><br>• Obesity (postmenopausal)<br><br>Other Factors<br>• Personal history of endometrial or ovarian cancer<br><br>• Alcohol consumption<br><br>• Height (tall)<br><br>• High socioeconomic status<br><br>• Ashkenazi Jewish heritage<br><br><u>Others</u><br>• Women with a personal history of high risk breast biopsy results, including atypical hyperplasia and lobular carcinoma in situ |

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

| Guideline Title | Genetic/Familial High Risk Assessment: Breast and Ovarian | Familial Breast Cancer. Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer | Breast Cancer Treatment Guidelines | BRCA in Breast Cancer: ESMO Clinical Recommendations | Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility | Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update | Breast Cancer Screening |
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| | | - A 10% or greater chance of a gene mutation being harboured in the family or<br>- A greater than 8% risk of developing breast cancer in the next 10 years or<br>- A 30% or greater lifetime risk of developing breast cancer | | | | | <u>MRI Screening</u><br>• American Cancer Society recommends MRI screening for women with a 20% or greater lifetime risk of developing breast cancer, including women with the following:<br>- Known *BRCA1/2* mutation<br>- Have a first-degree relative with *BRCA1/2* mutation and have not had any testing themselves<br>- Lifetime risk of breast cancer of 20% or higher, according to risk assessment tools based mainly on family history<br>- History of radiation therapy to the chest between age 10 – 30 years<br>- Other genetic syndromes including Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome or one of these in a first-degree relative |

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

| Guideline Title | Genetic/Familial High Risk Assessment: Breast and Ovarian | Familial Breast Cancer. Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer | Breast Cancer Treatment Guidelines | BRCA in Breast Cancer: ESMO Clinical Recommendations | Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility | Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update | Breast Cancer Screening |
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| | • A known mutation in a breast cancer susceptibility gene within the family<br><br>• Early age onset breast cancer<br><br>• Triple negative (ER-, PR-, HER2-) breast cancer<br><br>• Two breast primaries in a single individual | | | | | | |
| Who to Refer: Breast Cancer BRCA Screening for Women With Personal History of Breast or Ovarian Cancer | • Breast cancer at any age, and<br>- ≥1 close blood relative with breast cancer ≤50 years, or<br>- ≥1 close blood relative with epithelial ovarian cancer at any age, or<br>- ≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age<br>- From a population with increased risk (requirements for inclusion may be modified, e.g. of Ashkenazi Jew descent with breast/ovarian/pancreatic cancer at any age) | | | | | • Patient with diagnosis of bilateral breast cancer | |

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

| Guideline Title | Genetic/Familial High Risk Assessment: Breast and Ovarian | Familial Breast Cancer. Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer | Breast Cancer Treatment Guidelines | BRCA in Breast Cancer: ESMO Clinical Recommendations | Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility | Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update | Breast Cancer Screening |
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| | • ≥1 family member on the same side of the family with a combination of breast cancer and ≥1 of the following (especially if early onset):<br>- Pancreatic cancer<br>- Prostate cancer (Gleason score ≥7)<br>- Sarcoma<br>- Adrenocortical carcinoma<br>- Brain tumours<br>- Endometrial cancer<br>- Leukaemia/ lymphoma<br>- Thyroid cancer<br>- Dermatologic manifestations and/or macrocephaly<br>- Hamartomatous polyps of GI tract<br>- Diffuse gastric cancer<br><br>• Ovarian cancer<br><br>• Male breast cancer | | | | | | |
| Mutation Detection | • Individual from a family with a known deleterious *BRCA1*/ *BRCA2* mutation<br><br>• Personal history of breast cancer and 1 of more of the following:<br>- Diagnosed ≤45 years<br>- Diagnosed ≤50 years with: | • Tests aimed at mutation finding should first be carried out on an affected family member where possible<br><br>• If possible, the development of a genetic test for a family should usually start with the testing of an affected individual | • Three or more breast and/or ovarian cancer family cases<br>- With at least one <50 years<br>- Two breast cancer cases <40 years<br>- Male breast cancer and ovarian cancer or early onset female breast cancer | • Three or more breast and/or ovarian cancer family cases<br>- With at least one <50 years<br>- Two breast cancer cases <40 years<br>- Male breast cancer and ovarian cancer or early onset female breast cancer | • Testing for BRCA mutations should only be done when:<br>- An individual has personal or family history that suggests an inherited cancer susceptibility<br>- An individual has access to a health professional who is trained to provide | | Family history to be considered:<br><br>• Breast cancer cases, ovarian cancer cases, prostate cancer cases, and other types of cancer cases in first-, second- and third-degree relatives, including the age of onset for the family members with cancer |

