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Clinical cancer genetics

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ABSTRACT Over the past 14 years, since the discovery of the first gene for breast cancer (*BRCA1*), cancer genetics has become an increasingly important part of the workload of clinical genetics services, now accounting for approximately half of all referrals. Such referrals may occur for a number of different reasons – where a healthy patient is concerned that their family history of cancer places them at a significant risk of cancer themselves; where a patient with cancer is worried about the risk of cancer to their relatives; where a clinician feels that a patient has a strong family history that suggests a genetic predisposition; and where a clinician feels that a patient has an unusual form of cancer that suggests a genetic predisposition. The role of the clinical geneticist is to assess cancer risk, develop individualised management strategies for those at increased risk of cancer, offer genetic testing if appropriate and facilitate family communication.

KEYWORDS *BRCA1*, *BRCA2*, cancer risk, family history, genetic counselling, genetic testing

DECLARATION OF INTERESTS No conflict of interests declared.

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WHAT IS CLINICAL GENETICS?

Clinical genetics is the medical specialty involved in the diagnosis and management of disorders that may have an inherited component. It includes 'genetic counselling' – the provision of information about the genetic basis of disease to patients, to allow them to make informed choices about genetic testing and the management of their conditions. In addition to consultants and specialist registrars in clinical genetics, patients may also be seen by genetic counsellors. Genetic counsellors have a background in nursing or science, with additional training to allow them to undertake genetic counselling and protocol-based management of genetic conditions.

WHY ARE PATIENTS WITH CANCER, OR A FAMILY HISTORY OF CANCER, REFERRED TO CLINICAL GENETICS?

Cancer is very common, affecting 30% of the population at some point during their lifetime. It is, therefore, not uncommon to have a family history of cancer. A genetics clinician assessing a patient with cancer, or a family history of cancer, has the following tasks:

1. To decide whether there is evidence of a significant inherited risk of cancer in the family. If there is an increased risk, how high is this?
2. If there is a significant inherited risk of cancer, to identify any gene testing that will be helpful for the patient.
3. To decide on the appropriate management for an individual at significantly increased risk of cancer. This might include screening to detect cancer at an early stage or prophylactic treatment to reduce cancer risk.
4. To communicate the information about risk to the patient, to allow him or her to make an informed decision about testing and any management decisions.

In order to understand the uses and limitations of gene testing in the clinical setting, it is helpful to have a brief understanding of the mechanisms of inheritance of cancer in families. These are discussed briefly below.

GENETIC BASIS OF INHERITED CANCER RISK

Although the majority of cancers arise because of a series of somatic genetic mutations causing a cell to acquire a malignant phenotype, clinical cancer genetics is mainly concerned where there is a significant inherited component to the cancer risk, that is, the responsible gene changes are transmitted in the germ line.

In some cases, the inherited risk is transmitted as a Mendelian trait, usually in an autosomal dominant fashion. More commonly, the risk of cancer is transmitted as a multifactorial trait. In order to understand the practice of clinical cancer genetics, it is helpful to understand a few of the basic scientific concepts.

Multifactorial inheritance of cancer risk

There are estimated to be between 30,000 and 40,000 genes in the human genome. Genes are carried on chromosomes. An individual has 22 pairs of chromosomes (the autosomes) and either two X chromosomes for a female or an X and a Y chromosome for a male. An individual, therefore, has two copies of each gene carried on the autosomes, one inherited from their mother and one from their father. Any gene can contain sequence variations, known as polymorphisms, that may affect the function of that gene. This is the basis of human genetic variation.

