Genetic testing for cancer risk in women's health

Rachel E Harrison

Abstract

Identifying people with an increased risk of developing cancer allows prophylactic surgery or screening to be offered, to try to reduce the chance of cancer developing or to detect it earlier. Family history information may indicate who should be assessed for cancer predisposition syndromes, but individual clinical and tumour characteristics are equally important to consider. Technological advances have expanded the availability of genetic analysis, which is now becoming mainstreamed into cancer diagnostic pathways. Identifying inherited mutations in cancer predisposition genes or somatic genetic variants within cancers has important implications for treatment decisions. Genomic analysis of tumours will increasingly be exploited to enable more accurate diagnosis, prognosis and targeted therapies with improved patient outcomes.

Keywords cancer genetics; genomics; mainstreaming

Cancer is common, with one in two people born in the UK after 1960 expected to develop some form of cancer during their lifetime. The majority of cancer arises as a result of multiple new mutations occurring in cells ('somatic mutations') and does not have an inherited cause. For example, the majority of cervical cancer is associated with HPV infection, which leads to the development of multiple somatic mutations. However, some people inherit germline mutations (present in all body tissues) in cancer predisposition genes, and have an increased chance of developing cancer. It is estimated that approximately 15% of ovarian cancer and 5% of endometrial cancer has an inherited cause.

Why offer genetic tests for cancer risk?

Identifying individuals and families with cancer predisposition syndromes allows us to offer prophylactic surgery or target screening to those at high risk, with the aim of preventing cancer or detecting it at an earlier stage. Equally, when a cancer predisposition syndrome has been identified in a family, a genetic test showing that a relative has not inherited the condition provides reassurance and prevents unnecessary screening.

Importantly, the results of genetic analysis will increasingly influence cancer treatment. For example, breast and ovarian cancers associated with *BRCA* mutations are more sensitive to platinum-based therapies and PARP inhibitors such as olaparib specifically target the molecular pathways that are deficient in tumours with *BRCA* mutations.

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Who should be offered genetic tests?

The traditional model of cancer genetics relies on individuals with a strong family history of cancer being referred to Clinical Genetics Departments or Family History clinics, where family history information is assessed and confirmed. This has been necessary for many years as genetic analysis has been slow and laborious, so resources have been targeted at those with the greatest chance of having an inherited cause for cancer. Common cancer predisposition syndromes that are important in women's health include *BRCA1*, *BRCA2*, and Lynch syndrome. More rare conditions that may be identified include Cowden syndrome, Peutz-Jeghers syndrome, Li-Fraumeni syndrome, hereditary leiomyomatosis and renal cell cancer, *POLD1*, *RAD51D*, *RAD51C*, and *DICER1*-related disorders (Table 1).

Genetic tests to identify a cancer predisposition syndrome should usually be performed in an individual who has had cancer themselves (rather than an unaffected relative who may not have inherited the condition). If no DNA has been stored from affected relatives then opportunities for genetic analysis are much more limited and difficult.

The majority of cancer predisposition syndromes are inherited in an autosomal dominant manner, so children of an affected individual have a one in two chance of inheriting the same condition. However, reduced penetrance means that some people who inherit a cancer predisposition syndrome will not develop cancer during their lifetime. When a mutation causing a cancer predisposition syndrome is identified in a family, predictive genetic tests can be offered to relatives to identify who has inherited the condition and should be offered additional surveillance or prophylactic surgery. Relatives who want to consider a predictive genetic test should be referred to Clinical Genetics for information and support through this process.

Guidelines have been developed to indicate which patients should be referred to Clinical Genetics departments (see Figure 1 for an example) but these vary according to local pathways and resources.

How is cancer genetics changing?

It is recognized that the traditional model of cancer genetics is not able to identify all individuals with cancer predisposition. Small family sizes, lack of contact with relatives and reduced penetrance mean that family histories cannot always reliably identify those at high risk. Healthy relatives are often referred for investigation of their family history after their relatives with cancer have died, limiting the opportunities for genetic tests in the family. Practice in cancer genetics is evolving to address these challenges.

Over the last few years, new methods of genetic analysis ('next-generation sequencing technologies') have been introduced to molecular genetic laboratories, greatly increasing the speed of genetic analysis. The associated reduction in cost has allowed genetic tests to be offered to more families and individuals. Clinical Genetics departments can now use less stringent personal and family history criteria to offer genetic tests, making them available to more families. In addition, analysis of multiple genes can be performed simultaneously for one individual, increasing the chance of detecting a molecular cause for cancer predisposition (5).