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

| Guideline Title | Genetic/Familial High Risk Assessment: Breast and Ovarian | Familial Breast Cancer. Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer | Breast Cancer Treatment Guidelines | BRCA in Breast Cancer: ESMO Clinical Recommendations | Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility | Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update | Breast Cancer Screening |
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| | - An additional primary<br>- ≥1 close blood relative with breast cancer at any age<br>- An unknown or limited family history<br>- Diagnosed ≥60 years with:<br>- ≥1 close blood relative with breast cancer diagnosed ≤50 years<br>- ≥2 close blood relatives with breast cancer diagnosed at any age<br>- ≥1 close blood relative with epithelial ovarian cancer<br>- ≥2 close blood relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age<br>- A close male blood relative with breast cancer<br>- For an individual with ethnicity associated with higher mutation frequency (e.g. Ashkenazi Jewish), no additional family history may be required<br><br>• Personal history of epithelial ovarian cancer | (mutation searching/ screening) to try to identify a mutation in the appropriate gene (such as *BRCA1*, *BRCA2* or *TP53*)<br><br>• Genetic testing for a person with no personal history of breast cancer but with an available affected relative<br>- Offer genetic testing in specialist genetic clinics to a relative with a personal history of breast and/or ovarian cancer if that relative has a combined *BRCA1* and *BRCA2* mutation carrier probability of 10% or more<br><br>• Genetic testing for a person with no personal history of breast cancer and no available affected relative to test<br>- Offer genetic testing in specialist genetic clinics to a person with no personal history of breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more and an affected relative is unavailable for testing | • Three or more breast and/or ovarian cancer family cases<br>- With at least one <50 years<br>- Two breast cancer cases <40 years<br>- Male breast cancer and ovarian cancer or early onset female breast cancer<br><br>• Ashkenazi Jew with breast cancer <60 years<br><br>• Young onset bilateral breast cancer; and breast and ovarian cancer in the same person<br><br>• Presence of medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no over expression of *HER2neu*) in women younger than 50 years<br><br>• Three or more breast and/or ovarian cancer family cases<br>- With at least one <50 years<br>- Two breast cancer cases <40 years | • Three or more breast and/or ovarian cancer family cases<br>- With at least one <50 years<br>- Two breast cancer cases <40 years<br>- Male breast cancer and ovarian cancer or early onset female breast cancer<br><br>• Ashkenazi Jew with breast cancer <60 years<br><br>• Young onset bilateral breast cancer; and breast and ovarian cancer in the same person<br><br>• In some countries, the criterion for testing is based on an a priori 10-20% probability of finding a mutation based on predictive models such as BRCAPRO, BOADICEA or Manchester Score, while less specific criteria include a potential benefit in the medical or surgical management of the individual or his/her relatives | • Testing for BRCA mutations should only be done when:<br>- An individual has personal or family history that suggests an inherited cancer susceptibility<br>- An individual has access to a health professional who is trained to provide genetic counselling and interpret test results<br>- Test results will aid in decision-making<br><br>• Initial testing of a family member with breast or ovarian cancer is the preferred strategy in most cases, but it is reasonable to test if no affected relative is available<br><br>• Type of mutation analysis required depends on family history. Individuals from families with known mutations or from ethnic groups in which certain mutations are more common (e.g. Ashkenazi Jewish women) can be tested for these specific mutations | | |

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

| Guideline Title | Genetic/Familial High Risk Assessment: Breast and Ovarian | Familial Breast Cancer. Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer | Breast Cancer Treatment Guidelines | BRCA in Breast Cancer: ESMO Clinical Recommendations | Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility | Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update | Breast Cancer Screening |
|---|---|---|---|---|---|---|---|
| | • Personal history of male breast cancer<br><br>• Personal history of pancreatic cancer or prostate cancer (Gleason score ≥7) at any age with ≥2 close blood relatives with breast and/or ovarian and/or pancreatic cancer (Gleason score ≥ 7) at any age<br>- For pancreatic cancer, if Ashkenazi Jewish ancestry, only one additional affected relative is needed<br><br>• Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):<br>- First- or second-degree blood relative meeting any of the above criteria<br>- Third-degree blood relative with breast cancer and/or ovarian cancer with ≥2 close blood relatives with breast cancer (at least one with breast cancer ≤ 50 years) and/or ovarian cancer | • Genetic testing for a person with breast or ovarian cancer<br>- Offer genetic testing in specialist genetic clinics to a person with breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more | - male breast cancer and ovarian cancer or early onset female breast cancer<br><br>• Ashkenazi Jew with breast cancer <60 years<br><br>• Young onset bilateral breast cancer; and breast and ovarian cancer in the same person<br><br>• Presence of medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no over expression of *HER2neu*) in women younger than 50 years.<br><br>• Three or more breast and/or ovarian cancer family cases<br>- With at least one <50 years<br>- Two breast cancer cases <40 years<br>- Male breast cancer and ovarian cancer or early onset female breast cancer<br>• Ashkenazi Jew with breast cancer <60 years | •The addition of pathological features of breast cancer such as medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no overexpression of *HER2neu*) in women younger than 50 has been evaluated as a cost-effectiveness strategy for mutation detection.<br><br>• 2% to 12% of high risk families may harbour a large genomic alteration | • Individuals without linkages to families or groups with known mutations receive more comprehensive testing. Testing should begin with a relative who has breast or ovarian cancer to determine if affected family members have a clinically significant mutation | |

