MEDICAL GENETICS IN PRACTICE

Referral for cancer genetics consultation: a review and compilation of risk assessment criteria

H Hampel, K Sweet, J A Westman, K Offit, C Eng

Background: There have been many papers on the diagnostic criteria for specific hereditary cancer susceptibility syndromes and the likelihood that an individual has a germline mutation in one of the various cancer susceptibility genes. To assist health care professionals in deciding when a cancer genetics consultation is appropriate, available reports were critically reviewed in order to develop a single set of risk assessment criteria.

Methods: The criteria were based on a comprehensive review of publications describing diagnostic criteria for hereditary cancer syndromes and risk to first degree relatives of cancer patients. Priority was given to diagnostic criteria from consensus statements (for example, those from the National Comprehensive Cancer Network). Expert opinion from study personnel was then used to adopt a single set of criteria from other publications whenever guidelines differed.

Results: Based on family history, a set of criteria was developed to identify patients at risk for a hereditary cancer susceptibility syndrome, patients with moderate risk who might benefit from increased cancer surveillance, and patients who are at average risk. The criteria were applied to 4360 individuals who provided their cancer family history between July 1999 and April 2002, using a touch screen computer system in the lobby of a comprehensive cancer centre. They categorised an acceptable number of users into each risk level: 14.9% high risk, 13.7% moderate risk, and 59.6% average risk; 11.8% provided insufficient information for risk assessment.

Conclusions: These criteria should improve ease of referral and promote consistency across centres when evaluating patients for referral to cancer genetics specialists.

Health care providers have been encouraged to collect and analyse systematically the family histories of cancer in their patients, so as to facilitate prevention efforts and screening of relatives. Further, “duty to warn” litigation has underscored the importance of notifying cancer patients (and immediate family members) if they are at risk for a hereditary cancer susceptibility syndrome. This task usually involves, first, obtaining a cancer family history; second, determining whether a hereditary susceptibility exists; and third, communicating this risk assessment to patients and their families. To this end, health care providers are beginning to obtain cancer family histories from their patients in a concerted effort to provide risk assessment. Providers generally obtain information about first and second degree relatives affected by cancer, including the type of cancer and the age at diagnosis. For more information about taking a cancer family history, visit the National Cancer Institute Cancer Genetics PDQ at <http://www.cancer.gov/cancerinfo/pdq/genetics/risk-assessment-and-counseling#section_18>. Interpretation of these family history data, however, remains the greatest challenge to healthcare providers, who may not have expertise in the area of cancer genetics.

A major limitation of cancer family risk assessment has been the variability of the risk assessment criteria used among institutions and individual clinicians. Many centres do not have written risk assessment criteria and rely on the expert opinion of the individual performing the assessment. In some cases, there are explicit criteria for the assessment of hereditary risk that may be missed by a limited review of the family history. For example, hereditary non-polyposis colon cancer syndrome (HNPCC) is an inherited cancer syndrome characterised primarily by colorectal and endometrial cancers. If the assessment during an annual gynaecological examination or mammogram is restricted to questions about breast or ovarian cancer, it is possible that HNPPC families may go undetected.

In order to facilitate and provide consistency in risk assessment, we sought to develop a set of criteria for use by clinicians gathering cancer family history information. The criteria are currently being used at two separate comprehensive cancer centres which collect family history data in different ways—one with a touch screen computer and the other with computer scanned forms. It would be ideal if these criteria could be used in a wide variety of settings by anyone collecting cancer family history information.

METHODS

Search strategy and selection criteria

A literature search was conducted using the MeSH headings “genetic predisposition to disease,” “genetic screening,” “neoplasms,” and “genetic counseling.” Risk assessment criteria differed from study to study and most only addressed a single hereditary cancer susceptibility syndrome. The papers identified underwent critical review with priority given to:

- diagnostic criteria from consensus statements, for example the National Comprehensive Cancer Network, and so on;
- research studies providing empirical data on the likelihood of having a mutation in a cancer susceptibility gene;

