Cancer genetics:
An information resource for non-specialists

August 2008
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A publication from the BMA Science and Education department and the Board of Science.

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Introduction

This resource provides a brief overview of the evolving field of cancer genetics, with particular emphasis on common situations encountered in primary care. Links to readily accessible websites and references that provide more in-depth information or help are provided throughout. The links have been selected specifically for accuracy, ease of access and use by a non-specialist audience. The resource aims to be of practical use rather than attempting to be all encompassing. Technical terms referred to in the resource are linked to the definitions given in the glossary.

Genetic risk for cancer in the family will usually present with one or more close relatives affected by cancer. This resource gives a brief outline of how to approach the assessment of a patient seeking advice about risk and early surveillance, and in particular the key features that require intervention. The three possible responses to such an enquiry might be reassurance that the situation is not particularly unusual (given the population risks for that cancer), a referral to secondary care for earlier or additional surveillance, or for those that seem to be at high risk, referral for a genetic assessment. This guide covers the basic principles to apply when assessing the family history and the main features to look out for that might indicate a genetic diagnosis.

Cancer and cancer genes

- Cancer arises due to the acquisition of a series of alterations in key genes that control cell growth and cell death, usually over a long period of time.
- A small proportion of cancers arise because of an inherited genetic alteration that confers a very high lifetime risk of developing cancer.

Cancer is a genetic disease at the cellular level but most cancers are not due to high-penetrance disease associated alleles. A tumour (benign or malignant) arises because the normal balance between cell growth, cell division and cell loss is disturbed. Cells acquire mutations during cell division, and cancers develop when these mutations involve genes that permit and promote invasion of normal tissue and metastatic spread. These are known as somatic mutations as they are present only in the tissues (soma) and not the germ cells. Most of the mutations that drive cancer are acquired rather than inherited, and have generally accumulated over many cell divisions and a long period of time. These acquired mutations do not pass on to the next generation. They often occur due to random chance errors in the DNA replication process during normal cell division, but DNA damage can also be induced by environmental carcinogens. For further information on carcinogens, please visit: http://www.cancer.org/docroot/PED/content/PED_1_3x_Known_and_Probable_Carcinogens.asp

The replication of DNA usually occurs with very high fidelity; a gene mutation occurs by chance roughly every one in a million bases copied. Each time a cell replicates, the six billion bases coding the entire diploid human genome are copied, so for each cell undergoing one replication cycle, approximately 6,000 coding errors are created. Many of these acquired mutations have no effect, but some promote or permit...
an abnormal pattern of growth. The cancer cell starts as a normal tissue cell which then, over a long period of time, acquires a critical number of somatic mutations and epigenetic changes. The changes influence the expression of genes involved in regulating normal cell growth. Usually these genetic phenomena confer some advantage in growth over the surrounding cells, resulting in more rapid division of the mutated cell over the normal cell. More frequent cell divisions encourage the acquisition of further mutations and eventually loss of the normal balance between cell division and cell death (apoptosis). If a cell exhibits disordered growth and proliferation, it may be recognised as foreign by the immune system and destroyed. Cancers that present clinically have usually acquired mutations in genes that enhance their ability to grow, to escape immune surveillance mechanisms and to metastasise. There are many genes that are involved in cancer development and progression. Some of these types of genes, including proto-oncogenes, tumour suppressor genes and genes involved in the process of repairing mutated DNA (DNA repair genes), are important not only in the development of isolated cancers but also in inherited forms of cancer. For further information, please visit:
http://info.cancerresearchuk.org/cancerandresearch/learnaboutcancer/whatcausescancer/?a=5441

Cancer in the family

- Clusters of cancer among close relatives, especially if occurring at young ages, is evidence of a genetic contribution to cancer risk.
- Exceptionally young age at diagnosis and multiple primary cancers in one person may indicate genetic risk.

Most cancers arise by chance; it is useful to have a concept of which cancers are common and the typical age at onset in the general population (http://info.cancerresearchuk.org/cancerstats/). Common cancers at typical ages might occur more than once in a family without necessarily inferring a strong genetic risk, but the presence of more than one cancer of the same type in a family may indicate some level of genetic predisposition. It is worth noting that families usually share similar environments and lifestyles as well as genes. Possible genetic predisposition is indicated when there is more than one occurrence of the same cancer (or associated cancers) in close relatives at younger than expected ages. For further information, please visit:
http://info.cancerresearchuk.org/cancerandresearch/learnaboutcancer/whatcausescancer/inheritance/

Familial cancer

- Most clusters of cancer cases in a family will be due to polygenic influences.
- A small percentage of all cancers will arise on a background of strong genetic risk due to a single highly penetrant ‘faulty’ gene.
Family history is known to be a risk factor for most common adult cancers. Although an estimated 20-30 per cent of attributable cancer risk is genetic, less than 5 per cent of common adult onset cancers are due to the inheritance of a single high risk (high penetrance) predisposition allele. Currently, genetic testing is only clinically relevant in the small percentage of cases where a single, high penetrance gene, is likely to be being transmitted in a family.

Familial clustering of cancers most often results from a combination of several low penetrance genetic ‘variants’ or polymorphisms. These polymorphisms are present in more than 1 per cent of the general population but can occur in up to 50 per cent of individuals in a population; each may be associated with very small increases in risk and may be balanced by genetic variants that reduce cancer risks. Common low penetrance genetic variants influencing disease susceptibility are currently being identified using mainly very large case-control studies.

A number of commercial companies offer ‘direct to consumer’ genetic testing incorporating this type of common genetic variant. Testing for this type of genetic variant cannot be considered a clinically useful test for specifying future disease risks in an individual. This is because there are potentially hundreds of risk alleles (both increasing and decreasing risks fractionally). None has an effect alone of sufficient magnitude (penetrance) to be relevant to the future cancer risks in an individual, and many risk alleles published to date in small sample sizes have turned out to be statistical artefacts. Case-control studies involving tens of thousands of individuals are needed to demonstrate robust associations. It is plausible that these low penetrance risk alleles will be useful in the future to formulate a composite cancer risk, but at present the development of methods to incorporate all known risk factors for an individual risk assessment are a significant challenge for the next decade. Media coverage reflects some of the current medical scepticism around genetic testing for common genetic variants to determine disease susceptibilities for individuals. It is important, however, to distinguish clearly between this type of polymorphism testing from clinically useful tests for single gene disorders that confer high lifetime risks of developing cancer at specific sites. For further information, please visit:

http://www.sciencedaily.com/releases/2008/04/080424151117.htm
http://www.economist.com/research/articlesBySubject/PrinterFriendly.cfm?story_id=10250288

**Hereditary cancer**

- Most high penetrance cancer susceptibility genes for adult cancers are transmitted as an autosomal dominant trait.
- Penetrance is age dependent, may be sex dependent and is usually less than 100 per cent.
- Phenotypic expression may vary.

