GENETIC COUNSELLING AND GENETIC TESTING: HEREDITARY CANCER SYNDROMES

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Dr Lee Soo Chin
Consultant
Department of Haematology-Oncology
National University Hospital

In this paper, issues that are related to genetic counselling and genetic testing of hereditary cancer syndromes are discussed. These are largely adult-onset syndromes, and many of the issues will be related to the individual and the family in the adult context. Specific issues such as testing in minors and reproductive issues will be discussed only briefly, predominantly in the context of familial adenomatous polyposis.

Introduction

A number of distinct hereditary cancer syndromes have been described in the last decade, including familial adenomatous polyposis,[1, 2] hereditary breast and ovarian cancer syndrome due to *BRCA1/2* mutations,[3, 4] hereditary non-polyposis colorectal cancer,[5] and Li Fraumeni syndrome.[6] The causative genes have been elucidated for some of these syndromes,[1, 3, 4, 7-11] and genetic testing to identify mutation carriers of certain distinct hereditary cancer syndromes is now clinically available.[12-16] As genetic testing is a complex issue that may have medical, psychological, ethical, social, and legal implications on the individual and the family, pre- and post-test genetic counselling is an integral part of the testing process.[17] Many reputable laboratories offering cancer genetic testing require pre-test counselling before processing the sample.

Specialised clinics providing cancer risk assessment and genetic counselling have been established in the two major cancer centres in Singapore, National University Hospital and the National Cancer Centre, for about four years. The common hereditary cancer syndromes for which genetic testing is currently available to local patients include the following:

1. *BRCA1/2* sequencing for hereditary breast and ovarian cancer syndrome.
2. *hMLH1/hMSH2* sequencing for hereditary non-polyposis colorectal cancer.
3. Protein truncation test for the *APC* gene for familial adenomatous polyposis.
4. Microsatellite instability testing for hereditary non-polyposis colorectal cancer.[18]
5. Testing for common mutations in the RET-proto-oncogene for patients suspected to have multiple endocrine neoplasia type II.[19, 20]

Who Should Receive Genetic Counselling?

Only individuals or families suspected clinically to have hereditary cancer syndrome (strong familial cancer clustering or young onset cancer) will benefit from genetic counselling and genetic testing.[17] Genetic counselling and genetic testing for hereditary cancer syndromes will not benefit the general risk patient and should not be offered routinely.

As a general rule, genetic counselling and the option of genetic testing in the context of hereditary cancer syndromes should only be offered to adults above the age of 18 who are able to make an autonomous and informed decision regarding genetic testing (*see testing of minors for exceptions*).

Who Should Conduct Genetic Counselling?

Pre- and post-test genetic counselling is an integral part of genetic testing. A person who understands the medical, psychological, social, ethical, and legal implications of genetic testing should conduct the counselling. The counsellor should be able to evaluate hereditary cancer syndromes, be familiar with indications for genetic testing, be able to interpret test results, and be familiar with potential psychological, ethical, social, and legal issues that may arise. Inadequate pre-test counselling may result in ethical, social, and legal implications that were not anticipated by the patient. In the United States, a physician, nurse educator, or genetic counsellor with appropriate training typically carries out cancer genetic counselling. The American Society of Clinical Oncology periodically holds workshops to update management issues in cancer genetics for providers, and has developed continuing medical education materials.[21, 22] Providers may also be credentialed in Familial Cancer Risk Assessment and Management through the Institute of Clinical Evaluation, USA. Two medical oncologists in Singapore have been credentialed in this way.