Abbreviations: CRC, colorectal cancer; FDR, first degree relative; HBOC, hereditary breast and/or ovarian cancer syndrome; HNPCC, hereditary non-polyposis colon cancer syndrome; LFL, Li-Fraumeni-like; LFS, Li-Fraumeni syndrome; MEN, multiple endocrine neoplasia; NCCN, National Comprehensive Cancer Network, SDR, second degree relative.
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<th>Table 1</th>
<th>Risk assessment criteria</th>
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<tr>
<td><strong>BREAST-OVARIAN</strong>&lt;br&gt;Non-Jewish families</td>
<td><strong>High risk breast-ovarian</strong>&lt;br&gt;Any of the following:&lt;br&gt;- 1 case of breast cancer ≤ 40 y in an FDR or SDR&lt;br&gt;- 1 FDR or SDR with both breast and ovarian cancer, at any age&lt;br&gt;- ≥ 2 cases of breast cancer in FDRs or SDRs if one is diagnosed at ≤ 50 y or is bilateral&lt;br&gt;- 1 FDR or SDR with breast cancer diagnosed at ≤ 50 y or bilateral and 1 FDR or SDR with ovarian cancer&lt;br&gt;- 3 cases of breast and ovarian cancer (at least one case of ovarian cancer) in FDRs and SDRs&lt;br&gt;- 2 cases of ovarian cancer in FDRs and SDRs&lt;br&gt;- 1 case of male breast cancer in an FDR or SDR if another FDR or SDR has (male or female) breast or ovarian cancer</td>
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<td><strong>BREAST-OVARIAN</strong>&lt;br&gt;Jewish families</td>
<td><strong>High risk breast-ovarian</strong>&lt;br&gt;Any of the following:&lt;br&gt;- 1 case of breast cancer ≤ 50 y in an FDR or SDR&lt;br&gt;- 1 case of ovarian cancer at any age in an FDR or SDR&lt;br&gt;- 1 FDR or SDR with breast cancer at any age if another FDR or SDR has breast and/or ovarian cancer at any age&lt;br&gt;- 1 case of male breast cancer in an FDR or SDR</td>
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<td><strong>COLON</strong>&lt;br&gt;High risk HNPCC</td>
<td>Any of the following:&lt;br&gt;- 3 FDRs or SDRs affected with any HNPCC associated cancers*; all cases can occur in one generation, no age restriction&lt;br&gt;- 1 FDR or SDR with two or more HNPCC associated cancers*&lt;br&gt;- 1 FDR with CRC ≤ 50 y</td>
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<td><strong>MELANOMA</strong>&lt;br&gt;High risk melanoma</td>
<td>Any of the following:&lt;br&gt;- 3 FDRs or SDRs affected with melanoma and or pancreatic cancer, at least two generations (must include more than one case of melanoma)</td>
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<td><strong>LI-FRAUMENI SYNDROME</strong>&lt;br&gt;High risk Li-Fraumeni</td>
<td>All of the following:&lt;br&gt;- 1 FDR or SDR with sarcoma, brain, or adrenal cancer diagnosed at ≤ 45 y; and&lt;br&gt;- 1 FDR or SDR with sarcoma, breast, brain, adrenal or leukaemia at any age; and&lt;br&gt;- 1 FDR or SDR with any cancer diagnosed at &lt; 60 y</td>
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• studies describing the characteristics of various hereditary cancer syndromes.

In cases where criteria differed among studies, the expert opinion of the authors was used to choose those least likely to miss patients with a hereditary cancer predisposition.

The risk assessment criteria were written to categorise individuals into three different risk levels.

High risk: Family histories suggestive of a hereditary cancer susceptibility syndrome where the individual would benefit from referral to a cancer genetics professional and increased cancer surveillance;

Moderate risk: Family histories not diagnostic of a hereditary cancer susceptibility syndrome but conferring an increased risk for cancer, requiring increased cancer surveillance;

Average risk: Family histories that do not require increased cancer surveillance and for whom the screening recommendations for the general population apply (that is, in the USA, those of the American Cancer Society).

The risk criteria are intended for use with both healthy at-risk individuals and cancer patients. If the individual providing their family history has had cancer, they should be counted as a first degree relative (FDR) affected with cancer when applying the risk assessment criteria. For example, if the user was diagnosed with breast cancer at age 39, they meet the criteria “FDR diagnosed with breast cancer under age 40 and should be categorised as high risk breast and referred for genetic counselling.”

Each risk category results in a different recommended intervention (fig 1). Individuals who meet the high risk criteria should be referred for clinical cancer genetics consultation and offered surveillance for the cancers associated with the suspected cancer predisposition syndrome. Cancer genetics professionals—including genetic counsellors, geneticists, oncologists, and nurses with experience in this area—can be found in the USA by visiting the National Cancer Institute website (http://www.cancer.gov/search/genetics_services/) or the National Society of Genetic Counselors website (http://www.nsgc.org), or by phoning the NCI information service at 1-800-4-CANCER.

The goal of the high risk criteria was to identify individuals or families that meet published diagnostic criteria for a particular cancer susceptibility syndrome or exceed a threshold of a 10% likelihood of finding a germline genetic mutation in a cancer susceptibility gene. This threshold is consistent with the American Society of Clinical Oncology statement that genetic testing might be offered to anyone who has a >10% chance of having a mutation in a cancer susceptibility gene. If the user or a first degree relative would have a 10% likelihood of having a mutation in a cancer susceptibility gene, we recommend referral for cancer genetics consultation. If the user is a healthy at-risk relative, they will learn in their consultation that genetic testing would be best initiated by a relative who has had cancer and probably has a greater chance of having a mutation.

While the criteria used to classify a family as high risk are based on the likelihood of having a cancer gene mutation, the outcome is referral for cancer genetic consultation and not testing, as some individuals will decide against testing for various reasons. Further, it is understood that some individuals with less than a 10% chance of having a cancer gene mutation would benefit from a cancer genetics consultation and these individuals could certainly seek out this service on their own. However, for the sake of large scale or high throughput risk assessment, the numbers of individuals being referred for genetic consultation must be limited in some way, and requiring a high likelihood of having a cancer gene mutation seems the most equitable.