Inherited single gene mutations that when inherited confer a high risk of the individual developing cancer are most commonly transmitted through the family as an autosomal dominant characteristic with incomplete penetrance. The phenotypic expression of the faulty gene may be limited by sex (male carriers of a gene predisposing to ovarian cancer will not develop the disease although they may express the gene
in other ways). Phenotypic expression may also be modified by both extrinsic (environmental) and intrinsic (genetic) influences.

The family history is the main tool for assessing two related but different probabilities:
1) the likelihood of cancer developing in the future; and
2) the probability that an individual carries a highly penetrant disease predisposition allele.

The former likelihood determines initial management choices and the latter guides choices about genetic testing to refine cancer risk estimates for the individual and their family.

In general, features that suggest the possibility of an underlying genetic predisposition to cancer are:
- multiple blood relatives with the same or related cancers
- multiple generations affected
- more than one primary cancer in a family member
- younger than average age at diagnosis.

The assessment of these probabilities is more difficult in the case of a single ‘severely’ affected individual. Most patients, even at young ages, with a primary cancer and no family history do not have a highly penetrant predisposition allele to account for their cancer. Possible flags to a strong genetic predisposition in a single affected person might be particularly relevant if the individual is adopted or a breast/ovarian cancer patient has no information about her father’s female relatives. Possible flags are:
- very young age at onset
- more than one primary tumour.

For further information, please visit:
http://www.cancerbackup.org.uk/Aboutcancer/Genetics/Cancergenetics

Assessment of genetic risk

- Assessment of the family history is key to estimating:
  a) the likelihood of cancer developing; and
  b) the probability that an individual carries a high risk susceptibility allele.

The family history of an individual remains the main tool for assessing the likelihood of a genetic predisposition to cancer in a family. Patients and families should be encouraged to research their own family history. Construction of the family tree is a very useful starting point to explore what advice may be appropriate and will be useful if the patient needs to be referred on to the genetic services. There are several (free) web-based tools that patients may find useful in researching and drawing their family pedigree:
- pedigree drawing (https://familyhistory.hhs.gov/)
- death certificates (https://www.secure1.gov-certificates.co.uk/).
Computer programmes are available to assist in calculating the chance of developing cancer or the probability that an individual carries a high risk allele (see further sources of information). However, each type of risk prediction programme has its biases and shortcomings, and the provision of an actual percentage risk figure requires contextualising so may not be entirely appropriate to direct patients towards. Many guidelines use broad categories of cancer risk (population, moderate increase and high risk) which may be more relevant to clinical practice than absolute figures. It is also important to bear in mind how cancer risk is expressed, for example cumulative risk (which is age dependent), lifetime risk (to age 70 or sometimes to age 80 years) or the relative risk (usually relative to the risk at the same age in the general population).

**Clinical genetics services**

- Genetic services in the UK are regionally based and accept referrals direct from primary or secondary care.
- Many regional genetics services have referral guidelines for individuals concerned about genetic cancer risks.

Genetic counselling is the process by which patients or relatives at risk of a disorder that may be hereditary, are advised of the consequences of the disorder, the probability of inheriting or transmitting it, and the ways in which it can be prevented, avoided or ameliorated.

Clinical genetics services are usually based in major teaching hospitals but most offer peripheral clinics much nearer to an individual’s home. The British Society for Human Genetics website lists the details of all the Regional Genetics Services for the UK. For further information, please visit: [http://www.bshg.org.uk/genetic_centres/uk_genetic_centres.htm](http://www.bshg.org.uk/genetic_centres/uk_genetic_centres.htm)

**Genetic medicine and cancer genetics service development**

Genetic medicine is now becoming relevant to all branches of medicine as an increasing number of loci that predispose to common diseases are being discovered. Many thousands of genes associated with disease are now recognised. The potential of genetic testing to improve healthcare, not only in rare diseases but also in common disease, has become clear over the last decade or so and was a particular driving factor behind the 2003 Government white paper ‘Our inheritance our future’ ([http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4006538](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4006538)). The 2008 review of progress following some investment in genetic services demonstrates the breadth of developments, including several projects in primary care, and illustrates how genetic predisposition to cancer has a prominent position in clinical practice.

Over the last two decades, clinical cancer genetics services have started to be established in the UK within the 21 regional genetics centres. With the recognition of the potential for cancer genetics to impact disease prevention in particular, a framework for service provision was considered by a working party
chaired by Professor Sir Peter Harper in 1998. A clear message following this working party review was that genetic risks for cancer could be grouped into three categories: risks similar to the general population; moderately increased risks; and high risk. Education at both primary and secondary care would be necessary if appropriate use was to be made of specialist genetic services. One of the first responses to this report was the development of educational material for GPs that improved the efficacy of risk assessment and triage of patients presenting in primary care with a breast and ovarian cancer family history. Patients concerned about genetic predisposition to cancer now represent one of the main categories of referral from primary care into the tertiary genetics service.

Cancer genetic services

- For patients likely to have an increased cancer risk, but unlikely to carry a high risk susceptibility allele, referral to secondary care for early surveillance is appropriate.
- For patients likely to carry a high risk susceptibility allele, referral to genetics services is appropriate.
- Approaches to genetic risk assessment and risk management across the devolved nations are broadly similar.

The emergence of specialised cancer genetics services within the Clinical Genetics Services in the 1980s and early 1990s was in response to the discovery of several of the high risk genes involved in breast (e.g. BRCA1 and BRCA2) and colon cancer (APC; hMLH1, hMSH2 and hMSH6) predisposition. It was recognised that the basic skills for risk assessment using family history would be needed in primary and secondary care in order that appropriate referrals could be made into the tertiary specialist genetics services. The Genetics Services can offer investigation and diagnosis of high risk single gene disorders, but are required also to help educate those delivering clinical services at primary and secondary care level in order that patients seeking advice are dealt with at the appropriate level. The UK Cancer Genetics Group (http://www.ukcgg.org) is a constituent professional society within the British Society for Human Genetics (http://www.bshg.org.uk/) which provides a pan UK focus for sharing and developing expertise in the relatively new clinical discipline of cancer genetics through collaborative research and educational activities.