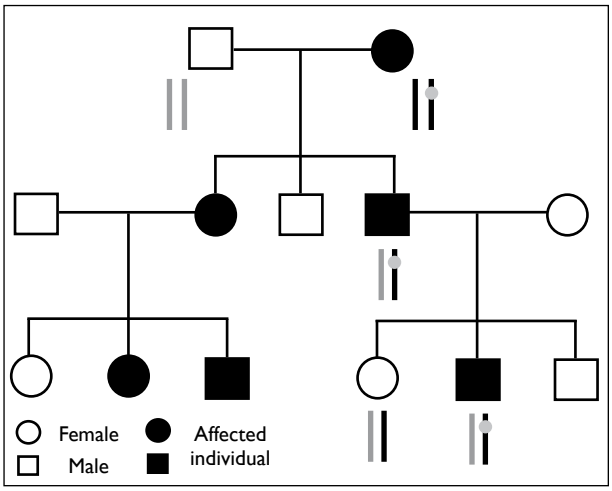

FIGURE 1 Autosomal dominant inheritance of a rare disease-causing mutation.

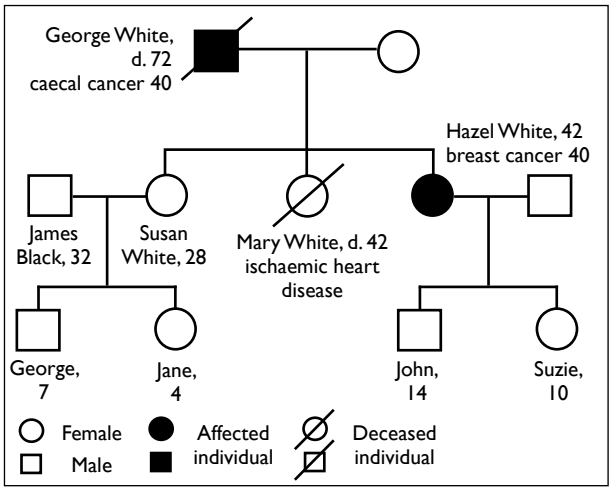

FIGURE 2 Family tree.

In multifactorial inheritance, the interaction between the genetic polymorphisms that an individual has and the environment in which they live determines the risk of a disease. Although this is likely to be the case for most cancers, research has been slow to identify the polymorphisms responsible for the multifactorial risk of cancer. It is likely that for any one cancer there are many genetic polymorphisms involved, each of which has a small effect on cancer risk. As an individual inherits half their genes from one parent, if that parent develops cancer, the individual will be at some increased risk above that of the general population as they are likely to have inherited a number of polymorphisms from the affected parent that cause an increased cancer risk.

Although genetic testing is not currently available in this situation, the risk of an individual developing cancer if a relative has been affected can be estimated from empirical studies.

Mendelian inheritance of cancer risk

Much less commonly, an increased risk of cancer can be inherited as a Mendelian trait. In this case, a change in a single gene, or mutation, is sufficient to cause a risk of cancer. In most cases of Mendelian inheritance of cancer, an individual has one mutated copy of a gene and one working copy. As there is a 50% risk that they would pass on the mutated copy of the gene, there is a 50% chance that their child would inherit the risk of developing cancer. This is illustrated in Figure 1.

Where there is a single mutation causing a cancer risk, the type of cancer for which there is a risk depends on the gene involved. One classification, with examples, is given in Table 1. However, for many genes, the mechanism of action remains uncertain.

CLINICAL CANCER GENETICS IN PRACTICE: ASSESSMENT OF PATIENTS – BASIC PRINCIPLES

Construction of a family tree

The assessment of any patient in clinical cancer genetics involves taking a clinical history and constructing a detailed family history. Clinical examination may be relevant where a specific cancer syndrome is suspected. Where possible, a family history should have information at least up to third-degree relatives (first cousins, great uncles and aunts). In clinical genetic practice, many pedigrees become much larger than this as a family is investigated. Where an individual is adopted, no family history may be available. The family tree should contain the names and ages of individuals, information of all cancer diagnoses, the ages at which an individual is diagnosed with cancer, whether individuals are alive or dead and, if dead, at what age they died. An illustration of how to draw a family tree, and the basic notation used, is given in Figure 2.

In many situations, a patient may be uncertain about the diagnosis of a relative. Part of the construction of a family tree includes confirming diagnoses where required. This necessitates the consent of an affected relative if they are still alive, and such consent is usually arranged by mail. Cancer diagnoses may be confirmed from medical records, cancer registers and death certificates.