The moderate risk criteria aim to identify individuals with a relative risk of $\geq 2.0$ for developing a particular cancer but who do not meet the specific criteria for a cancer predisposition syndrome. These individuals are at least twice as likely as someone in the general population to develop that particular cancer, and could benefit from increased cancer surveillance.
Table 2  Consensus guidelines for hereditary breast-ovarian cancer

<table>
<thead>
<tr>
<th>NCCN</th>
<th>ACMG/NYS</th>
<th>Kaiser Permanente</th>
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<tr>
<td>1. Member of known BRCA1/BRCA2 kindred</td>
<td>1. Family member with an identified mutation</td>
<td>1. Women or men with a maternal or paternal relative who has previously been tested and found to have a clinically significant alteration in a breast cancer (BRCA) gene.</td>
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<tr>
<td>2. Personal history of breast cancer</td>
<td>2. Three or more affected FDRs or SDRs on the same side of the family, regardless of age at diagnosis</td>
<td>2. Women or men with a personal and family history of breast and/or ovarian cancer in maternal or paternal relative(s) as defined by at least one of the following:</td>
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<td>- Diagnosed age &lt;40 y, with or without family history</td>
<td>3. Patient diagnosed with breast cancer at &lt;45 y</td>
<td>- Women with breast cancer at &lt;49 y plus one or more FDR or SDR with breast cancer diagnosed at &lt;49 y</td>
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<td>- Diagnosed age &lt; 50 y or bilateral, with ≥1 close blood relative with breast cancer or ≥1 close blood relative with ovarian cancer</td>
<td>4. One or more cases of ovarian cancer at any age and ≥1 case of breast cancer at any age</td>
<td>- Women with breast cancer at any age plus:</td>
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<td>- Diagnosed at any age, with ≥2 close relatives with ovarian cancer at any age, or breast cancer, especially if ≥1 woman is diagnosed before age 50 y or has bilateral disease</td>
<td>5. Multiple primary cancers or bilateral breast cancer in patient or family member</td>
<td>- Breast cancer in ≥2 FDRs or SDRs where any of the affected relatives is diagnosed at &lt;49 y</td>
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<tr>
<td>- Close male blood relative has breast cancer</td>
<td>6. One or more cases of male breast cancer</td>
<td>- Ovarian cancer in ≥1 FDR or SDR</td>
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<tr>
<td>- Personal history of ovarian cancer</td>
<td>7. If of Ashkenazi Jewish descent, no additional family history is required</td>
<td>- Women with ovarian cancer plus:</td>
</tr>
<tr>
<td>- If of Ashkenazi Jewish descent and diagnosed age &lt;50 y, no additional family history required or at any age if positive family history of breast and/or ovarian cancer</td>
<td></td>
<td>- Breast cancer in ≥1 FDR or SDR</td>
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<tr>
<td>3. Personal history of ovarian cancer</td>
<td></td>
<td>- Ovarian cancer in ≥1 FDR or SDR</td>
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<tr>
<td>- One or more close relatives with ovarian cancer</td>
<td></td>
<td>- Men with breast cancer plus breast and/or ovarian cancer in ≥1 FDR or SDR</td>
</tr>
<tr>
<td>- One or more close female relatives with breast cancer at age ≤50 y or bilateral breast cancer</td>
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<td>3. Women with a personal history (but no family history) of breast and/or ovarian cancer as defined by at least one of the following:</td>
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<td>- Two or more close relatives with breast cancer</td>
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<td>- Breast cancer at &lt;29 y</td>
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<tr>
<td>- One or more close male relatives with breast cancer</td>
<td></td>
<td>- Breast cancer &lt;40 y and of Ashkenazi Jewish descent</td>
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<tr>
<td>- If of Ashkenazi Jewish descent, no additional family history is required</td>
<td></td>
<td>- Ovarian cancer and of Ashkenazi Jewish descent</td>
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<tr>
<td>4. Personal history of male breast cancer plus one or more of the following:</td>
<td></td>
<td>- Breast cancer and ovarian cancer</td>
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<tr>
<td>- One or more close female relatives with breast or ovarian cancer</td>
<td></td>
<td>- Multiple primary breast cancers</td>
</tr>
<tr>
<td>- If of Ashkenazi Jewish descent, no additional family history is required</td>
<td></td>
<td>4. Women or men with a family history (but no personal history) of breast and/or ovarian cancer in maternal or paternal relatives as defined by at least one of the following:</td>
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<td>5. Family history only</td>
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<td>- Breast cancer in at least:</td>
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<td>- Close family member meeting any of the above criteria.</td>
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<td>- ≤2 FDRs or SDRs both diagnosed at &lt;49 y and at least one of the relatives is a FDR</td>
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<td></td>
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<td>- ≥3 FDRs or SDRs with ≥1 relative diagnosed at &lt;49 y</td>
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<td></td>
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<td>- Breast cancer in ≥2 FDRs or SDRs</td>
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<td></td>
<td></td>
<td>- Breast cancer in ≥1 FDR or SDR and ovarian cancer in ≥1 FDR or SDR</td>
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ACMG/NYS, American College of Medical Genetics and New York State Department of Health; BRCA, breast cancer mutation; NCCN, National Comprehensive Cancer Network.