Guidelines from the devolved nations

England, Wales, Scotland and Northern Ireland have each developed guidelines for the management of individuals with a family history of cancer who may be at genetic risk. In general where guidelines exist, the most current version for the country of relevance should be used. It is important for clinicians and their patients to recognise that clinical guidelines vary in particular in areas where the evidence for interventions is less robust or non-existent. Lack of evidence leaves only expert opinion on which to base guidance. A good example of this is the variable recommendations for ovarian screening (no clear evidence of benefit). The Genetics Commissioning Advisory Committee was set up to take a strategic overview of developments in genetics services and has representation from all the devolved nations.
Guidelines in England


Guidelines in Scotland
In 1998 a Scottish Government Report laid down a framework for the development of cancer genetics services (http://www.sehd.scot.nhs.uk/mels/1998_73.htm) which is broadly similar to other countries and also recognised the role of specialist genetic counsellors. Four genetics services cover the population of Scotland. Guidance on management of individuals at genetic risk was published in 2001 (http://www.sehd.scot.nhs.uk/mels/HDL2001_24.htm) and an update to this paper specifically dealing with management of women with a family history of breast cancer was made available in 2007 (http://www.sehd.scot.nhs.uk/mels/HDL2007_08.pdf) essentially endorsing the NICE guidance for management of familial breast cancer.

Guidelines in Wales
Welsh guidance in this area has developed in close collaboration with English guidance. Welsh guidelines are not available separately via a web link. There is a single genetics service for Wales based in Cardiff but with outreach clinics across the whole country (http://www.wales.nhs.uk/sites3/home.cfm?orgid=525).

Guidelines in Northern Ireland
In 2003 a review of the clinical genetics service for Northern Ireland also recognised the increase in referrals for cancer genetics advice and the role of genetic counsellors in delivering cancer genetics services (www.dhsspsni.gov.uk/clinical_genetics_rev_sept03.pdf). Cancer genetics services are centred in the Northern Ireland Regional Genetics Service in Belfast offering outreach clinics. Guidelines for referral of patients with a family history of cancer to the Genetics Service were sent directly to GPs in Northern Ireland in 2001 but are not currently available via a web link.
Genetic testing for cancer predisposition

- Genetic analysis in a new family deemed high risk and therefore eligible for genetic testing should commence with a cancer affected person from the family.
- If no DNA sample is available from an affected individual, meaningful genetic analysis may not be possible.
- Predictive genetic testing (for a high risk susceptibility allele in an unaffected family member) requires the nature of the disease causing mutation to have been clarified in the individual’s family.

If the family history suggests the possibility of a dominant high risk gene causing the disease, the best starting place to investigate this further is to refer a person affected by cancer in the family directly to the regional genetics service for evaluation. NHS genetic testing requires prior assessment in a specialist genetic clinic. The reasons for this include the best use of laboratory resources and to ensure clear clinical interpretation of results for the individual and to facilitate dissemination of information and advice to benefit the wider family. There are many genes that can predispose to cancer, so the assessment of the family history ideally includes the following steps:

- construction of the family tree
- confirmation of key diagnoses in other family members (using cancer registry data, pathology reports or death certificates)
- review of tumour types and sub-types and, in some cases, specific additional tumour based pathology and molecular tests.

If a specific genetic predisposition syndrome is suspected after all evidence is taken into account then the geneticists will request analysis of the coding sequence of one or a few specific genes in a DNA sample, ideally from a cancer affected family member. If a disease causing gene mutation can be detected in that individual then more precise information about inheritance and consequences can be given to at risk family members.³

Where no relevant mutation can be discovered in an affected individual there are a number of possible explanations that need to be considered:

- the person tested does not carry the faulty gene causing cancer in other family members (this is more likely to be the explanation if an unaffected person in the family is tested). It is important to test the most extremely affected person available (choose the youngest or the person with two primaries if possible)
- the family history is not due to a single high risk gene fault (most likely when testing is initiated where the family history is not strongly suggestive of a clear dominant genetic predisposition)
- the technique used has failed to detect a causative mutation that is present (this depends on the technique used for genetic testing; no single technique is adequate to pick up all classes of causative mutation). It is important that the testing laboratory has appropriate professional accreditation
• the wrong gene was tested – careful clinical assessment is required before genetic testing is ordered and to interpret the outcome in context.

The most frequent explanation is likely to be that the cluster of cancers in the family is not due to a single high risk gene but is due to complex inheritance of low penetrance risk genes. Advice about risk and surveillance is then based on the family history detail.

Breast cancer family history

Risk estimation
There are two broad questions that need to be considered when assessing the need for intervention on the basis of a family or personal history of cancer.

• Is there likely to be an underlying high risk single gene disorder (a cancer predisposition syndrome)?
• What is the risk of cancer and is this sufficiently increased above the population risk for targeted surveillance to be beneficial?

The commonest reasons for referral to cancer genetics clinical services are a personal or family history of breast cancer.

Guidelines
The National Institute for Clinical Excellence (NICE) convened a panel of experts to review evidence and draw up guidance for managing familial breast cancer (http://www.nice.org.uk/guidance/index.jsp?action=byD&o=10994). These guidelines are detailed and include algorithms for determining the most appropriate action to be taken when a family history of breast cancer is being evaluated (see page 6 and 7 of the quick guide http://www.nice.org.uk/guidance/index.jsp?action=download&o=30244).

Familial breast cancer
Breast cancer is the commonest cancer among women in the UK. Over 44,000 cases are diagnosed each year, and 5 per cent of cases are diagnosed before 40 years of age. It is the commonest cause of death among women aged 45-65 years (http://info.cancerresearchuk.org/cancerstats/types/breast/).

The National Health Service breast screening programme calls all women from 50 to 70 years of age for mammography every three years (http://www.cancerscreening.nhs.uk/breastscreen/). For a woman who has more than one relative with breast cancer (figure 1), or where one close relative (mother or sister) had breast cancer before 40 years of age, referral for early annual mammography from 40 years of age is recommended by NICE but not yet fully implemented in all UK centres. This additional screening is recommended on the basis of an estimated increase in risk that is at least double the population age specific risk between 40 and 50 years of age (ie at least a 3% risk of developing breast cancer over the 10-year period). It is important for patients to appreciate that these risks are still fairly small in absolute
terms. This approach to moderate risk management in secondary care is endorsed in the Cancer Reform Strategy document (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_081006). This may improve and harmonise the provision of these services in time.