Cancer predisposition syndromes with commonly associated tumours

Condition/gene		Associated tumours (lifetime risk in women)
BRCA1		Breast cancer (50–80%), Ovarian cancer (30–50%)
BRCA2		Breast cancer (50–80%), Ovarian cancer (10–20%), Pancreas (3%)
Lynch syndrome	*MLH1*	Colorectal cancer (40%), Endometrial cancer (40%), Ovarian cancer (10%)
	MSH2	Colorectal cancer (45%), Endometrial cancer (55%), Ovarian cancer (15–20%)
	MSH6	Colorectal cancer (15–20%), Endometrial cancer (55%), Ovarian cancer (10–15%)
	PMS2	Colorectal cancer (15–20%), Endometrial cancer (20–30%)
Cowden syndrome	*PTEN*	Breast cancer (70–95%), Endometrial cancer (17–40%), Colorectal cancer (5–17%), Thyroid cancer (20–50%), Renal cell cancer (17–50%)
Peutz-Jeghers syndrome	*STK11*	Breast cancer (30–60%), Colorectal cancer (40%), Gastric cancer (30%), Ovarian sex cord tumours with annular tubules (20%), Cervical cancer (10%), Endometrial (10%)
RAD51C		Ovarian cancer (~10%)
RAD51D		Ovarian cancer (~10%)
POLD1		Colorectal cancer and adenomatous polyposis, Endometrial cancer
DICER-1		Multinodular goitre (80–100%), Pleuro-pulmonary blastoma (10–20%), Ovarian sex cord-stromal tumors, Botryoid-type embryonal rhabdomyosarcoma of the cervix
Li-Fraumeni syndrome	*TP53*	Breast cancer (50–85%), Sarcomas [not Ewings], Brain tumours, Leukaemias and Lymphomas, Adrenocortical carcinoma, Phyllodes Breast tumours
PALB2		Breast cancer (30–65%)
HLRCC*	*FH*	Cutaneous leiomyomas, Uterine leiomyomas (fibroids), Renal cancer

*HLRCC – Hereditary leiomyomatosis and renal cell cancer.

Table 1

Practice around the UK has previously varied according to local organisational and funding arrangements. In an attempt to standardise practice and ensure equitable access to genetic tests in England, a National Test Directory is now being finalised that outlines genetic tests available along with standardised criteria for analysis (http://www.acgs.uk.com/media/1076196/annex_2_-_test_directory_description_28.09.17.pdf). It is anticipated that this will be in place by April 2019.

As genetic tests become more widely available, and the results of genetic analysis become more important in management, it is no longer practicable for all cancer genetic tests to be arranged by Clinical Genetics Departments. 'Mainstreaming' of cancer genetics allows cancer patients to access tests at one of their routine cancer clinic appointments (http://www.mcgprogramme.com). This is more cost-effective and reduces delays caused by referral to another department. Patients with positive results are referred to Clinical Genetics departments for further information and to discuss implications for relatives. This approach is available to cancer patients whose individual characteristics (e.g. age and tumour type) indicate a significant chance of a cancer predisposition syndrome, regardless of their family history (see Table 2 for suggested mainstreaming criteria for BRCA testing).

If cancer risk is predominantly linked to the family history then referral to Clinical Genetics is still recommended. Mainstreaming of cancer genetics is being developed across the UK, meaning that it is important for trainees and consultants in relevant specialties to become familiar with taking consent for cancer genetic tests. The national test directory will indicate which genetic tests can be requested by different specialties and which should be considered after assessment within clinical genetics.

Tumour tissue testing

Further new approaches are being introduced to try to identify individuals with cancer predisposition that may be missed by traditional models. One option is to use tumour tissue analysis as a routine screening method in large groups of patients, rather than selecting on the basis of family history. Immunohistochemistry or microsatellite instability testing has been shown to be a useful approach to screen for Lynch syndrome in colorectal cancer, and is now recommended by NICE for all individuals diagnosed with colorectal cancer, regardless of family history or age (https://www.nice.org.uk/guidance/dg27). Tumour tissue analysis of endometrial or ovarian cancers can also be used to screen for Lynch syndrome. However, results are less specific so this analysis is usually considered if there is a relevant family history, or cancer has developed at a young age and is not currently offered to all women with these cancers (see example of pathway in Figure 1).

Genetic analysis of cancer tissue is also becoming increasingly important as new classes of drugs are developed that target specific somatic mutations driving cancer progression. For example, women who have somatic *BRCA* mutations within their ovarian cancers are eligible for treatment with olaparib (https://www.nice.org.uk/guidance/ta381), as well as those who have inherited *BRCA* mutations.

