Part one

Cancer genetic counselling
Genetic counselling in a familial cancer clinic

Demand for cancer risk assessment based upon the estimation of the genetic component of cancer risk to a given individual is increasing rapidly. This is both because of increased public awareness of the genetic aspects of cancer susceptibility and as a result of requests from clinicians for evaluation of their patients so that appropriate surveillance protocols can be developed. Risk prediction in common cancers is based upon careful assessment of family history of cancer and cancer-related syndromes, and a personal history and examination (where appropriate). The genetic risk assessment requires confirmation of the diagnosis in affected relatives whenever possible. Close links with oncologists and clinicians involved in organising surveillance are essential. Joint or multidisciplinary clinics may be appropriate in this context and, ideally, a cancer family clinic network should be developed throughout each region, province or state. Education for primary care physicians should be provided, with guidelines for appropriate referrals.

Genetic counsellors and trained genetic nurses may be increasingly employed in specialised familial cancer clinics in cancer units and primary care, with the remit of assessing empiric cancer risks on the basis of personal and family histories, and to arrange surveillance protocols (audited centrally, if possible) for individuals at moderately increased risk, reassure those at low risk, and refer those at high risk of a genetic cancer susceptibility to the Regional Genetics Centre for further evaluation, advice and management. In most countries, training in genetic counselling involves completing a 2-year Masters in Genetic Counselling, followed by Board Certification and membership of a national association (in the USA, the National Association of Genetic Counselors, and in Canada, the Canadian Association of Genetic Counsellors).

Unfortunately, in the USA and elsewhere, the demand for trained genetic counsellors exceeds the supply, and currently, it may be impractical to deploy such trained individuals in primary care or even oncology clinics. As a result, the identification of potential genetic risk for cancer is dependent on the busy primary care physician or other caregiver or in certain institutions, based on uniform questionnaires. Once a patient or family with potential genetic risk is identified, they are referred to either “high-risk clinics” or preferably clinical cancer genetics programmes, often housed in Comprehensive Cancer Centres or in broad multi-disciplinary institutes or centres of human genetics.
Most risk estimates for cancer development are empiric, based on the likelihood of a genetic contribution in the individual, and this risk estimate is increased if the individual has several affected relations on the same side to the family with the same or related cancers, multiple or early onset cancers, and if the proband has clinical features of a cancer-predisposing condition or has previously had cancer or a cancer precursor lesion (Table 1.1) (Hampel et al., 2004; Garber and Offit, 2005). Computer programs for the assessment of risk and the provision of referral guidelines have been developed and can be adapted for use in primary care or even potentially by the families themselves. Various methods of assessing the risk of an inherited *BRCA1/2* mutation being present in a family have been developed, one of the most well known being BRCAPRO, that uses a Bayesian probabilistic model (Berry et al., 2002). Several non-computer based models, such as LAMBDA (which is currently restricted to the Ashkenazim) (Apicella et al., 2003) and the Evans model (Evans et al., 2004), may outperform BRCAPRO, particularly in families with other cancers such as pancreas, prostate and peritoneal. Other programs can also predict the risk of

Table 1.1. *Family history of cancer (example guidelines for referrals)*

There are a number of questions that can help when trying to assess an individual’s risk.

Ask about:

(a) Age of onset in the family member
(b) Site of primary tumour
(c) Number of affected members in the family
(d) Multiple primary tumours

Possible indications for referrals

Personal history

- Early onset of cancer (e.g. breast cancer diagnosed <40 years, colorectal cancer diagnosed <45 years, etc.)
- Multiple primary cancers

Family history

- Three close relatives (same side of family) with cancer of the same or syndromically related type (e.g. breast and ovarian or colorectal and uterine)
- Two close relatives (same side of family) with cancer, or the same or related type, with at least one affected under 50 years
- One first-degree relative (mother or sister) with early onset cancer (e.g. breast cancer) diagnosed <40 years, or <45 years if colorectal cancer
- One first-degree relative with multiple primary cancers
- Two or more relatives with uncommon cancers (e.g. sarcomas, gliomas, pancreatic cancer, glioma haemangioblastomas, etc.)
breast cancer accurately, taking into account unmeasured polygenic factors (Antoniou et al., 2004). In this appropriately named BOADICEA model, the predicted mutation probabilities and cancer risks in individuals with a family history of breast and/or ovarian cancer can differ markedly from those predicted by other models. When available as a computer package, this model is likely to become commonly used in the clinic setting.