Guidelines for Cancer Predisposition Testing

In 1996, the American Society of Clinical Oncology recommends that practicing physicians recognise three categories of indications for genetic testing of hereditary cancer syndromes:[17]

Category I

Category I includes families with well-defined hereditary cancer syndromes, for which genetic test results will change medical care. Category I is considered standard management. For example, genetic testing for familial adenomatous polyposis is considered standard as effective surveillance and preventive options exists for mutation carriers.[12, 23, 24] Other conditions that are included in Category I include multiple endocrine neoplasia type II[19, 20, 25] and retinoblastoma.[26, 27]

Category II

Category II includes hereditary syndromes in which the medical benefit of identifying a mutation carrier is presumed but not established. Genetic testing of these conditions may provide some medical benefit, but the risks and limitations must be extensively discussed with the patient. In this category, a positive test result may lead to earlier surveillance or consideration of preventive options, although these risk management options have not been proven to reduce morbidity and mortality. A negative test result may be of value if it occurs in the context of a known mutation in the family. Examples include *BRCA1/2* in hereditary breast and ovarian cancer syndrome and *hMLH1*/*hMSH2* in hereditary non-polyposis colorectal cancer.[28, 29]

Category III

Category III includes hereditary syndromes for which genetic testing is unlikely to change clinical management. This category includes syndromes in which germline mutations have been identified only in a small number of families, such that genetic testing is of low yield and likely to be uninformative. It also includes syndromes for which the medical benefits of identifying mutation carriers are not apparent. Examples of syndromes included in Category III include *CDKN2A* for melanoma families[30, 31] and *STK11* for Peutz-Jeghers syndrome.[32, 33]

The American Society of Clinical Oncology recommends offering clinical genetic testing only for syndromes in Category I and Category II. Genetic testing for Category III is considered research with unknown clinical implications and should not be offered in the clinical setting.[17]

Pre-Test Counselling

This is a process in which the patient and/or the family is given information on the nature of the hereditary cancer syndrome that is being suspected, the tests available to make a diagnosis, and the screening and preventive recommendations. This is a non-directive and interactive process, and the patient is given information on potential benefits and risks of testing to facilitate an informed decision.[34-36]

Components of pre-test counselling[21]

Assess
- Personal and family medical history
- Risk perception and motivation for testing

Educate
- Basic genetics and inheritance
- Cancer genetics and risk

Discuss
- Potential benefits, risks, and limitations of genetic testing
- Test procedure

- Management options (surveillance and preventive measures)
- Anticipatory guidance
- Psychological issues

These issues are discussed carefully and extensively to allow the patient to make an informed decision regarding genetic testing. Counselling should be conducted in a language the patient understands and in a manner appropriate for the patient's intellect and level of medical knowledge. Printed materials summarising key issues that have been discussed can facilitate the retention of information. For example, patient education pamphlets on hereditary breast and colorectal cancer syndromes are available to patients counselled at the Clinical Cancer Genetics Service in the National University Hospital. More than one session may be required to discuss all issues and to allow the patient to assimilate the information. Adequate time should be given to patients to make a decision regarding genetic testing.

Assessment of Risk

The patient's personal and family cancer history is reviewed to determine the likelihood that the patient has a hereditary cancer syndrome.[37-40] In general, genetic testing is only recommended if the predicted risk of finding a mutation is at least 10%.

Exploration on Risk Perception and Motivations for Genetic Testing

The patient's perception of cancer risk and risk of having a hereditary cancer syndrome is assessed. The motivations for seeking genetic counselling / genetic testing are explored.[41-45] These may include using genetic information to make medical decisions (e.g. screening, preventive strategies), to help family members such as children and siblings, to make reproductive decisions or other major life decisions, or for empowerment, etc. By understanding the motivations for seeking genetic testing, the counsellor may assess whether the patient's expectations may be met through genetic testing. For example, a high-risk breast cancer patient who hopes to seek reassurance that she does not have a hereditary condition, through genetic testing as an index patient, is unlikely to have her expectation met, as a negative test result in such a situation is uninformative. On the other hand, it would be reasonable for a patient to undergo *BRCA1/2* genetic testing with a view to proceed with prophylactic bilateral mastectomy if tested positive.

Education on Basic Genetics and Inheritance

The patient and the family is educated on basic genetics, including the likelihood that the patient may have the syndrome, the mode of inheritance of the hereditary cancer syndrome in question, the cancer risks if one is found to have the syndrome,[46-49] and the medical implications on the individual and his family. Testing strategies to confirm the

diagnosis are discussed, including the interpretation of test results and the limitations of testing.