Beyond that recommended for the general population. Consideration was given to the availability and efficacy of cancer surveillance procedures. Thus cancers omitted from this review process resulted in a set of risk assessment criteria include pancreatic, lung, stomach, oesophagus, small intestine, brain, and haematological malignancies. It is recognised that there are screening methods for some of these cancers (for example, upper endoscopy for gastric cancer and spiral computed tomography for lung cancer detection); however, they are not of proven efficacy in moderate risk individuals. In addition, there are other cancers for which the screening guidelines for the general population (from resources such as the American Cancer Society) are also appropriate for individuals at twice the general population risk for developing the cancer. These include cervical, endometrial, and non-melanoma skin cancers. Individuals who do not meet the high risk or moderate risk criteria, meet the average risk criteria by default. These individuals should follow guidelines for cancer screening in the general population (the US guidelines written by the American Cancer Society can be found on-line at http://www.cancer.org).

RESULTS
The review process resulted in a set of risk assessment criteria (table 1), with the rationale summarised below, by organ
The genetic differential diagnosis for breast cancer includes hereditary breast and/or ovarian cancer syndrome (HBOC), Cowden syndrome, and Li-Fraumeni syndrome. In contrast, the genetic differential diagnosis for ovarian cancer includes HBOC and HNPCC. Germline mutations in BRCA1 or BRCA2 genes are associated with HBOC, believed to be the most common inherited breast cancer syndrome. There is an extensive literature on risk assessment criteria for breast and ovarian cancers. Professional society guidelines are based on empirical data regarding the likelihood that a particular family history can be attributed to a mutation; however, in view of the fact that research studies often use detection technologies that may only be 60–90% accurate, these population based studies, an age cut off of 35 years may be appropriate given the proximity to a 10% prior risk for mutation prevalence tables from the only laboratory providing clinical BRCA testing in the USA indicate that 7.6% of women with breast cancer under the age of 50 have a mutation, even if there is no family history of ovarian cancer or breast cancer under the age of 50.10 From these population based studies, an age cut off of 35 years may be appropriate given the proximity to a 10% prior risk for mutation. However, in view of the fact that research studies often use detection technologies that may only be 60–90% sensitive,11 the mutation likelihood of those diagnosed under the age of 35 is likely to be falsely diminished and so an age cut off of 40 is adopted here.

In addition to young age at diagnosis, our high risk breast-ovarian cancer criteria also consider the presence of multiple affected members in a family, ovarian cancer, male breast cancer, and bilateral breast cancer. The three Society guidelines recommend referral of individuals with three family members affected with breast or ovarian cancer or both (the NCCN requires at least one of the diagnoses to be ovarian cancer or a breast cancer that is diagnosed under the age of 50 or bilateral, while the others do not). The high risk breast-ovarian criteria presented here mirror the NCCN criteria. Models based on data derived from multiple studies12–14 are available to estimate probabilities of detecting BRCA mutations depending on personal or family history of cancer. While these models are reasonable predictors of the likelihood that a patient has a BRCA mutation, they have to be used with professional judgment in the context of broad and in-depth knowledge of the cancer genetics literature. For systems. In general, with rare exceptions, selection of high risk criteria reflect the known hallmarks of any hereditary cancer susceptibility syndrome—young age at diagnosis, multifocal tumours, bilateral, presence of more than one associated cancer, and multiple affected members in a family.

### Risk assessment criteria for breast and ovarian cancers

The genetic differential diagnosis for breast cancer includes hereditary breast and/or ovarian cancer syndrome (HBOC), Cowden syndrome, and Li-Fraumeni syndrome. In contrast, the genetic differential diagnosis for ovarian cancer includes HBOC and HNPCC. Germline mutations in BRCA1 or BRCA2 genes are associated with HBOC, believed to be the most common inherited breast cancer syndrome. There is an extensive literature on risk assessment criteria for breast and ovarian cancers. Professional society guidelines are based on empirical data regarding the likelihood that a particular family history can be attributed to a mutation; therefore these professional guidelines were used for the high risk criteria. Epidemiological studies estimating the risk that an individual will develop breast or ovarian cancer based on her family history were used to develop the moderate risk criteria.

### High risk breast-ovarian cancer criteria (non-Jewish families)

Because of the high frequency of three specific BRCA1 and BRCA2 founder mutations among the Ashkenazi (with a 2.5% likelihood of having one of these mutations in the general Ashkenazi Jewish population), criteria for people of Jewish descent are reviewed separately (below). There are several professional society guidelines that describe individuals at increased risk for HBOC. The National Comprehensive Cancer Network (NCCN)—an affiliation of 17 US cancer centres given comprehensive status by the US National Cancer Institute—has developed guidelines for genetic/familial high risk screening using a committee of cancer genetics experts from the member institutions. The guidelines are very similar to those developed by the Kaiser Permanente managed care organisation and the American College of Medical Genetics (ACMG) and New York State Department of Health (table 2).