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

| Guideline Title | Genetic/Familial High Risk Assessment: Breast and Ovarian | Familial Breast Cancer. Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer | Breast Cancer Treatment Guidelines | BRCA in Breast Cancer: ESMO Clinical Recommendations | Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility | Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update | Breast Cancer Screening |
|---|---|---|---|---|---|---|---|
| | - Clinical judgement should be used to determine if the patient has reasonable | | • Young onset bilateral breast cancer; and breast and ovarian cancer in the same person<br><br>• Presence of medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no over expression of *HER2neu*) in women younger than 50 years. | | | | |
| Member Votes | | | | Unanimous | | | |

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 2. International Guidelines Reviewed for Lynch Syndrome

| Guideline Title | Recommendations from the EGAPP Working Group: Genetic testing Strategies in Newly Diagnosed Individuals with Colorectal Cancer Aimed At Reducing Morbidity and Mortality from Lynch Syndrome in Relatives | Genetic/Familial High Risk Assessment: Colorectal | American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008 | Revised Guidelines for the Clinical Management of Lynch Syndrome (HNPCC): Recommendations by a Group of European Experts | ACMG Technical Standards and Guidelines for Genetic Testing for Inherited Colorectal Cancer (Lynch Syndrome, Familial Adenomatous Polyposis, and MYH-associated Polyposis) |
|---|---|---|---|---|---|
| Date Released | January 2009 | 2014 | 2009 | December 2012 (Revised January 2013) | September 2013 |
| Guideline Developer | Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group - Independent Expert Panel | NCCN | American College of Gastroenterology - Medical Specialty Society | Vasen et al | Working Group of the American College of Medical Genetics and Genomics (ACMG) Laboratory Quality Assurance Committee |
| Reference | Genetics In Medicine. 2009 Jan;11(1):35-41 | NCCN: National Comprehensive Cancer Network (US) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. 2015 Version 1. Page 10 | Am J Gastroenterol 2009;104:739-750 | Gut 62.6 (2013):812-823 | Genetics In Medicine. 2014 Jan;16(1):101-116 |
| Description of Method of Guideline Validation | Recommendations concerning laboratory and genetic testing in colorectal cancer from the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncologists (ASCO) were reviewed | The NCCN Guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to cancer treatment | This guideline has been reviewed and approved by the Practice Parameters Committee of the American College of Gastroenterology (ACG) and by the ACG Board of Trustees | External peer review. The guidelines were discussed during 2 workshops and all authors were involved in the discussion. | These technical standards and guidelines were approved by the ACMG Board of Directors on 20 May 2013. |
| MSI Testing | | All CRC patients or CRC patients diagnosed at <70 years and also those ≥70 who meet the Bethesda guidelines | Patients who meet the Bethesda criteria should undergo microsatellite instability testing of their tumour or a family member's tumour and/or tumour immunohistochemical staining for mismatch repair proteins | All CRC (or individuals with CRC <70 years) and all EC (or individuals with EC <70 years) by immunohistochemistry of the 4 MMR proteins or MSI. These tests should be accompanied by methods that identify MLH1 promotor methylation. | MSI testing:<br>1. CRC diagnosed <50<br>2. Presence of synchronous or metachronous CRC or other hereditary non-polyposis CRC-related tumour, regardless of age<br>3. CRC in an individual <60 years of age exhibiting tumour-infiltrating lymphocytes<br>4. CRC at any age, plus CRC or hereditary non-polyposis CRC-related tumour diagnosed <50 years in at least one first-degree relative |

CRC: Colorectal cancer; EC: Endometrial cancer; LS: Lynch syndrome; MSI: Microsatellite instability
*4 of 5 members voted not to include universal screening in the current SCAN guidelines.