**Figure 1: A typical family history likely to arise through sharing of low penetrance genetic variants**

![Family History Diagram]

Please [click here](#) for a key for figure 1.

Figure 1 illustrates a typical family history that is unlikely to be due to a single high risk gene but is nevertheless estimated to confer a moderate (two to three fold) increase in lifetime cancer risk for immediate relatives due to polygenic factors. Early surveillance is the current recommendation for most women with a family history of breast cancer presenting in primary care since most family histories will be multifactorial with an underlying polygenic mechanism. Current advice outlined in the NICE guidelines on management of familial breast cancer is to start annual mammographic surveillance at 40 to 50 years of age, then continue in the NHS breast screening programme thereafter.

Clinical trials have concluded that treatment with the oestrogen receptor blocking drug Tamoxifen can reduce the incidence of oestrogen receptor positive breast cancer by up to 50 per cent, but has little or no effect on the incidence of estrogen receptor (ER) negative breast cancer. It is not yet clear what implications this has for reducing breast cancer mortality overall.

**Recognising high risk genes**

The most frequently occurring breast cancer high risk predisposition syndrome is Hereditary Breast and Ovarian cancer syndrome due to an inherited mutation in either the BRCA1 or the BRCA2 genes. The family history illustrated in figure 2 would be very suspicious of an underlying BRCA1 gene mutation with early onset breast cancer, ovarian cancer and multiple affected individuals, one with a dual primary cancer.
Although this is a relatively uncommon cause for breast cancer, when present within a family the effect on cancer risk is dramatic for family members who inherit the predisposition. It is therefore important to recognise the diagnosis and refer on for specialist assessment by the genetics services. Identification of the causative gene mutation in a family can take some time. If the gene fault can be found in an affected family member then other relatives can have a genetic test to determine whether they are at high risk or not. Early surveillance and, if required, surgery to remove or reduce the very high risk can be offered to those at high risk. The assessment of genetic risk starts with the family history and takes into account unaffected relatives on the relevant side of the family as well as the affected family members. Transmission of a faulty BRCA1 or 2 gene may be from either the paternal or maternal side. The gene expression is altered by the sex of the transmitting individual.

BRCA1 and BRCA2 mutations are estimated to affect between one in 150 and one in 800 people in the general population. Some facts worth remembering about BRCA1 and 2 in relation to breast and ovarian cancer are given below.

Breast cancer:
- the lifetime risk of developing breast cancer for both BRCA1 and BRCA2 gene carriers can be as high as 80 per cent (four in every five gene carriers)
- the average age at breast cancer diagnosis is around 42 years for BRCA1 carriers and around 48 years for BRCA2 gene carriers
- NICE recommends early breast screening starting not younger than 30 years using both MRI and mammography
- women at high genetic risk for breast cancer should have the opportunity to discuss risk reducing surgery. For further information, please visit: [http://www.cancerbackup.org.uk/Aboutcancer/Genetics/Risk-reducingbreastsurgery/Whyconsiderit](http://www.cancerbackup.org.uk/Aboutcancer/Genetics/Risk-reducingbreastsurgery/Whyconsiderit).
Ovarian cancer:

- ovarian cancer lifetime risk may be as high as 60 per cent
- ovarian screening is of unproven clinical value and is still undergoing research evaluation
  ([http://www.breakthrough.org.uk/about_breast_cancer/family_history/research_and_trials/clinical_trials/uk_familial.html](http://www.breakthrough.org.uk/about_breast_cancer/family_history/research_and_trials/clinical_trials/uk_familial.html))
- women at high genetic risk for ovarian cancer should consider risk reducing surgery
  ([http://www.breakthrough.org.uk/about_breast_cancer/family_history/prevention_and_treatment/riskreducing.html](http://www.breakthrough.org.uk/about_breast_cancer/family_history/prevention_and_treatment/riskreducing.html)).

Depending on the prior level of risk, bilateral salpingo oophorectomy (BSO) before the usual age of menopause not only reduces ovarian cancer risk but also reduces breast cancer risk in high risk gene carriers. The question of whether to use Hormone Replacement Therapy (HRT) for premenopausal women should be considered before surgery. The gynaecologist, the geneticist and the individual woman may all have a view about the use of HRT; all contraindications are relative and the severity of menopausal symptoms should dictate management decisions. The available evidence suggests that the breast cancer risk for a gene carrier, who has a BSO, has not previously had breast cancer and chooses to have HRT is similar to a woman who keeps functioning ovaries over the same time period. However, for a woman who has had a previous diagnosis of breast cancer the balance of risks and benefits is different and the oncological considerations are important.

**Rare genetic conditions and breast cancer**

Some rare genetic conditions that increase breast cancer risk are recognised:

- Li Fraumeni syndrome: due to inherited mutation in the TP53 gene in which breast cancer of very early onset is often associated with childhood malignancy and other tumours ([http://www.ascocancerfoundation.org/patient/Cancer+Types/Li-Fraumeni+Syndrome](http://www.ascocancerfoundation.org/patient/Cancer+Types/Li-Fraumeni+Syndrome))
- Cowden Syndrome in which, typically, macrocephaly and skin trichilemmomas occur as well as benign and malignant breast and thyroid tumour ([http://www2.mdanderson.org/app/pe/index.cfm?pagename=opendoc&docid=2190](http://www2.mdanderson.org/app/pe/index.cfm?pagename=opendoc&docid=2190))
- Peutz Jegher syndrome in which GI hamartomatous polyps and typical freckling of the lips, buccal mucosa and perioral and periocular skin occur with an increased incidence of benign and malignant breast disease ([http://www.clevelandclinic.org/registries/inherited/pjs.htm](http://www.clevelandclinic.org/registries/inherited/pjs.htm)).

Note that screening recommendations for very rare conditions are often not evidence based. The potential advantages and disadvantages of any suggested surveillance strategy needs to be carefully considered and discussed with each patient.
Colorectal cancer family history

Risk estimation
As for other common adult cancers, there are two broad questions that need to be considered when assessing the need for intervention on the basis of a family or personal history of cancer.

- Is there likely to be an underlying high risk single gene disorder (a cancer predisposition syndrome)?
- What is the risk of cancer and is this sufficiently increased above the population risk for targeted surveillance to be beneficial?

The second most common reason for referral to cancer genetics clinical services is a personal or family history of colorectal cancer.