Process of Informed Consent

To facilitate informed consent, the potential benefits, risks and limitations of genetic testing are discussed.[17, 34, 50, 51]

Potential benefits of genetic testing

The potential benefits of genetic testing include identifying the cause of young cancers or clustering of cancers in the family, accurate cancer risk assessment for the individual and the family, the use of the risk assessment information to plan screening[52-55] and preventive measures,[20, 56-61] and the use of the information to proceed with predictive gene testing of cancer-free family members. The information may empower the individual and increase compliance to screening and preventive measures.[62-64]

Potential risks of genetic testing

The process of genetic counselling or genetic testing may cause psychological distress[65-68] as the individual faces the prospect of possibly having a hereditary condition and the difficult decision of whether to undergo genetic testing to confirm the diagnosis. As genetic testing may affect other family members, a decision for or against testing can cause changes in family dynamics, particularly when different family members have different motivations or share different views on testing. A positive gene test result may also cause potential genetic discrimination by employers and insurers.[69-71] An indeterminate result or a negative result in an index patient is uninformative but may cause confusion or a false sense of security in the patient, thus reducing compliance to screening.

Limitations of genetic testing

One of the major limitations of genetic testing is the fact that a negative test result in an index patient does not exclude the possibility of a hereditary condition. This is because several genes may be implicated in a particular hereditary syndrome, and only a few of the most important may be tested clinically. Furthermore, due to technical limitations, not all mutations in the gene of interest are detectable. In addition, mutations of uncertain significance may be identified.[72] These are missense mutations that are neither clearly benign polymorphisms nor deleterious. Mutations of uncertain significance and a negative gene test result in an index patient are uninformative, and will not help the patient. Even if an individual tests positive for a deleterious mutation, it is still only probable and not certain that cancer will develop. Similarly, an individual who tested negative for a mutation that existed in his family is simply not at risk for hereditary cancer, but may still develop sporadic cancer. Finally, as many hereditary cancer syndromes have only been characterised for a relatively short period of time,

many interventions that are currently recommended clinically have unproven efficacy due to the lack of long-term data.[54, 55, 59, 60]

Management Options

Management options available to the patients are discussed. For proven mutation carriers, this may include early surveillance programs, and preventive measures such as preventive medications or preventive surgery. For example, celecoxib reduces the number of adenomatous polyps in familial adenomatous polyposis,[73] preventive total colectomy reduces colorectal cancer risk in familial adenomatous polyposis,[74, 75] and preventive mastectomy and oophorectomy reduces breast cancer risk in *BRCA1/2* mutation carriers.[59, 60] Patients are also given management options based on risk estimates from personal and medical history if they choose not to be tested or if test results are uninformative. The individual may then compare the two sets of management options and make an individual decision regarding the potential impact of genetic testing on management options.

Anticipatory Guidance

The technique of anticipatory guidance may be used to facilitate decision-making during the genetic counselling process.[21] The patient is given a hypothetical situation and encouraged to discuss how he or she might feel or do in that situation. For example, the patient may be asked 'How would you feel if you tested positive for a gene mutation?' or 'How do you think genetic testing may help you or your family?' The same technique may be used to help patients consider how their family may respond to genetic testing, or their possible reactions to the patient being a mutation carrier. This can help patients consider how, when, and which family members they wish to share information with.[76] This technique allows the patient to anticipate the potential impact of genetic testing on themselves and their family.

Addressing Potential Psychological Issues Related to Genetic Testing

A number of psychological issues may arise as a result of genetic counselling or genetic testing.[65-68, 77, 78] Patients may experience anxiety or fear with the prospect of being labelled as someone with a 'bad gene'. Individuals may feel guilty that they have a 'bad gene' that they could potentially pass to their children. A positive gene test result may lead to loss of self-esteem or depression. Mutation carriers may also face stigmatisation by family members, friends, the workplace, or society. Identifying a gene mutation in the family could impact family dynamics, dividing the family into two distinct groups: a high-risk group with a 'bad gene' and a low-risk group with the 'good gene'. Mutation carriers or close family members of mutation carriers may experience grief or depression because of anticipatory loss.