Criteria for referral of solitary presentations of breast cancer rests on whether the a priori risk of finding a germline mutation is ≥10% when diagnosed before a certain age. The main difference between the guidelines is cut off age at diagnosis: 30 years (Kaiser-Permanente), 40 years (NCCN), and 45 years (ACMG). The empirical data are variable, ranging from a 5.9% BRCA1 and BRCA2 mutation frequency in women diagnosed before the age of 36 to 9.4% of those diagnosed before 35. Mutation prevalence tables from the only laboratory providing clinical BRCA testing in the USA indicate that 7.6% of women with breast cancer under the age of 50 have a mutation, even if there is no family history of ovarian cancer or breast cancer under the age of 50. From these population based studies, an age cut off of 35 years may be appropriate given the proximity to a 10% priori risk for mutation. However, in view of the fact that research studies often use detection technologies that may only be 60–90% sensitive, the mutation likelihood of those diagnosed under the age of 35 is likely to be falsely diminished and so an age cut off of 40 is adopted here.

In addition to young age at diagnosis, our high risk breast-ovarian cancer criteria also consider the presence of multiple affected members in a family, ovarian cancer, male breast cancer, and bilateral breast cancer. The three Society guidelines recommend referral of individuals with three family members affected with breast or ovarian cancer or both (the NCCN requires at least one of the diagnoses to be ovarian cancer or a breast cancer that is diagnosed under the age of 50 or bilateral, while the others do not). The high risk breast-ovarian criteria presented here mirror the NCCN criteria. Models based on data derived from multiple studies are available to estimate probabilities of detecting BRCA mutations depending on personal or family history of cancer. While these models are reasonable predictors of the likelihood that a patient has a BRCA mutation, they have to be used with professional judgment in the context of broad and in-depth knowledge of the cancer genetics literature.
example, the Couch model requires averaging the ages of breast cancer diagnoses in a given family and can only be used for families with at least two cases of breast cancer. Further, these models do not lend themselves to large scale screening efforts. As a result, we recommend that individuals familiar with their limitations apply these models.

Moderate risk breast cancer criteria (non-Jewish individuals)

The two most frequently used models for predicting lifetime risk for developing breast cancer are the Gail model from the breast cancer detection and demonstration project (BCDDP) and the Claus data from the cancer and steroid hormone (CASH) study. As our risk assessment model is based solely on family history, we do not collect the information necessary to do the Gail risk calculation (age at menarche, parity, age at first childbirth, number of breast biopsies, and presence of atypia in these biopsies). We have elected to use the CASH data instead, as they incorporate more extensive information about family history and have been found to offer the most comprehensive assessment of family history for women with one or more first or second degree relatives with breast cancer.

High risk breast-ovarian cancer criteria (Jewish families)

There are three founder mutations in the BRCA genes found in 2.5% of the Ashkenazi Jewish population. As a result, a Jewish individual has a greater than 10% likelihood of carrying a breast or ovarian cancer mutation, depending on family history. The high risk breast-ovarian criteria for Jewish individuals are based on the presence of two or more first degree relatives with breast cancer and/or one breast cancer and one ovarian cancer. The high risk criteria for Jewish individuals are based on the presence of two or more first degree relatives with breast cancer and/or one breast cancer and one ovarian cancer. The high risk breast-ovarian criteria for Jewish individuals are based on the presence of two or more first degree relatives with breast cancer and/or one breast cancer and one ovarian cancer.
risk criteria are built around established guidelines for its
diagnosis (table 4). The International Consortium on
Hereditary Nonpolyposis Colorectal Cancer (ICG-HNPCC)
established a set of clinical diagnostic criteria, known as
the Amsterdam criteria, to promote consistency among
research studies. 25 The Amsterdam criteria have been
criticised for not taking into account the extracolonic cancers
that are often associated with HNPCC. To resolve this
problem, new clinical criteria (Amsterdam II criteria) were
proposed 26 to identify families that are very likely to have
HNPCC. However, these criteria are not intended to serve as a
guide to exclude families from cancer genetics consultation or
mutation analysis. Therefore less restrictive criteria were
adopted for the high risk colon category by extending the
Amsterdam II criteria to include stomach, ovarian, and
pancreatic cancers in the list of extracolonic cancers, because
of data consistently associating them with HNPCC. Uterine
and renal pelvic cancers are also HNPCC associated cancers
but are too specific to be included on most cancer family
history questionnaires. “Kidney” cancer was accepted in lieu
of these cancers for the purposes of mass screening. The exact
subtype can be determined at subsequent interactions.
Finally, for families with three cases of HNPCC associated
cancers, we removed the age (one diagnosis under age 50)
and multiple generation requirements in order to be more
inclusive.