Colorectal cancer is one of the commonest cancers among both men and women. The majority of cases occur after age 50 years, and 5 per cent of cases are diagnosed before 50 years of age (http://info.cancerresearchuk.org/cancerstats/types/bowel/). As for other common cancers, a small proportion of colorectal cancers arise because of a single faulty gene giving rise to an increased risk of colorectal neoplasia.1 The same principles of genetic predisposition apply as for breast cancer, with polygenic factors accounting for the majority of genetic risk and leading to mild to moderate increases in the chance that colorectal cancer will develop for an individual. A family history of colorectal cancer is usually the best indication at present of a genetic component to disease, although the option for targeting colon cancer gene testing by additional tumour-based tests is a reality in colon cancer, so that individuals with young onset colorectal cancer may be suitable for genetic testing even in the absence of a family history of the disease. As for other cancers, very large case-control association studies are beginning to discover low penetrance genes in colorectal cancer. The implications of each of these low penetrance genetic variants are not yet sufficiently understood, however, and currently such testing has little or no validity in the clinical setting.

Individual or family features suggesting possible genetic predisposition to colorectal cancer are:

- young onset colorectal cancer (< 50 years)
- more than one primary colorectal tumour in one person (adenomas under 40 years and carcinomas under 50 years)
- more than one close relative affected by colorectal cancer with average age under 60 years.

Familial colorectal cancer
This diagnosis is attached to families where the known high risk syndromes including Hereditary Non-Polyposis Colorectal Cancer, and the Polyposis syndromes (as described below) have been excluded. Most familial clustering of colorectal cancer is due to common genetic variants. Each confers only a small increase in colon cancer risk (typically less than 1.5 fold), and studies to identify these genes require DNA samples from many thousands of colon cancer cases and unaffected controls.11-13 Genetic testing for this
type of susceptibility is not yet clinically useful. The family history remains the guide to risk and forms the basis for screening recommendations. Unfortunately there are no consensus guidelines currently of the type issued following the NICE review process for Familial Breast Cancer. This leads to somewhat variable approaches to screening in the presence of a family history. In general it is helpful to diagnose the high risk predisposition as these confer the highest risks and require annual or biennial colonoscopy surveillance starting in adolescence or as young adults (http://www.bsg.org.uk/pdf_word_docs/ccs8.pdf). If these conditions can be reasonably excluded as likely causes then colonoscopy more than every five years is unlikely to be beneficial for most patients.14

**Hereditary colorectal cancer**

The most common of the high risk genetic syndromes that predispose to colorectal cancer is the Lynch syndrome, also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC). This accounts for an estimated 5 per cent of all colorectal cancers, but a higher proportion of young onset colorectal cancer (under 50 years of age at diagnosis). The lifetime risk for colorectal cancer in HNPCC is estimated at 40-80 per cent, varies between genes and between families and is undoubtedly influenced by environment and genetic modifiers. Female gene carriers on average have a lower lifetime colorectal cancer risk than male gene carriers. Female gene carriers have a significantly increased risk of endometrial cancer (up to 60 per cent lifetime risk).

The original clinical criteria (the Amsterdam Criteria) were devised to capture families with likely HNPCC. These were specific (a high likelihood of a harmful mutation being detected) but not sensitive. More recent sensitive (identifying as many cases with a mutation as possible) but not specific criteria have been developed. These more inclusive criteria (the Bethesda Criteria) should be used as a tool for selecting individuals or families in whom tumour based testing could be implemented (see next section entitled ‘Testing colorectal cancer tissue to identify HNPCC’). The most commonly used criteria are the Bethesda Criteria.

Revised Bethesda Criteria:

- colorectal cancer diagnosed before 50 years of age
- more than one colorectal cancer (CRC) or one CRC plus another HNPCC-related tumour (endometrium, ureter, urothelium, small bowel, ovary and keratoacanthoma)
- colorectal cancer with microsatellite instability diagnosed before 60 years of age
- colorectal cancer with one or more first degree relatives with CRC or HNPCC related tumour (at least one diagnosed aged less than 50 years)
- colorectal cancer with two or more relatives with colorectal cancer or other HNPCC related cancer regardless of age.

For more information, please visit: [http://www.medscape.com/viewarticle/468147_1](http://www.medscape.com/viewarticle/468147_1)

Referral for genetic assessment is appropriate for families meeting these criteria. The assessment by the genetic service may require further testing of the tumour from an affected individual in the family to see if it demonstrates characteristics that make HNPCC more likely.
**Testing colorectal cancer tissue to identify HNPCC**

Microsatellite instability observed in tumour tissue indicates that the normal cellular mechanisms that repair DNA mismatches is faulty. For further information, please visit: [http://www.genetichealth.com/CRC_HNPCC_Microsatellite_Instability_Testing.shtml](http://www.genetichealth.com/CRC_HNPCC_Microsatellite_Instability_Testing.shtml).

Immunohistochemistry can be used to demonstrate the proteins produced by the main mismatch repair genes. Loss of staining for one of the mismatch repair gene proteins may indicate a diagnosis of HNPCC.

A combination of normal results from these two tests in a tumour from an individual means that the cause of the colon cancer in that individual is highly unlikely to be HNPCC. For further information, please visit: [http://www.phgfoundation.org/pages/serviceprojects.htm#biomarkers](http://www.phgfoundation.org/pages/serviceprojects.htm#biomarkers) (Biomarkers in familial colorectal cancer).

**Genetic testing for the family**

A web-based option for assessing the chance of finding a high risk gene mutation in one of the mismatch repair genes is [http://www.dana-farber.org/pat/cancer/gastrointestinal/crc-calculator/default.asp](http://www.dana-farber.org/pat/cancer/gastrointestinal/crc-calculator/default.asp). In the genetic clinic, if the family history is strong (ie meets the Amsterdam Criteria [http://www.medscape.com/viewarticle/468147_4](http://www.medscape.com/viewarticle/468147_4)), and/or tumour testing indicates HNPCC is possible and if there is a living family member who has had a relevant cancer and is willing to give a blood sample, then testing for mutations in the three main mismatch repair genes hMLH1, hMSH2 and hMSH6 is initiated. If a mutation that is thought to be the cause of cancer predisposition is found, testing can be offered to other family members. In the absence of genetic testing to help refine risk, advice for screening is based on estimated genetic risk, position in the family and age of the individual at risk.