Identifying families with rare cancer syndromes

Rarely, the initial inspection of a family tree may indicate a rare syndromic form of inherited cancer. In these cases, the presence of one or several unusual tumours in the same family may indicate the involvement of a specific gene. For example, a family in which one individual is affected with a haemangioblastoma and another individual with clear cell renal cancer at the age of 40 would suggest von Hippel-Lindau (VHL) disease and a mutation in the VHL gene. A family member with bilateral acoustic

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TABLE 1 Classification of cancer-causing genes

Oncogenes	*When activated, these genes promote cell division. Mutations that activate an oncogene will cause an increased risk of cancer.*
RET proto-oncogene	Multiple endocrine neoplasia type 2a
	Multiple endocrine neoplasia type 2b
	Familial medullary thyroid cancer
Tumour suppressor genes	*When activated, these genes suppress cell division. Mutations that inactivate a tumour suppressor will cause an increased cancer risk.*
Retinoblastoma gene	Retinoblastoma
VHL gene	Von Hippel-Lindau disease
Merlin	Neurofibromatosis type 2
Mutator genes	*Genes responsible for DNA repair. Mutations in these genes make cells more likely to lose the ability to repair DNA.*
MLH1	Hereditary non-polyposis colorectal cancer
MSH2	Hereditary non-polyposis colorectal cancer

neuromas who had a sibling that died from a meningioma would suggest neurofibromatosis type 2 with a mutation in the *Merlin* gene. In these cases, it is the rarity of the presenting tumour itself that suggests a cancer syndrome.

In most cases, the family history of cancer is one of common forms of cancer, such as breast cancer or bowel cancer.

Assessing risk with a family history of common cancer

The clinical purpose of assessing a family history of common cancer is to arrive at an estimate of risk that a patient faces of developing cancer, and to decide whether or not an individual in the family should be tested for a cancer-predisposing mutation. Currently, in the UK, the most common reason for seeking a cancer genetics referral is a family history of breast cancer; the second most common reason is a family history of bowel cancer. However, a number of referrals are of patients with a more complex family history of cancer that cannot be easily categorised and require specialist interpretation.

1. Estimating cancer risk

Although there are a number of different models that can be used to estimate cancer risk based on family history, none are currently in widespread use in family history clinics in the UK. For current clinical practice, empirical criteria are set that divide family histories into three categories:

a. *Population risk* (sometimes misnamed 'low risk'). A family history that suggests an individual is not at significantly increased risk of cancer, and does not require further intervention.
b. *Moderate risk.* A family history suggestive of a significantly increased risk of cancer.
c. *High risk.* A family history suggesting a high risk of cancer, meriting increased screening for cancer and possibly indicating a mutation in a cancer-causing gene.

2. Gene testing

It is important to differentiate between testing in a family where it is not known if there is a cancer-causing mutation, and testing an individual in a family where there is a known mutation.

When dealing with a family history of breast or bowel cancer, national criteria are set to identify families where there is a high likelihood of finding a cancer-causing mutation. Testing for such a gene change is usually only possible if there is a living relative who has been affected with cancer and who can be tested. Even following selection by national criteria, a mutation is usually only identified in a minority of families who are tested. If a mutation is identified in the first affected individual tested, then testing can be offered to other family members.

When there is a known mutation in a family, an individual at risk of inheriting the mutation can be tested for that mutation. If they carry the mutation, then they will be at high risk of developing cancer. If they do not have the mutation, then their risk will be close to the population risk and no further follow-up is indicated.

When no mutation is found in a family, clinical management needs to be based on clinical risk assessment.

MANAGING A FAMILY HISTORY OF BREAST CANCER

Women attending clinical genetics services because of a family history of breast cancer have their risk of breast cancer and eligibility for breast screening assessed according to the criteria set out in Tables 2 and 3. In addition, they are offered advice on breast awareness and lifestyle factors such as diet, exercise, alcohol intake, use of oral contraceptives or HRT and breastfeeding, which may influence their risk of breast cancer.