Supplementary Table 2. International Guidelines Reviewed for Lynch Syndrome (Con't)

| Guideline Title | Recommendations from the EGAPP Working Group: Genetic testing Strategies in Newly Diagnosed Individuals with Colorectal Cancer Aimed At Reducing Morbidity and Mortality from Lynch Syndrome in Relatives | Genetic/Familial High Risk Assessment: Colorectal | American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008 | Revised Guidelines for the Clinical Management of Lynch Syndrome (HNPCC): Recommendations by a Group of European Experts | ACMG Technical Standards and Guidelines for Genetic Testing for Inherited Colorectal Cancer (Lynch Syndrome, Familial Adenomatous Polyposis, and MYH-associated Polyposis) |
|---|---|---|---|---|---|
| MSI Testing | | | | | 5. CRC at any age, plus CRC or hereditary non-polyposis CRC-related tumour diagnosed <50 years in 2 or more first- or second-degree relatives<br><br>-If an MSI unstable tumour harbours the BRAF gene *p.V600E* mutation, it is most likely sporadic and germline testing is not necessary |
| Member Votes | | | | | Unanimous |
| Genetic Testing | Offer genetic testing for LS to individuals with newly diagnosed CRC | [LS testing - clinical]<br><br>Meets revised Bethesda guidelines or Amsterdam criteria<br><br>Endometrial cancer <50 years or<br><br>Known LS in family or<br><br>Consider testing individuals with ≥5% risk of LS on any mutation model (e.g. MMRpro, PREMM, MMRpredict) | Patients who test positive for MSI should undergo genetic testing<br><br>If evaluation for HNPCC not indicated<br><br>Patients with:<br><br>Single first-degree relative with CRC or advanced adenoma diagnosed at age ≥60 years<br><br>Single first-degree with CRC or advanced adenoma diagnosed at age <60 years or 2 first-degree relatives with CRC or advanced adenomas | Molecular screening of EC, sebaceous adenomas and carcinomas have been effective | CRC patient <50 including;<br><br>- Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch-related tumour, one who was diagnosed <50 years of age<br><br>- Colorectal cancer diagnosed in 2 or more relatives of regardless of age |
| Member Votes* | | Unanimous | | | |

CRC: Colorectal cancer; EC: Endometrial cancer; LS: Lynch syndrome; MSI: Microsatellite instability
*4 of 5 members voted not to include universal screening in the current SCAN guidelines.

Supplementary Table 3. International Guidelines Reviewed for Familial Adenomatous Polyposis

| **Guideline Title** | **Genetic/Familial High Risk Assessment: Colorectal** | **American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008** | **ACMG Technical Standards and Guidelines for Genetic Testing for Inherited Colorectal Cancer (Lynch Syndrome, Familial Adenomatous Polyposis, and MYH-associated Polyposis)** |
|---|---|---|---|
| Date Released | 2014 | 2009 | September 2013 |
| Guideline Developer | NCCN | American College of Gastroenterology - Medical Specialty Society | Working Group of the American College of Medical Genetics and Genomics (ACMG) Laboratory Quality Assurance Committee |
| Reference | NCCN: National Comprehensive Cancer Network (US) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. 2015 Version 1. Page 21 | Am J Gastroenterol 2009; 104:739-750 | Genetics In Medicine 2014 Jan;16(1):101-116 |
| Description of Method of Guideline Validation | The NCCN Guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to cancer treatment | This guideline has been reviewed and approved by the Practice Parameters Committee of the American College of Gastroenterology (ACG) and by the ACG Board of Trustees | These technical standards and guidelines were approved by the ACMG Board of Directors on 20 May 2013 |
| Genetic Testing | APC Testing Criteria:<br>1. Personal history of >10 adenomas<br>2. Personal history of desmoid tumour<br>3. Known deleterious mutation of APC in family | 1. Patients with classic FAP (>100 adenomas) should be advised to pursue genetic counselling and genetic testing, if they have siblings or children who could potentially benefit from this testing<br>2. Patients with classic FAP, in whom genetic testing is negative, should undergo genetic testing for bi-allelic MYH mutations. Patients with 10 – 100 adenomas can be considered for genetic testing for attenuated FAP and if negative, MYH-associated polyposis | Indications for testing:<br>1. CRC diagnosed <40 years<br>2. CRC diagnosed in ≥1 first-degree relatives<br>3. Other adenomas and cancers<br><br>FAP testing criteria:<br>1. Presence of 100 or more polyps<br>2. Autosomal dominant inheritance<br>3. Possible additional findings, such as congenital hypertrophy of retinal pigment epithelium, osteomas, supernumerary teeth, odontomas, desmoids, epidermoid cysts, duodenal and other small-bowel adenomas, gastric fundic gland polyps<br><br>AFAP testing criteria:<br>1. Presence of <100 adenomas*<br>2. Frequent right-sided distribution of polyps<br>3. Adenomas and cancers at an age older than that for classic FAP and other gastrointestinal manifestations |
| Member Votes | | | Unanimous |

AFAP: Attenuated familial adenomatous polyposis; APC: Adenomatous polyposis coli; CRC: Colorectal cancer; FAP: Familial adenomatous polyposis
*Average 30 polyps. Individuals with 100 or more polyps occurring at older ages (35 – 40 years or older) may be found to have AFAP.