Physicians/genetic counsellors should be cognizant of these potential psychological issues while counselling patients. During the process, the patient's experience with cancer, perceptions of cancer, its prognosis, and its treatment options are explored to anticipate reactions to test results. Patients' perceptions on prophylactic measures such as surgery to reduce cancer risk should also be explored. The involvement of a psychiatrist early in the process could be important in patients at high-risk for psychological events. In many established centres in the west, the cancer genetics team often comprises of a psychiatrist to manage such issues.

Genetic Testing Procedure

This generally involves a blood test. Genetic testing performed for clinical use should be carried out in a certified laboratory.

Testing of Index Patients

The initial testing of a cancer-affected individual for a hereditary cancer syndrome is termed testing the index patient. Testing the index patient is laborious and expensive, as the entire gene of suspicion has to be scanned to identify a mutation. The major limitation is that the inability to identify a mutation does not exclude a hereditary condition. A cancer-free subject cannot be tested unless a cancer-affected index patient has been tested in the family and a mutation identified. Possible outcomes of testing index patients include finding a mutation (positive result, informative), finding no mutation (negative result, uninformative), or finding a mutation of uncertain significance (uninformative).

Predictive Testing

Once a mutation is identified in an index patient, the subsequent testing of cancer-free family members to determine if they carry the same mutation is termed predictive testing. This is highly specific, testing only for the presence or absence of the particular mutation that has been identified in the index patient. Test results are either positive or negative for a mutation, both of which are informative results.

Post-Test Counselling

Issues that will be discussed during this session include:

i. Test disclosure.
ii. Test interpretation (meaning of a positive, negative and indeterminate test result).[13, 72]
iii. Screening recommendations based on genetic test result.
iv. Preventive recommendations based on genetic test result.
v. Predictive testing of other family members if a mutation is identified.

vi. Addressing psychological issues in response to genetic test result.
vii. Addressing ethical and social concerns in relation to genetic test result.

Procedure of test disclosure

During this session, genetic test results are conveyed to the patient. Test disclosure via telephone or mail is strongly discouraged, and is best conducted face-to-face. This allows the counsellor to assess the patient's response to the test results, and to provide clarification and emotional support.[21] Results are generally given on a one-to-one basis, even if multiple family members were tested at the same sitting. This allows each individual to have privacy while receiving the test results and expressing reactions, without having to consider the family's reactions. After disclosing individual results and obtaining consent to share test results, the family can be counselled as a group to address further issues, particularly those that may affect family dynamics.[79]

During the post-test counselling session, apart from discussing the medical implications of the genetic test result, a good part of the session may be spent on evaluating potential psychological and social impact on the individual and the family.

Addressing Psychological Issues

Possible responses to a positive result

Patients may become depressed when they learn that they carry a mutation in a cancer-susceptibility gene.[80] This is because an otherwise healthy individual is now predicted to have a high risk of cancer and there is no medical intervention to correct the defective genes. Patients may feel guilty[44] that they have had children and could have passed the mutation to them. On the other hand, many patients who have borne the burden of having a strong family history of cancer for years may actually experience feelings of relief and a sense of closure when they receive a positive test result. Some may feel that uncertainty has been removed, and they are now able to 'move on' and focus on surveillance and preventive measures. Identifying the causative gene mutation that accounted for the patient's cancer or his/her family's cancers can give a sense of empowerment, as the patient may now feel 'in control'.

Possible responses to a negative result

In the setting of an identified mutation in the family, a negative test result constitutes a true negative. This result means that the individual is at normal risk for cancer despite the strong family history, and does not require early surveillance that his mutation-carrying family members may require. Relief is a common reaction.[41] Paradoxically, some individuals may experience survivor guilt on learning that they have 'escaped' and not inherited the 'bad gene'.[81] Some may still feel anxiety despite reassurance that they are at normal risk of cancer, and may be reluctant to reduce surveillance.[64]

Possible responses to an uninformative result

Failure to identify a mutation in an index patient and identification of a mutation of uncertain significance are two limitations of genetic testing. Both results are uninformative. This may cause frustration or disappointment, as the test result cannot help the patient. Such a result may cause confusion in the patient, or even worse, a false sense of reassurance. It is thus very important to stress to the patient that this is an uninformative result, and not a true negative result. An indeterminate result may also lead to increased anxiety about cancer risk and management.