**Polypsis syndromes**

The Polyposis syndromes are less common than HNPCC. They are usually associated with very young ages at onset of polyp growth (teens and young adulthood) and a high lifetime cancer risk. Affected patients and their close relatives should be referred to the genetic services.

**Familial Adenomatous Polyposis**

The most common condition is Familial Adenomatous Polyposis (FAP) [15](http://hopkins-gi.nts.jhu.edu/multimedia/database/intro_84_FAP-Book.pdf). FAP was one of the earliest recognised dominantly inherited cancer predisposition syndromes. An inherited mutation in the APC gene is responsible for FAP and mutations may be present anywhere in the APC gene. Predictive genetic testing and screening for FAP gene carriers commences routinely at about 10-12 years of age but may commence earlier if symptoms cause concern. In most cases colorectal polyps start to develop during puberty and untreated almost 100 per cent of patients with an APC mutation will develop colorectal cancer. Once polyps become numerous or dysplastic, a colectomy is scheduled and often, though not always, becomes necessary during the teenage years. Some US surveillance guidelines recommend starting colorectal surveillance at age seven, some advocate screening for hepatoblastoma – a rare but recognised association.
**MutYH Associated Polyposis (MAP)**

This condition was only recognised recently and is recessively inherited. The colorectal findings are very similar to FAP with hundreds of polyps in the colon. The diagnosis is important since heterozygotes are not thought to be at significantly increased risk for colon cancer, so offspring do not need the intensive annual colonoscopy surveillance used for FAP from an early age. The full spectrum of this condition is still uncertain and management decisions are usually based on polyp load and degree of dysplasia. Once polyps become numerous or dysplastic then colorectal cancer is inevitably likely to ensue and prophylactic colectomy is advised.

**Hamartomatous Polyposis syndromes**

- Juvenile Polyposis (JP) relies largely on the recognition of juvenile colonic polyps by the pathologist. These can be multiple or just a few and are usually associated with young colon cancers in the family where there is a family history. It is probably under diagnosed due to its rarity and the great variation in the pathological appearance of the polyps [here](http://www.clevelandclinic.org/registries/inherited/jp.htm).
- Peutz Jegher Syndrome (PJS) is easier to recognise as it is associated in most cases with unusual skin freckling, particularly around the eyes and mouth and often affecting the lips and buccal mucosa, and is associated with an increase in malignancy risk throughout the GI tract and elsewhere [here](http://www.clevelandclinic.org/registries/inherited/pjs.htm).

Although estimates of penetrance and cancer risks for these Polyposis syndromes are very high in the published literature (both colon and extracolonic), these are rare conditions and there is inevitably considerable ascertainment bias.

Other genetic conditions which cause polyps in the colon but are not associated with a significantly increased risk for colon cancer need to be distinguished. Some are associated with other malignancy risks and include:

- Cowden syndrome
- Gorlin syndrome
- MEN2B
- Neurofibromatosis type 1.

**Surveillance recommendations in the UK**

The general population:

The NHS bowel screening programme is being rolled out to men and women in the general population aged 60-69 years of age [here](http://www.cancerscreening.nhs.uk/bowel/). The screening uses faecal occult blood testing not endoscopy.

Familial non-HNPCC cancer predisposition:
Recommendations vary according to the strength of family history, the tumour morphology and additional testing if possible in an affected relative, and the age of the person at risk. If an assessment of the information makes HNPCC or one of the Polyposis syndromes (eg Familial Adenomatous Polyposis, Juvenile Polyposis, Peutz-Jehger Syndrome) an unlikely diagnosis in a family then colonoscopy screening more frequently than every five years is not necessary as there is no evidence that any adenomas that do occur will progress rapidly to cancer. Surveillance recommendations vary (http://www.cancerhelp.org.uk/help/default.asp?page=2818) but one colonoscopy after the first referral for assessment and one at around 55 years of age would be typical.

Hereditary Non-Polyposis Colorectal Cancer (HNPCC):
In HNPCC polyps and flat adenomas may progress very rapidly to cancers so a full colonoscopy (not sigmoidoscopy) every one to two years, starting at 25 years of age, is the current recommendation in the UK. Some families with very young onset cancer may be offered screening from an earlier age. (http://www.bsg.org.uk/pdf_word_docs/ccs8.pdf).
Screening for extracolonic malignancy is not currently proven to be effective but many authorities suggest endometrial and ovarian screening using one to two yearly ultrasound and endometrial biopsy (http://www.insight-group.org/).

Familial Adenomatous Polyposis:
Genetic testing if possible is offered usually at about 10 to 12 years of age at a time when a child who has inherited the FAP gene from one or other parent would need to start surveillance, and before the risk of colon cancer has started to rise dramatically. Annual surveillance until such time as prophylactic colectomy is recommended (when the polyps become numerous) (http://www.genetichealth.com/CRC_FAP_Screening_and_Prevention.shtml#Anchor2).

Rare cancers including childhood cancers

It is not possible to list all rare cancers that might be associated with a genetic predisposition, but the guiding principle in assessing whether a situation has arisen by chance or because of a genetic predisposition is that ‘lightening rarely strikes twice’. Thus if an individual presents with two rare cancers or two individuals closely related have both had a rare cancer or an exceptionally young onset of a malignancy, it is reasonable to ask whether there might be a genetic reason for this.

For example, phaeochromocytoma is a rare usually benign tumour (incidence 1:1000) (http://www.patient.co.uk/showdoc/40001342/). If another blood relative has had a phaeochromocytoma or an individual is diagnosed with more than one primary phaeochromocytoma, then there is a strong possibility this could be due to a genetic predisposition. There are several genes where an inherited mutation confers a high risk of phaeochromocytoma. These include:

- Von Hippel Lindau Disease gene (http://www.vhl.org/)
- Multiple endocrine neoplasia type 2 (MEN) gene [http://www.amend.org.uk/]
- SDHB, C or D genes.\(^{17}\)

All of these diagnoses have implications for the individual and the wider family and it is imperative that genetic advice is sought.

Childhood tumours are rare and like adult cancers usually isolated. Some can be the result of an inherited gene mutation and may be associated with future malignancy risks to the child and to the wider family. Where there is more than one incidence of a rare cancer (which includes a very unusually early age at onset) in an individual or in a family, referral for a genetic opinion is appropriate. The genetic implications of the following typical childhood onset tumours need particular consideration:

- Retinoblastoma [http://www.bartsandthelondon.nhs.uk/Retinoblastoma/]
- Wilms tumour [http://www.patient.co.uk/showdoc/40000408/]
- Rhabdomyosarcoma [http://www.cancerindex.org/ccw/guide2t.htm].