How should risk be communicated? Risk can be given as a risk of developing cancer per year, or before a certain age, or as an overall life-time risk relative to the population risk. It is appropriate to compare this risk with the background population risk (relative risk).

Screening and preventative options should be discussed, with consideration of the possibility of false-positive and false-negative results of tests and the anxiety these could cause. It should be made clear that no surveillance programme is totally reliable and it should be emphasised that the individual being screened should never ignore abnormal symptoms between screening procedures. The current state of knowledge about the efficacy of screening should be fully explained. The individual's perception of his or her cancer risk should be assessed, as should its possible effects on the individual's health–behaviour.

Predictive testing is only possible in a small proportion of families in which the germline cancer-predisposition mutation can be defined in an affected relative. Family history indicators of a high probability of finding such a mutation are given in the relevant chapters. Such guidelines are not inflexible and depend on continuing studies to determine the prevalence of mutations in different family history types.

To identify a pathogenic germline mutation in a family, it is usual to start testing with blood (or tissue) from an affected relative, following informed consent for testing for a genetic cancer susceptibility. This requires an initial approach from the individual being counselled, and some family and confidentiality problems can arise over this. It is essential that the affected relative understands the nature of the tests being performed, the possible emotional impact of a positive (or a negative) result, and its relevance in terms of insurance and employment. In many cases, such a test will not reveal a pathogenic mutation, and in a few cases a sequence change may be detected in a cancer-predisposing gene, whose significance may not be clear, necessitating further tests to clarify this (e.g. does the mutation segregate with the disease in the family?). In such cases it is important to have a rapport with the tested individual, with a clear plan for the communication of results. When a pathogenic mutation is detected in a family in which the significance of inheriting such a mutation is understood, and when the affected individuals agree to the release of their results to the family, predictive testing can be offered to at-risk individuals in that family.
Such testing optimally requires two pre-test counselling interviews at which issues such as the emotional, family, insurance and employment implications of any result can be discussed prior to testing, and the mode of inheritance and penetrance of the mutation can be explained.

Often, it is advisable to have an interval of up to 3 months between these sessions, along the lines of predictive testing for Huntingdon disease. The results should be given as soon as possible after they are available to the person tested, with a confidant (unless some prior arrangement to deliver the results to a third party has been made). Such a protocol may be varied with relevance to the condition tested for and the attitude and knowledge of the individual undertaking the test. Individuals with a low-risk result may also require post-test support because they can suffer from “survivor guilt”. High-risk individuals should be offered psychological support and a clear protocol for surveillance and possible preventive action.

Insurance issues are still being debated. Currently in the UK, for policies under £500,000 for mortgages on a residence, the family history of the person whose life is insured is taken into account, but the results of genetic tests are not. There is currently a moratorium for requesting genetic test results in the UK until 2011. In the USA, despite fear and much debate, to our knowledge, no individual has been discriminated against by health insurance companies or third party payors because of visiting a cancer family clinic or because of a gene test result to date. There are US federal and often state laws protecting against discrimination by group health insurance. In a group health insurance, such protection prevents individuals from being dropped or individual premiums from being raised. Often however individuals who are self-insured can be open to such theoretical discrimination by third party health insurers.

It should not be forgotten that individuals who have had cancer may be psychologically affected by the news that they have an inherited cancer susceptibility, particularly as it may indicate that they have an increased risk for metachronous cancers, and that they could be “responsible” for handing on the susceptibility to their children – a potential cause of profound guilt feelings. A positive result also has management implications, such as the option of bilateral prophylactic mastectomy when treating unilateral breast cancer in a BRCA1 or BRCA2 mutation carrier.