Addressing Ethical, Legal and Social Issues

Ethical, legal, or social concerns in relation to genetic counselling or genetic testing

A number of ethical, legal or social issues may arise in relation to genetic counselling or genetic testing. Genetic counselling for hereditary cancer syndromes should therefore be restricted to trained medical practitioners (physicians or genetic counsellors) who are able to explain these issues during the pre-test counselling process so that the patient may make an informed decision regarding genetic testing. It is important to emphasise to the patient that genetic testing is more complex than most other medical tests (e.g. cholesterol testing, liver function testing). This is because while most other medical tests affect only the individual, genetic testing could have implications on other members. Genetic test results may also have social and ethical implications. Inadequate pre-test counselling may result in ethical, social, and legal implications that were not anticipated by the patient.

Ethical issues in relation to genetic testing [17, 21, 82]

Autonomy versus Beneficence

This is a situation whereby there is conflict between respecting patient autonomy and beneficence to the patient. For example, patient A tests positive for a mutation in a cancer-susceptibility gene but decides against receiving her test results. The physician knows that patient A is at very high risk of developing cancer. The physician now faces the dilemma of promoting patient beneficence or challenging patient autonomy by disclosing test results. The physician may have to counsel patient A again to explain the implications of the result. If patient A insists on not knowing the results, the physician would generally recommend appropriate screening and preventive options without revealing test results.

Autonomy versus Beneficence to others

As an example, patient A learns that she carries a mutation in a cancer-susceptibility gene, but refuses to share the results with her family, including her sisters, her husband, and her children. The physician now faces the dilemma between respecting the patient's autonomy and beneficence to the patient's family

members. The physician may have to counsel patient A to explain the implications of her result on her family. If patient A insists on not sharing her test result, immediate family members may be recommended to undergo frequent screening as would be done for high-risk individuals, without revealing test results (*See '7.3.2. Duty to warn family members'*).

Unwanted disclosure

This may occur in a situation when a key person in the family refuses testing. For example, patient A's maternal aunt tested positive for a mutation in a cancer-susceptibility gene. Patient A wants to know if she carries the same mutation. Under optimal circumstances, patient A's mother would be tested first. Patient A would only be tested if her mother carried a mutation. However, patient A's mother refuses testing as she is afraid to learn that she may be a gene carrier. Given this situation, patient A, who is keen to know her mutation status, proceeds with testing, and finds that she carries the same mutation as her maternal aunt. This means that her mother must also carry the same mutation (obligate carrier). If patient A undertakes certain preventive measures (e.g. undergo bilateral preventive mastectomy), her mother may indirectly learn of her own genetic status.

Coercion

In the arena of genetic testing, in order for a cancer-free individual to undergo predictive testing, a high-risk cancer-affected family member (index patient) has to be tested first. A situation may be encountered in which cancer-free family members are keen to have genetic testing, while the cancer-affected family member is not. The former may then coerce the latter to undergo testing.

Reproductive decisions

Individuals who have yet to complete their families may be concerned to know how genetic testing may impact reproductive decisions. Some individuals want to know about prenatal diagnosis.[83] As hereditary cancer syndromes are not uniformly lethal, and the manifestation is in adulthood, prenatal diagnosis with a view to terminate pregnancy is not generally recommended. Patients should be counselled that there is a 50% chance that the foetus is normal, inheriting the defective gene does not mean that cancer will definitely develop, and that future medical advances, including gene therapy, improved cancer screening, diagnosis, treatment and prevention, may become available to the next generation, and may significantly reduce cancer risk or improve cancer cure rates.

Testing of minors[84, 85]

Genetic testing should only be considered for children if the test is for a childhood-onset disease for which there are known effective interventions, and if the test can be adequately interpreted. Generally, genetic testing should be performed just before the age at which screening for the disease would be appropriate. Examples

of hereditary cancer syndromes for which minors may be tested include familial adenomatous polyposis, multiple endocrine neoplasia type IIA and IIB, and retinoblastoma.