Two additional criteria were adopted for the high risk
HNPCC category. These include any family with a first degree
relative diagnosed with colon cancer under the age of 50 or a
first or second degree relative with two or more HNPCC
associated cancers. This is based on the large population
based HNPCC screening study in Finland. 27 Using these
criteria, 27 of the 28 patients with colorectal cancer found to
carry HNPCC mutations in that study would have been
identified. Moreover, the Bethesda guidelines suggest that
further evaluation for HNPCC (through microsatellite
instability testing) is warranted in any individual with more
than one HNPCC associated cancer and for anyone diagnosed
with colon cancer under the age of 45. 28 The Bethesda criteria
were recently found to have the highest sensitivity in
detecting mutation positive HNPCC cases when compared
with either of the two Amsterdam criteria. 29 The American
Gastroenterology Association adjusted the Bethesda criteria
to suggest microsatellite instability for any colorectal cancer
diagnosed under age 50, providing further support for this
age cut off. 30 At a recent follow up meeting (11–13 December
2002) for the revision of the Bethesda guidelines, it was
decided to increase the age from 45 to 50. For the criteria
presented here, the age of 50 was selected to maintain
sensitivity while balancing the need to limit unnecessary
“false positive” referrals. Around 8% of individuals diagnosed
with colorectal cancer are under the age of 50 according to
the population based series of colorectal cancer cases in
Finland. 30

Moderate risk colon cancer criteria

The population data regarding lifetime risks for colorectal
cancer and not the likelihood of having an HNPCC gene
mutation were reviewed to develop the moderate risk
category. It has been found that an individual with one first
degree relative diagnosed with colorectal cancer under the
age of 45 has a relative risk of 3.7 to 6.4 for developing this
condition. 30, 31 If the relative with colorectal cancer was
diagnosed after the age of 45, the relative risk decreased to
1.8 to 2.7. For individuals with two first degree relatives
diagnosed at any age, the relative risk was 5.7. 31 Individuals
with one first degree and one second degree relative diag-
nosed with colorectal cancer had a relative risk of 4.16. 31 Our
moderate risk criteria, therefore, include individuals with two
first degree relatives or one first degree and one second
degree relative with colorectal cancer, when the first degree
relative is diagnosed at age 50 or greater (otherwise they
would meet the high risk criteria).

High risk polyposis

It is advisable to include a question in all cancer family
history collection tools to ascertain whether any family
members have been diagnosed with polyposis (defined
loosely as more than 10 colonic polyps) in their lifetime.
Anyone answering in the affirmative should be referred for
cancer genetics consultation. Pathology reports can be
reviewed and a physical examination done to evaluate the
family further for the possibility of familial adenomatous
polyposis, MYH polyposis, Peutz-Jeghers syndrome, juvenile
polyposis, mixed polyposis, or Cowden syndrome/Bannayan–
Ruvalcaba–Riley syndrome.

Prostate cancer criteria

High risk prostate cancer criteria

Researchers are actively studying families with multiple cases
of prostate cancer in a search for the genes responsible for
hereditary prostate cancer. This search has been complicated
by the discovery that many loci (HPC1, HPC2, CELFC2, and
PCAP) are involved. To date, only two genes—HPC1/RNASEL, HPC2/ELAC2)—have been isolated, but each accounts for
very few hereditary cases. The high risk prostate criteria are
based on the fact that families with more than three affected
individuals are eligible for prostate cancer genetic research
studies and could benefit from cancer genetics consultation.
The relaxed criteria requiring two affected individuals (one
diagnosed under the age of 60) are included in order to
accommodate possible X linked inheritance patterns; these
could limit the number of affected individuals because of the
lack of male to male transmission and the unaffected status of
obligate carrier mothers.

Moderate risk prostate cancer criteria

The moderate risk prostate criteria are based on population
studies of prostate cancer risk. These studies suggest that
first degree relatives of prostate cancer patients have a
relative risk of 2.0 to 3.2 for developing the disease. 40– 43
Although prostate cancer is more common in African-
Americans in the USA, the relative risk for developing
prostate cancer when a first degree relative was affected
was found to be similar among black and white individuals,
and our risk assessment criteria do not take race into account.
These relative risks infer that individuals with a single first
degree relative affected by prostate cancer should meet the
moderate risk criteria; however, we elected to add an age
restriction so that individuals only meet this criterion if the
first degree relative was diagnosed under the age of 60. In the
USA, the American Cancer Society recommends that men
begin prostate cancer screening at age 50. As it is generally
agreed that surveillance should begin at least 10 years before
the earliest diagnosis in the family, individuals would only
need to begin prostate cancer screening early (before the age
of 50) if they have a first degree relative diagnosed under the
age of 60.

Steinberg et al also found a relative risk of 4.9 for
individuals with two first degree relatives affected by
prostate cancer and 8.8 for individuals with one first
degree and one second degree relative affected. 44 Given
these high relative risks (>2.0) for developing prostate
cancer, the moderate risk criteria include both individuals
with two first degree relatives with prostate cancer over
the age of 60, and also those with one first degree and one
second degree relative affected by prostate cancer over
the age of 60.
Melanoma criteria

High risk melanoma criteria

A review by the Melanoma Genetics Consortium found that 20–40% of families with three or more affected first degree relatives have a mutation in the CDKN2A gene, while mutations were only found in 5% of families with two affected first degree relatives.98 Approximately 15% of individuals with multiple primary melanomas will be found to have a CDKN2A mutation.99 Based on these data, our high risk criteria require at least three relatives affected by melanoma in at least two generations, or any individual with multiple primaries. In addition, there is evidence that mutations in the CDKN2A gene also lead to an increased risk for pancreatic cancer.100–102 Accordingly, pancreatic cancers are included in the risk criteria.