Rare recessive childhood onset chromosome breakage disorders are associated with increased risks for malignancy (often haematological). Examples include:

- Fanconi anaemia [http://www.emedicine.com/PED/topic3022.htm]
- Xeroderma Pigmentosum [http://www.patient.co.uk/showdoc/40024814/].

These rare recessive conditions are often associated with developmental anomalies and are not usually associated with a high risk for cancer in other generations. There is a high risk of recurrence (1 in 4) among siblings. Children with these diagnoses are most likely to be referred to genetics services by the paediatric services.

Deleterious mutations in some of the genes involved in these rare recessive diseases are now known to be associated with a mild to moderate increase (about twice the general population risk) of breast cancer risk for heterozygotes (ie the mothers of affected children will be at moderately increased risk for breast cancer).\(^{18,19}\)

**Genetic changes in cancers affect treatment**

Acquired genetic mutations in cancer cells are the mechanism by which drug resistance is acquired. Sometimes acquired mutations provide a useful target against which to direct novel therapeutics. Herceptin is a therapeutic monoclonal antibody aimed at the Human Epidermal growth factor Receptor 2, HER2. HER2 is overexpressed in a small proportion of breast cancers (about 15\%) and is associated with aggressive, poor prognosis breast cancer. The development of antibodies to this receptor has had an enormous impact on cancer treatment for a small proportion of patients. Many other novel treatment categories are emerging, often based on a developing understanding of genetic events underlying the process of carcinogenesis and prognosis [http://www.cancerbackup.org.uk/Treatments].
Further information on epidemiological risk factors for common cancers, cancer diagnosis and cancer treatment can be found at the following references and websites:

UK:  [http://info.cancerresearchuk.org/](http://info.cancerresearchuk.org/)
USA:  [http://www.cancer.gov/cancertopics/pdq](http://www.cancer.gov/cancertopics/pdq)


ABC of breast diseases:  [http://www.mindfully.org/Health/Breast-Cancer-ABCs.htm](http://www.mindfully.org/Health/Breast-Cancer-ABCs.htm)
Further sources of information

Genetics societies

**British Society for Human Genetics (BSHG)**

[www.bshg.org.uk](http://www.bshg.org.uk)

The BSHG is an independent body that represents human genetics professionals in the UK. It publishes a newsletter three times a year, and holds an annual conference. The BSHG has five constituent organisations, one of which is the Cancer Genetics Group (CGG), detailed below. The Royal College of Physicians, British Society for Human Genetics and Royal College of Pathologists also have a joint committee on medical genetics.

**Cancer Genetics Group (CGG)**

[www.srl.cam.ac.uk](http://www.srl.cam.ac.uk)

The CGG is a constituent organisation of the BSHG. It is a national, multidisciplinary organisation, with the aim of improving the care of patients and families with conditions resulting in hereditary tumours. Membership is open to those interested in hereditary predisposition to cancer, including clinicians, counsellors and scientists.

**European Society for Human Genetics**


The ESHG is an independent body that represents human genetics professionals in Europe.

Cancer charities (UK)

**Cancer Research UK**

[www.cancerresearchuk.org](http://www.cancerresearchuk.org)

Cancer Research UK is a charity dedicated to cancer research. It funds research in hospitals, universities and institutes across the UK, and also works with politicians and policy-makers. It provides a wealth of information on cancer for patients and families, health professionals and the public that is available from the website.

**Cancerbackup**

[www.cancerbackup.org.uk](http://www.cancerbackup.org.uk)

Cancerbackup is a charity that provides cancer patients and their families with information, practical advice and support. It also provides information for healthcare professionals.

**Macmillan Cancer Support**

[www.macmillan.org.uk](http://www.macmillan.org.uk)
Macmillan Cancer Support is a charity that offers support for individuals affected by cancer, including practical, medical, emotional and financial support.

**Government bodies (UK)**

**Department of Health (DH), England**
[www.dh.gov.uk](http://www.dh.gov.uk)

**Scottish Government Department of Health**
[www.scotland.gov.uk/Topics/Health/health/cancer](http://www.scotland.gov.uk/Topics/Health/health/cancer)
The Scottish Government Department of Health published the cancer strategy *Cancer in Scotland: action for change* in 2001 ([www.scotland.gov.uk/Publications/2001/07/9490/File-1](http://www.scotland.gov.uk/Publications/2001/07/9490/File-1)). This was followed in February 2008 by a consultation document entitled *Better Cancer Care* ([http://www.scotland.gov.uk/Publications/2008/02/06140628/0](http://www.scotland.gov.uk/Publications/2008/02/06140628/0)), the results of which are due to be published in summer 2008.

**Welsh Assembly and NHS Wales**
The Welsh Assembly published the cancer strategy *Designed to Tackle Cancer in Wales* in 2006 ([http://new.wales.gov.uk/topics/health/publications/health/strategies/designedcancer/?lang=en](http://new.wales.gov.uk/topics/health/publications/health/strategies/designedcancer/?lang=en)), and this is supported by strategic frameworks.

**Health and Social Care Northern Ireland/ The Department of Health, Social Services and Public Safety**
A Cancer Services Framework Group was set up in 2004, that considers the ongoing development of cancer services, led by the Chief Medical Officer ([www.dhsspsni.gov.uk/public_health_cancerservices](http://www.dhsspsni.gov.uk/public_health_cancerservices)).

**Gene Therapy Advisory Committee (GTAC)**
[www.advisorybodies.doh.gov.uk/genetics/gtac](http://www.advisorybodies.doh.gov.uk/genetics/gtac)
The GTAC is the national research ethics committee for gene therapy clinical research in the UK. It is the only UK ethics committee that has the power to approve gene therapy clinical trials.

**Human Genetics Commission (HGC)**
The HGC is the Government’s advisory body on human genetics, and particularly focuses on the social, ethical and legal aspects. One of its main roles is to gather opinions from the public and stakeholders through consultations and open meetings.

National Cancer Research Institute (NCRI)

The NCRI is a partnership between the Government, charity and industry. It works to achieve joint planning and coordination between its member organisations. The NCRI maintains a cancer research database, develops research initiatives, helps coordinate clinical trials and develops facilities and resources for research.

National Institute for Health and Clinical Excellence (NICE)

NICE is the independent body responsible for national guidance on public health, health technologies and clinical practice in England and Wales.