If the medical benefits from a genetic test will not be realised in childhood, genetic testing should be postponed until the child reaches adulthood and able to make an autonomous and informed decision.[84]

Genetic testing for minors for familial adenomatous polyposis

This is a condition due to germline mutations in the adenomatous polyposis coli (*APC*) gene, resulting in a propensity to form hundreds to thousands of adenomatous polyps in the colon, and a virtually 100% chance of developing colorectal cancer. Polyps typically form in the teens, and cancer development may occur as early as late teens to early twenties. Mutation carriers are recommended to start screening flexible sigmoidoscopy at age 12-13, and would benefit from prophylactic total colectomy to reduce the risk of cancer. Therefore, the children of a known mutation carrier may undergo genetic counselling with a view to predictive genetic testing as early as age 10-12, to determine if they are mutation carriers.[12, 21, 23, 24] Such counselling is best carried out by physicians or counsellors trained in counselling children. Counselling is typically carried out in the presence of the parents, and assent from the child should be obtained before testing may proceed.

Special issues in testing minors [84, 85]

If a minor is to be counselled about genetic testing, the child's autonomy should be respected. While it is recognised that the child may not be able to provide consent, assent from the child is required. Counselling should be conducted in a manner that is appropriate for the child's intellectual capacity and developmental stage. It is also important to understand the family dynamics, keeping in mind the possibility of fragile child syndrome if the child's test is positive, potential impact on parent-child bonding, and potential impact on the other siblings. Furthermore, when a young child undergoes testing, providers and parents should plan to share the results (whether positive or negative) with the child when he or she has sufficient cognitive and emotional maturity to understand them. The provider should convey this expectation to the parents during pre-test counselling. Another ethical dilemma in testing minors is the deprivation of the child of the choice whether to undertake genetic testing as an adult.

Legal implications of genetic testing

Duty to warn family members

There have been cases in the United States where legal action was taken against clinicians for failure to warn family members of their risk when a patient is diagnosed with hereditary cancer.[86-88] The American Society of Clinical Oncology

has recently updated its policy statement on genetic testing, and reiterated its stand on protecting patient confidentiality and fulfilling obligations to at-risk relatives through communication of familial risk to the person undergoing testing.[82] The American Society of Human Genetics concurs with the view, but states that the principle of confidentiality is not absolute, and that disclosure may be permitted if all the following conditions are met: (a) attempts to encourage disclosure on the part of the patient have failed; (b) the harm is highly likely to occur and is serious and foreseeable; (c) the at-risk relative is identifiable; and (d) the disease is preventable, treatable, or medically accepted standards indicate that early monitoring will reduce the genetic risk. The society suggests an approach of warning the patient during pre-test counselling of the circumstances that would result in disclosure of genetic information to other family members, regardless of the patient's intentions to disclose.[89]

Social implications of genetic testing

Genetic discrimination

Health and life insurance [69, 71, 90]

A cancer-free individual who tests positive for a genetic mutation that predicts high cancer risk may face discrimination when applying for health and life insurance. Such an individual may have difficulty obtaining insurance coverage for cancer. More insurance companies, especially in the West, are beginning to specifically include statements on genetic testing in the insurance application forms. There are now laws in the United States that protect individuals with a hereditary cancer syndrome from being discriminated against by insurance companies.[91]

Employment[70]

Similarly, a cancer-free individual who carries a mutation in a cancer susceptibility gene may face discrimination at the workplace. In some states in America, laws have been passed to prohibit or restrict the use of genetic tests as a condition of employment. However, these laws vary from state to state. Currently there are no federal prohibitions against this practice.

Longitudinal Follow-Up

Longitudinal follow-up for a family that has received genetic counselling and/or undergone genetic testing is important to allow periodic review of management plan, and the assessment and promotion of adherence to surveillance measures. In addition, such follow-up allows clarification of issues that the patient or family may have over time, and to provide psychological support. As family history is dynamic, periodic updates of family history may identify new cancers in the family that could change the familial risk assessment. In addition, as cancer genetics is a rapidly evolving field,

maintaining follow-up also allows the family to keep in touch and receive new information, technology or tests that may become relevant to their condition.

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