Moderate risk melanoma criteria

Population studies have shown that individuals with one or more first degree relatives affected by melanoma have a relative risk of 2 to 3 for developing melanoma.103 Therefore increased surveillance is recommended for anyone with at least one first degree relative with melanoma. Increased surveillance for melanoma is non-invasive and includes more frequent clinical skin examinations, full body photography, and routine self examination, more frequent clinical skin examinations, full body photography, and annual physical examination with appropriate biochemical testing and thyroid ultrasound as indicated.

Li-fraumeni criteria

High risk Li-Fraumeni syndrome criteria

The classic diagnostic criteria for the Li-Fraumeni syndrome (LFS) are based on the original epidemiological studies of Li-Fraumeni kindreds.50–52 Families meeting these criteria have a 71% chance of having a germline TP53 mutation.51 53 It is quite rare for a family to meet the classic definition of LFS, however, so broader criteria were developed to ensure that all potential LFS families are detected. Li-Fraumeni-like (LFL) families have been defined in many different ways.50 54 Depending on the definition of LFL used, as many as 22% are found to have germline mutations in TP53. For these high risk Li-Fraumeni criteria, the NCCN LFL criteria were adopted.2 As it is unlikely that a family history questionnaire will identify the specific adrenal pathology associated with LFS (adrenocortical tumours), our criteria allow for any type of adrenal tumour. However, if there is a documented case of adrenocortical carcinoma, the family should be referred for cancer genetics consultation (below).

Multiple endocrine neoplasias

It is difficult to provide an assessment for the multiple endocrine neoplasia (MEN) syndromes on the basis of information obtained in a family history collection tool because of the importance of the histopathology of each of the component tumours. For example, it is reasonable to ask about a family history of thyroid cancer but one cannot assume that family members would know the specific histology (papillary, follicular, or medullary). Similarly, one cannot easily assess by questionnaire whether a pancreatic cancer is an adenocarcinoma or an islet cell tumour, or whether an adrenal tumour is a phaeochromocytoma or another subtype. In addition, many of the component tumours are not malignant—such as parathyroid hyperplasia and pituitary adenomas—so individuals may not include these diagnoses in a cancer history.

High risk MEN 1 criteria

As the diagnosis of MEN 1 is based on the presence of pancreatic islet cell tumours, pituitary adenomas, and parathyroid hyperplasia, the risk assessment criteria attempt to identify families with at least two of these features. MEN 1 has historically been diagnosed when two close relatives or a single individual have at least two of the principal clinical features.55–57 A cancer genetics consultation is appropriate for families with two cases of pancreatic (islet cell) cancer, parathyroid (hyperplasia), or pituitary adenoma in first degree or second degree relatives (both diagnoses can occur in the same person).

High risk thyroid cancer criteria (MEN 2 and familial non-medullary thyroid cancer)

The features of MEN 2 include medullary thyroid cancer, phaeochromocytomas, and parathyroid hyperplasia. If a family has a single case of medullary thyroid cancer they should be referred for cancer genetic consultation because the likelihood of having a RET gene mutation exceeds 10%.58 However, it would be unusual for individuals to be able to report the exact histology of a relative's thyroid cancer. As the medullary histology is rare among all thyroid cancers, it would not be prudent to refer every person who had a single relative with “thyroid cancer” for cancer genetic consultation. For this reason, when one is unsure of the thyroid cancer histology, one additional feature is required for a family to be referred for a cancer genetics consultation. Even if the thyroid cancers in these families are non-medullary, they may be eligible for research studies aiming to identify the genes responsible for familial non-medullary thyroid cancer.

Moderate risk thyroid cancer criteria

It is known that individuals with a single first degree relative diagnosed with thyroid cancer have a relative risk of >2.0 for developing thyroid cancer regardless of subtype.59 60 These individuals may want to talk to their physician about increased thyroid cancer surveillance that might include annual physical examination with appropriate biochemical testing and thyroid ultrasound as indicated.

Single cases of cancer requiring cancer genetics consultation

There is evidence that a single individual diagnosed with medullary thyroid cancer,61 adrenocortical carcinoma,62 phaeochromocytoma,63 or paraganglioma (including carotid body tumours and glomus tumours)64 has a >10% chance of having a hereditary cancer susceptibility syndrome. Therefore, in keeping with the other high risk categories, we recommend that individuals diagnosed with the above cancers, or those with a first degree relative diagnosed with these cancers, be referred for cancer genetics consultation regardless of their age at diagnosis or their family history.

Wilms’ tumour and retinoblastoma are known to be hereditary when bilateral or multifocal. As this is difficult to determine by questionnaire, one can either refer all individuals with these rare tumour types or risk missing some hereditary cases. Thus we have elected to suggest referral of all patients with a diagnosis of these tumours in themselves or a first degree relative for further consultation. Pathology reports can be reviewed at that time to determine whether or not the tumours are likely to be hereditary.