Patient support groups are well established for familial cancer conditions such as retinoblastoma, but broader-based support groups are being developed, for breast and ovarian cancer susceptibility particularly, initiated both from the starting point of those originally concerned with support for cancer sufferers, and from genetic interest groups concerned with promoting the welfare of families with a broad spectrum of genetic disorders. “Carrier clinics” specifically for
carriers of mutations in $BRCA_1$ and $BRCA_2$ are being set up, so that specific management issues can be addressed, and patient support groups are arising from these. For example, a charity, the Hereditary Breast and Ovarian Cancer Foundation (http://www.hboc.ca/) is devoted entirely to women at increased genetic risk of breast and ovarian cancer.

Since it is generally true that early diagnosis of cancer improves outcome, it would seem appropriate to identify individuals at increased cancer risk, and offer them surveillance and/or prophylactic measures to reduce their risk of cancer, or provide the earliest possible stage at diagnosis. However, the development of such a system requires robust audit of outcomes, both in terms of cancer morbidity and mortality, and of psychological effects. Clearly a threshold level of risk at which to offer screening needs to be established in the light of outcome assessment. Screening methods must be carefully evaluated and long-term survival audited.

A further question is whether families should be ascertained actively or whether this should be reactive. The Calman–Hine model (Department of Health, 1995; 1999) proposed that individuals at population or only slightly increased risk should be managed in the primary care setting, those estimated to have a moderately increased risk, for which some surveillance may be appropriate, should ideally be managed in cancer units and primary care, and only those at high risk referred to genetics centres for specialised genetic counselling and predictive testing as appropriate. This has been developed in the Kenilworth model, and promoted as the optimal way of managing genetic cancer susceptibility from the population to tertiary care (NHS Cancer Plan, 2000; Hodgson et al., 2000). Certain difficulties have been encountered in trying to establish this model of care. Clearly there is a need to put in place clinics in primary and secondary care where family history taking and risk estimation can be undertaken, and education/guidelines provided to non-genetics professionals to help triage families at this service level. There is some reluctance in primary care to become too involved in this because of the time required to evaluate family histories. As a result, in the USA, CD-ROM’s or other computerised systems, such as GRAIDS, that aid in triage are being advocated (Westman et al., 2000; Sweet et al., 2002).

Specialist cancer genetics nurse-led clinics can be set up for groups of general practices or in district hospitals to undertake such evaluation, in collaboration with the local genetics centre. Nurses in these clinics are trained in pedigree taking and risk assessment, and can “triage” patients into those who can be reassured, those who can be referred for surveillance because of a moderately increased risk, and those who should be referred to the genetics centre. Close links are maintained with the genetics centre with regular discussion of difficult families or problems with risk assessment. Such health care delivery developments are being
piloted in the UK under the Department of Health White Paper Initiative on Genetics, in collaboration with Macmillan Cancer Relief. Telephone clinics are being assessed as part of these assessments. Computerised systems are needed to maintain pedigree data, ensure the smooth running of appropriate surveillance programmes, and document screening outcomes in relation to risk. These could be maintained in secondary and primary care but monitored in the genetics centre, if secure data transfer is made available. Audit of surveillance strategies in individuals at moderately increased risk is vital in order to assess the efficacy (specificity, sensitivity and cost–effectiveness) of such strategies in the long term. The genetics centre provides specialist genetic counselling for families in which it is likely that some individuals carry a mutation conferring a strong genetic susceptibility to specific cancers. Predictive testing can be offered to individuals from families in which a mutation is identified and screening and prophylactic measures offered only to those testing positive for the mutation. This also saves costs in screening for those at low risk. Multidisciplinary clinics for carriers of $BRCA1$ and $BRCA2$ carriers are helpful for managing these individuals and their families.