IDENTIFYING FAMILIES QUALIFYING FOR MUTATION ANALYSIS OF *BRCA1* AND *BRCA2*

Genetic testing begins with an individual who has breast and/or ovarian cancer (the affected family member). Testing is only offered to families who fulfil the high-risk criteria where there is a 20% or greater chance of finding a *BRCA1* or *BRCA2* mutation.

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TABLE 2 Risk stratification for a family history of breast cancer (adapted from NICE guideline 41)

Risk category	Criteria
Low	Women at or near population risk of developing breast cancer (i.e. a ten-year risk of less than 3% for women aged 40–49 years, or a lifetime risk of less than 17%). For example: Only one first- or second-degree relative diagnosed with breast cancer at older than 40 years, provided there are no other circumstances that might alter risk status.*
Moderate/raised	Ten-year risk of 3–8% of developing breast cancer for women aged 40–49 years, or a lifetime risk of 17% or greater but less than 30%. Some examples of moderate-risk family histories are outlined below. For example: • One first-degree female relative diagnosed with breast cancer at younger than 40 years, or • One first-degree male relative diagnosed with breast cancer at any age, or • One first-degree relative diagnosed with bilateral breast cancer where the first primary was diagnosed before age 5, or • Two first-degree relatives, or one first-degree and one second-degree relative, diagnosed with breast cancer at any age, or • One first-degree and/or second-degree relative diagnosed with breast cancer at any age, and one first- or second-degree relative diagnosed with ovarian cancer at any age (one of these should be a second-degree relative). Advice should be sought if any additional circumstances are present that may alter risk status.*
High	Ten-year risk of greater than 8% for women aged 40–49 years, or a lifetime risk of 30% or greater. Also includes a 20% or greater chance of *BRCA1*, *BRCA2* or *TP53* mutation in the family. Some examples of high-risk family trees are listed below. At least: • Two first- or second-degree relatives diagnosed with breast cancer at younger than average age of 50 years (at least one must be a first-degree relative), or • Three first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years (at least one must be a first-degree relative). • Families containing one relative with ovarian cancer at any age, and on the same side of the family one first- or second-degree relative diagnosed with breast cancer at a younger age than 50 years. • Families containing male breast cancer at any age, and on the same side of the family one first- or second-degree relative diagnosed with breast cancer at younger than 50 years.

* Further advice should be sought for families containing any of the following, in addition to breast cancer – Jewish ancestry, sarcoma in a relative younger than 45 years, glioma or adrenal cortical carcinomas, complicated patterns of multiple cancers at a young age, very strong paternal history, bilateral or male breast cancer, ovarian cancer. The effect of other lifestyle factors may also play a role in risk assessment in some cases.

Once a mutation is identified in an affected family member, other relatives (including men) can be offered a genetic test for the specific *BRCA1* or *BRCA2* mutation in the family.

COUNSELLING INDIVIDUALS WHO WISH TO BE TESTED FOR A FAMILIAL MUTATION IN *BRCA1* AND *BRCA2*

Pre-test counselling usually involves two sessions. The aim is to ensure that individuals have fully explored the implications of having the test for both themselves and their family. Consultees are encouraged to bring someone with them to these sessions for support.

Information is given about the test and the timeframe for the result (usually 6–8 weeks). The result will show whether an individual has inherited the mutation or not. Individuals are then helped to consider the implications of the two different possible results. Information is also given about insurance issues that should be considered before going ahead with the test.

For individuals finding out that they have inherited a *BRCA1* or *BRCA2* mutation, the impact is considerable and should not be underestimated. When considering how to manage their increased risk of breast and ovarian cancer, they will have to make difficult decisions when choosing between screening and/or prophylactic surgery (mastectomy and/or oophorectomy).