Familial aggregation of cancer

This broad category is critical for identifying families with cancer clusters suggestive of a hereditary predisposition. A cancer cluster can loosely be defined when a family has more cases of a particular cancer than one would expect to see by chance alone. To capture these clusters, the familial aggregation criteria state that any family with three cases (in first or second degree relatives) of the same malignancy on one side of the family should be considered high risk and
be referred for a cancer genetics consultation. There are known cancer predisposition genes for some of these clusters—for example, basal cell naevus syndrome (PTCH), familial gastric cancer (CDH1), familial papillary renal cell carcinoma (MET), and renal cell cancers associated with Von Hippel Lindau disease (VHL) and Birt-Hogg-Dubé syndrome (BHD). For other cancer clusters, the responsible genes are yet to be identified. In these cases, families can be offered participation in research studies and familial tumour registries (that is, familial non-papillary renal cell carcinomas, familial pancreatic cancer, familial testicular cancer, familial oesophageal cancer, and familial haematological malignancies).

### Other hereditary cancer predisposition syndromes

Cancer susceptibility syndromes not specifically addressed in these risk assessment criteria include Cowden syndrome, Von Hippel Lindau syndrome, tuberous sclerosis, neurofibromatosis, Carney complex, multiple osteochondromatosis, familial paraganglioma, Werner syndrome, and chromosome fragility syndromes (ataxia-telangiectasia, Bloom syndrome, Fanconi anaemia, and xeroderma pigmentosum). These syndromes include many non-cancer features and physical stigmata that are impossible to address in a large scale family history survey format. It is likely that families with Cowden syndrome could be identified by the high risk polyposis, thyroid, or breast-ovarian criteria. Some families with Von Hippel Lindau syndrome could be identified by a familial aggregation of renal cancers or apparently isolated presentations of phaeochromocytoma. In addition, the chromosome fragility and progeroid syndromes, Werner syndrome, and Rothmund–Thomson syndrome are usually autosomal recessive conditions where the diagnosis is made on the basis of dysmorphic features in the proband. Often only one family member is affected, making it difficult to detect these patients from their cancer family history.

### Use of the risk assessment criteria

Two free standing family history risk assessment units using touch screen computer technology have been placed in the lobby of the James Cancer Hospital/Comprehensive Cancer Center and the JamesCare Dublin ambulatory care facility. Patients, family members, or passers by can use these machines on a voluntary basis to provide information about their personal cancer history and their family history of cancer in first and second degree relatives. Information on family history was provided by 4360 users between mid-1999 and April 2002. These risk assessment criteria were applied and users were categorised into high, moderate, and average risk groups. Of all users, 651 (14.9%) were found to be high risk, 598 (13.7%) were found to be moderate risk, and 2598 (59.6%) were found to be average risk, based only on their family history. The limitations of the risk assessment can be discussed in the risk notification communication process. In addition, family histories are dynamic and need to be updated regularly because additional relatives may be diagnosed with cancer since the last “risk assessment” occurred.

The importance of documentation of recommendations for both cancer genetics consultation and appropriate cancer surveillance based on family history assessment cannot be overemphasised. Identifying high risk families can save lives. For example, if a MEN 2A family is identified, counselling and genetic testing will lead to prophylactic thyroidectomy in mutation positive children in the family. This can prevent the development of medullary thyroid cancer. Likewise, there is evidence that beginning colonoscopies earlier and repeating them more often will dramatically reduce (and maybe eliminate) deaths from colon cancer in HNPCC families. This should apply to individuals meeting moderate risk colon cancer criteria as well.

There will not be 100% compliance with the recommendation for a cancer genetics consultation. Thus high risk patients must be alerted to the risk for all cancers associated with a hereditary cancer syndrome. This is especially important because many families with site specific cancers are not aware of the increased risks for other associated cancers.

While published reports have defined some of the hereditary cancer syndromes, risk assessment criteria vary and expert opinion was also critical in the development of these criteria. Thus formal molecular based validation is necessary. Large scale validation may best be undertaken by an organisation such as the NCCN or a large consortium. Ideally, molecular analysis of large populations should be used to determine the percentage of hereditary cancer syndrome families that would be identified by and missed by the high risk criteria.

Cancer risk assessment criteria will continue to evolve as the definitions of hereditary cancer susceptibility syndromes are further refined. Adoption and oversight by a national body would promote the timely revision and standardisation of the risk assessment criteria as new cancer syndromes are discovered and our current knowledge changes. As risk assessment is only as accurate as the family history provided, the importance of documentation is evident.

Increasing numbers of clinicians are striving to document adequate family history information to determine whether a hereditary cancer susceptibility exists, and to notify patients of their risk assessment. While the family history collection tools and means of risk notification may vary, the risk assessment criteria should be standardised. This review
presents the first comprehensive evidence based risk assessment criteria for hereditary cancer syndromes, which constitute a first approximation of a uniform approach to familial cancer risk assessment that is usable in clinical practice.

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Authors’ affiliations

H Hampel, K Sweet, J A Westman, C Eng, Clinical Cancer Genetics and Human Cancer Genetics Programs, The Ohio State University, Columbus, Ohio, USA.
K Offit, Clinical Genetics Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

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