NHS National Genetics Education and Development centre

The centre works to facilitate the integration of genetics education into all levels of education and training for healthcare professionals. The aims of the centre include to identify the genetics knowledge, skills and attitudes that are useful for clinical roles, and to develop a genetics competency framework. The centre provides resources for healthcare professionals for learning and teaching genetics, and maintains a database of courses in genetics.

PHG Foundation

The PHG Foundation is an international, independent charity. It works to achieve the responsible and evidence-based application of biomedical science for health, through research policy analysis, education and service development.

UK Genetic Testing Network (UKGTN)

The UKGTN is a network of laboratories that provide testing for inherited disorders. It aims to provide equal access to high quality genetic testing services across the UK.

National Library for Health – genetics services

The National Library for Health has a genetic conditions specialist library, which is aimed at health information professionals, patients, families and carers.
Government USA

US National Cancer Institute (NCI)

www.cancer.gov

The NCI is a component of the US National Institutes of Health (NIH). It coordinates the US National Cancer Program, which conducts and supports research into cancer prevention, detection, diagnosis, treatment, rehabilitation and control. A wide range of information on cancer is available from the NCI website, including information for healthcare professionals.

Cancer and genetic risk specific sites

Cancer Research UK http://info.cancerresearchuk.org

Cancer Research UK is the biggest cancer research charity in the UK and this website is well constructed, accurate and easy to navigate. It is primarily aimed at the non-specialist population – there are sections for lay information and for professionals and is quite easy to understand. The process of cancer division for example is explained quite clearly. The epidemiology, risk factors and cancer statistics for most common and a lot of less common cancers are given.

http://info.cancerresearchuk.org/cancerandresearch/learnaboutcancer/whatcausescancer/inheritance/

focuses on inherited predisposition to cancer and links through to more detailed information about research study design and results in inherited cancer predisposition as well as more site specific information.

Cancerbackup http://www.cancerbackup.org.uk

A well constructed informative website from the cancer charity Cancerbackup

http://www.cancerbackup.org.uk/Aboutcancer/Genetics/Cancergenetics

This is the starting page on the ‘cancer genetics’ section, which has a big selection of information available to individuals wishing to know more about the cancer that could be inherent in their families. The website is approachable and accessible and would be a good option for someone seeking more information about cancer or about genetic risk.


This NCI (US) web-link is a useful resource and gives a very detailed description as to which individuals may be genetically predisposed to cancer, and what tests could be conducted. The later parts of the text are aimed at a non-professional medical audience but the information is sufficiently non technical that it would be accessible to an intelligent lay person. It provides a useful flowchart entitled ‘Genetic Testing Algorithm for Cancer Susceptibility’ which provides the reader with understandable instructions as to the path they would be advised to follow in a variety of different situations.

http://www.breastcancercare.org.uk/content.php?page_id=888
This site is mainly directed towards supporting women with breast cancer or concerned because of a family history of breast cancer. The information is very simple and explains the process of assessment of family history starting with a GP consultation. The website would be useful for any women who are particularly worried about their risks of breast cancer as it is very reassuring and calm, unlike some of the other websites which tend to be more matter-of-fact about the potential risks to an individual.

**Carcinogens**
http://www.cancer.org/docroot/PED/content/PED_1_3x_Known_and_Probable_Carcinogens.asp
Many of the websites discussing the IARC carcinogens and the process by which these lists of carcinogenic materials were constructed remain ambiguously clouded by technical language, which the average reader will find difficult. This website clearly sets out the ranking system of carcinogenic substances, as well as containing a comprehensive list of known and suspected carcinogens.

**Genes**
Online Mendelian Inheritance in Man
One of the most comprehensive catalogues of disease genes available online is the ‘Online Mendelian Inheritance in Man’ – aimed at specialists, it is a history of genetic disease and publications related to them. As such it is difficult for a non-specialist to read quickly; perhaps the most useful feature is that it can be searched for disease features and a list of all the genetic conditions in which that disease characteristic might be found are listed.

**Family history documentation**
https://familyhistory.hhs.gov/
Pedigree drawing tool online – useful for the IT literate and interested patient, probably not fast enough for use in a primary care consultation.

https://www.secure1.gov-certificates.co.uk/view_cart/
This website gives a very easy access point to information concerning the lives and deaths of ancestors and so would be incredibly useful for the construction of a genetic family tree, in that it would allow individuals to see whether or not their ancestors suffered from/died from a particular type of cancer and whether that pattern is consistent throughout their family if this information was not already available to them. However, there is a cost – £23 for one name/death.

**Models for assessing cancer risk**

**Breast cancer**
http://www.facingourrisk.org/hereditary_cancer/assessing_risk_genetic_counseling.html
This website again contains a (rather brief in comparison to some of the other sites) breakdown of risk assessment models for people who fear having a genetic disposition towards cancer. It is particularly
useful in highlighting some of the inadequacies of models such as the Gail Model. While not providing a
reasonable alternative, it offers solid enough arguments to calm anyone who had received worrying
results from a Gail Model test. It highlights the benefits and disadvantages of the Gail Model, the Claus
Model and the BRCAPro model used by experts, but concludes that there is nothing quite the same as
talking to an expert in cancer genetics. It then goes on to give a list of sites whereby one would be able
to go about finding a cancer specialist, as well as offering links to another extremely useful website that is
detailed below. It also provides further reading for those interested in learning more and advanced
reading for those who feel they have a substantial enough understanding of the subject material.

http://www.cancer.gov/bcrisktool/
This is a tool using the Gail Model, which is designed for women who do not have a strong family history
of breast cancer. The questions asked are not specifically geared towards the genetic history of an
individual but take into account particularly lifestyle risk factors, previous breast biopsies and to some
extent family history (present or absent). It is easy to use but needs a measure of background knowledge
to understand how the output should be used. This is particularly true in the context of a family history of
breast cancer – it does not give adequate weighting to genetic risk if there is more than a moderate level
of family history risk. Nevertheless since the majority of women in the population concerned about risk
will have moderate not high risk, it may have some value in discussing lifestyle modification.

http://www.halls.md/breast/risk.htm
Also uses the Gail Model but a more informal layout.

Colon cancer
This is a model for assessing the possibility of a colon cancer patient having HNPCC and is understandable
for both the individual and the GP. The website (http://www.dana-farber.org/pat/cancer/default.html)
provides a substantial amount of information in small, absorbable chunks and is quite easy to navigate.
References