During pre-test counselling, individuals are encouraged to explore their own coping strategies to help them deal with the emotional and psychological impact of a genetic

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TABLE 3 Breast screening surveillance (adapted from NICE Guideline 41)

Age	Mammography	Magnetic resonance imaging (MRI)
20–29 years	Not normally available	Normally available only to those at exceptionally high risk, e.g. *TP53* carriers
30–39 years[a]	Individualised strategies should be developed for women from families with *BRCA1*, *BRCA2* or *TP53* mutations (or women with equivalent high risk)	Should be available annually to: • women with a ten-year risk of greater than 8% • *BRCA1*, *BRCA2* and *TP53* mutation carriers • women who have not been tested but have a high chance of carrying a *BRCA1*, *BRCA2* or *TP53* mutation
40–49 years[a]	Should be available annually to women satisfying criteria for raised (moderate)[b] or high risk	Should be available annually to: • women with a ten-year risk of greater than 20% • women with a ten-year risk of greater than 12% whose mammography has shown a dense breast pattern • *BRCA1*, *BRCA2* and *TP53* mutation carriers • women who have not been tested but have a high chance of carrying a *BRCA1*, *BRCA2* or *TP53* mutation
50 and over	Should be available every three years as part of the NHS Breast Screening Programme. Individualised strategies should be developed for women from families with *BRCA1*, *BRCA2* or *TP53* mutations (or women with equivalent high risk)[c]	Not normally available for women older than 50 years

[a] An 8% risk aged 30–39 and a 12% risk aged 40–49 would be fulfilled by women with the following family histories:
- close relatives diagnosed with average age <30 years*
- close relatives diagnosed with average age <40 years*
- close relatives diagnosed with average age <50 years*

* All relatives must be on the same side of the family and one must be a mother or sister of the consultee.
A genetic test would usually be required to determine a ten-year risk of 20% or greater in women aged 40–49.

[b] Women with this level of risk may be eligible for mammography before the age of 40, depending on the earliest age of onset of breast cancer in their family.

[c] In Scotland, women at high risk are eligible for mammograms every 18 months until the age of 70.

test. Genetic testing has the potential to affect family relationships. Parents often feel guilty that their children are at risk of inheriting the mutation from them. Sometimes people feel angry at their own parents for having passed on the mutation. Difficulties can also arise in families when there are discordant results between siblings.

For an individual who has not inherited the mutation, there is no risk of passing it on. For a woman, it is assumed that her risk of breast and ovarian cancer is about population level, and screening will no longer be appropriate. Some people find it difficult to adjust to the fact that they are not at risk when they have been living with a presumed increased risk for a long time.

The results of the test are given in person, and the consultees are asked to bring someone with them to the appointment for support. Following disclosure of the result, consultees are offered further support and counselling as required. This can include referral to a psychologist and facilitating access to self-help groups.

MANAGING FAMILIES WITH KNOWN MUTATIONS IN *BRCA1* AND *BRCA2*

For individuals who carry a *BRCA* mutation, clinical genetics services can provide support, access to appropriate screening services and referral to a breast surgeon, plastic surgeon and gynaecologist as required.

However, clinical genetics services also have a duty towards other family members. This involves identifying those at risk and facilitating family communication about that risk. It often involves liaising with other genetics services in the UK and abroad.

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KEY POINTS

- Cancer genetics has become an increasingly important part of the workload of clinical genetics services.
- In most cases the risk of cancer is inherited in a multifactorial fashion, involving many genes and environmental factors. Occasionally there is a single gene change, inherited in a Mendelian (usually autosomal dominant) fashion.
- A family history that would suggest Mendelian inheritance of common cancer is one in which there are multiple affected family members with the same or a related cancer and family members affected with cancer at a younger age than expected.
- A rare cancer syndrome may be suggested by the occurrence of a single unusual cancer in the family.

FURTHER READING

- Eccles DM, Evans DG, Mackay J. Guidelines for a genetic risk based approach to advising women with a family history of breast cancer. UK Cancer Family Study Group (UKCFSG). *J Med Genet* 2000; 37(3):203–9.
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