The delivery of a comprehensive service of this type requires a good deal of co-ordination and audit, which is best organised centrally. The genetics centre should be responsible for providing education and continuing support for nurses and genetic counsellors working in primary and secondary care, and for providing educational study-days, literature and referral guidelines for non-genetics professionals. Courses aimed at educating health professionals to be able to run “family history clinics” are required in the development of such a service. Such nurse-led clinics could utilise computer packages, which additionally could provide printed risk information for the patients and for maintaining practice and hospital patient notes.
Part two

Genetics of human cancers by site of origin
Central nervous system

Primary central nervous system (CNS) neoplasms affect about 1 per 10,000 of the population. Although the incidence of brain tumours increases with advancing age, intracranial neoplasms are the most common cause of solid cancer in children. The distribution and histological type of brain tumour differ in children and in adults. In children, brain tumours most often arise in the posterior fossa, and the most frequent tumour types are medulloblastoma, spongioblastoma (including cerebellar astrocytoma and optic nerve glioma) and ependymomas. In adults, most tumours are supratentorial, and meningiomas and gliomas are the most frequent type. Familial brain tumours may occur as part of a rare specific inherited cancer syndrome (Table 2.1). Epidemiological studies have suggested that there is a small increased risk of cerebral neoplasms among relatives of brain tumour patients compared to controls: Choi et al. (1970), Gold et al., 1994 found a ninefold increase in the incidence of brain tumour among relatives of patients with glioma compared to controls, whereas Burch et al. (1987) found a (statistically insignificant) sixfold increase among relatives of brain tumour patients. Nevertheless, the absolute risk to relatives is small, 0.6 per cent in the study by Choi et al. (1970). Miller (1971) found a ninefold increase in the expected number of sib pairs among children with brain tumours,

Table 2.1. Genetic disorders associated with tumours of the CNS.
Details of individual conditions are given in Part Three

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<td>Familial adenomatous polyposis</td>
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<td>Turcot syndrome (including homozygous mismatch gene mutations)</td>
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and a similar excess of families in which one child died of brain tumour and another of cancer of bone or muscle. Soft tissue sarcomas and brain tumours occur as part of the Li–Fraumeni syndrome. Mahaley et al. (1989) found a family history of cancer in 16–19 per cent of patients with brain tumours (similar to the expected incidence), but that the incidence was 30–33 per cent in patients with glioblastoma multiforme, malignant lymphoma and neuroblastoma. A family history of neurofibromatosis was obtained in 1.6 per cent of cases. The genetic implications of specific CNS tumours are described below.

Vestibular schwannoma (acoustic neuroma)

This tumour accounts for around 8 per cent of all intracranial tumours and has an incidence of 13/million per year (Tos and Thomsen, 1984). Although sometimes called acoustic neuromas, these are Schwann cell tumours. They usually arise from the vestibular nerve, but they can develop on the fifth cranial nerve, and less often on the ninth and tenth nerves. Within the spinal canal, they usually arise on the dorsal spinal root. Familial and bilateral vestibular schwannoma are features of neurofibromatosis type 2 (NF2). About 4 per cent of vestibular schwannoma are bilateral and all patients with bilateral tumours have NF2 (see Part Three). Sporadic vestibular schwannoma is typically seen in the fifth and sixth decades of life, which is about 20 years later than in patients with NF2. The clinical features and diagnostic criteria for NF2 are discussed in Part Three. Although vestibular schwannoma in NF2 is usually bilateral, it can be unilateral. Multiple extracranial schwannomas (cutaneous and spinal) may be inherited as a dominant trait and is allelic with NF2 (Evans et al., 1997). Those mosaic for an NF2 gene mutation may present with milder- and later-onset disease (see p. 239). Although vestibular schwannoma in NF2 is usually bilateral, it can be unilateral. Multiple extracranial schwannomas (cutaneous and spinal) without vestibular schwannomas may be inherited as a dominant trait (Evans et al., 1997a). Although both sporadic and NF2-associated vestibular schwannoma show somatic NF2 tumour gene mutations and allele loss and extracranial schwannomas from familial schwannomatosis cases may have NF2 inactivation, linkage studies have mapped familial schwannomatosis to chromosome 22 but have excluded linkage to NF2 (Menon et al., 1990a; Irving et al., 1994; MacCollin et al., 2003).

Choroid plexus tumour

Choroid plexus neoplasms are rare (0.5 per cent of all brain tumours), and are most frequent in infancy. The majority of choroid plexus tumours are benign papillomas, but up to 30 per cent are classified as carcinomas.