More extensive genomic analysis of tumour tissue is being developed in the UK through the 100,000 Genomes Project, which aims to include 25,000 individuals with common cancers by the end of 2018 (https://www.genomicsengland.co.uk/). Analysis will compare the entire DNA sequence from cancer cells with germline (inherited) DNA, to identify somatic genomic

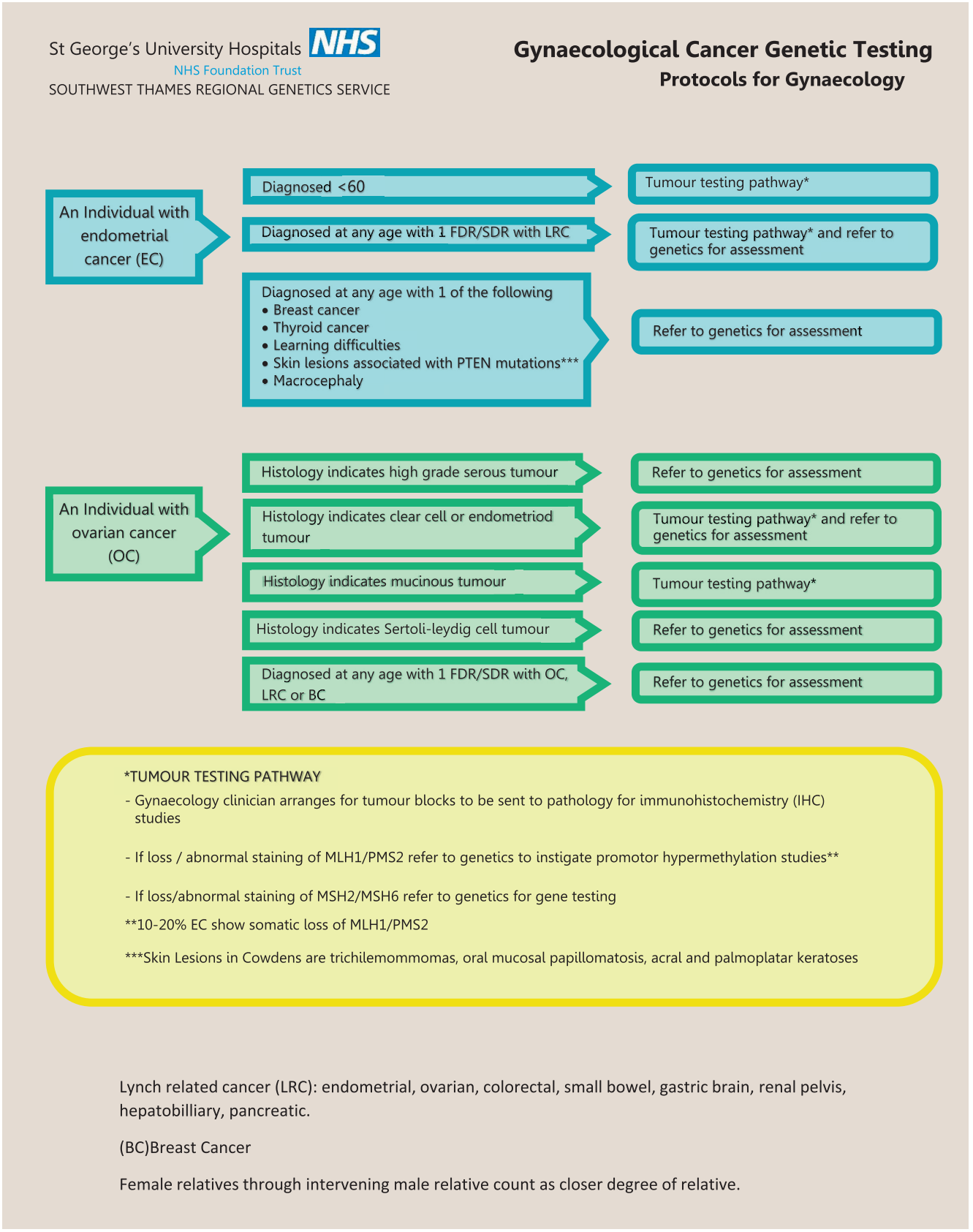

Figure 1 Gynaecology cancer genetic testing protocol. (Reproduced by kind permission of Dr Helen Hanson, Dr Katie Snape and Charlotte Eddy from St George's University Hospitals NHS Foundation Trust). FDR = first degree relative, SDR = second degree relative, EC = endometrial cancer, OC = ovarian cancer, BC = breast cancer, LRC = Lynch-related cancer (endometrial, ovarian, colorectal, small bowel, gastric brain, renal pelvis, hepatobiliary, pancreatic).

Suggested criteria for mainstreamed BRCA testing (http://www.mcgprogramme.com)

Patient with one or more of:

- Non-mucinous ovarian cancer, any age
- Breast cancer + ovarian cancer, any age
- Breast cancer <40 years
- Bilateral breast cancer, both <60 years
- Triple-negative breast cancer, any age
- Male breast cancer, any age

Table 2

alterations associated with the development of cancer. Analysis of germline DNA will also allow detection of cancer predisposition syndromes. It is anticipated that genomic analysis of tumours will become standard of care in the future to increase the accuracy of diagnosis and prognosis and to exploit targeted therapies to improve patient outcomes.

In conclusion

Genomic analysis is becoming increasingly routine, both to assess cancer risk and to guide cancer management. All those involved with diagnosis and treatment of cancer need to be aware of the importance of recognizing individuals who may benefit from genetic tests, and familiar with local pathways for assessment. ◆

FURTHER READING

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