GENETIC TESTING IN ONCOLOGY

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Dr Peter Ang
Consultant
Department of Medical Oncology
National Cancer Centre

Introduction

Cancer in Singapore accounted for 28.0% of deaths in 2002, making it the most important cause of mortality.\(^1\) This continues the trend of increasing cancer incidence and deaths over the last decade.\(^2\)

The path to understanding the genetic basis of cancer has led us to study the human genome in detail. The use of such genetic information in the clinics for adult-onset disorders like cancer has the potential to transform oncology practice.

As we seek knowledge, we should not deny patients and their families some of the benefits genetic testing might bring. In some families, early detection or preventive surgery has transformed the outcome for mutation carriers. In other instances, a person who does not carry the mutation that runs in the family has avoided uncomfortable and sometimes costly screening tests.

Although most of the familial cancers and the use of genetic testing has been in “rare” cancer families, this has changed with the discovery of susceptibility genes for the commoner cancers such as breast\(^3\) and colorectal cancers.\(^4, 5\)

However, we have been better at discovering new genes, which is not matched by our understanding of how these genes cause diseases. Given these limitations, we should recognise that inappropriate testing can sometimes cause harm.

What is Genetic Information?

Information about a person’s genetic makeup may be obtained in several ways:
1. by taking a family history of a genetic disease;
2. by observing external characteristics; and
3. by analysing blood or bodily tissue containing DNA, associated proteins or other biochemicals.

In almost all cases, genes are not the sole determinants of disease. There is environmental interaction including diet, smoking and other local factors. In addition, because the full pathway of genes causing disease is sometimes not fully elucidated, downstream influences from other genes may additionally modify the outcome of a particular gene effect.
We know that disease-causing mutations may be in single genes or may involve the interaction of several genes (polygenic diseases). Sequence variants, or polymorphisms, which refers to DNA sequence changes that have no effect or a minor effect on protein function and production, may sometimes confound our understanding of the genes and disease association. Current use of clinical genetic testing in oncology tracks mostly single genes as the cause of cancer, although more work now involves polymorphisms and the interaction of multiple genes.

In this paper, genetic information refers primarily to that obtained through analysis of blood or bodily tissues.

Genetic Information and Oncology

Work involving cancer genes has been especially rapid because cancer is a global disease. Studying these genes has improved our awareness of biochemical and signalling pathways and their role in carcinogenesis.

Treating cancer can be costly. Prevention can create enormous public health and economic impact. People who are highly likely to develop cancer can be identified for targeted prevention efforts. Genetic information can identify individuals at higher risk for certain cancers.

Definitions

A genetic test analyses the status of a particular gene and includes the analysis of human DNA, RNA, chromosomes, proteins and certain metabolites to detect heritable disease-related genotypes, mutations, phenotypes or karyotypes for clinical purposes.

Broadly, adult genetic testing can be divided into:

(a) Diagnostic Genetic Testing – to aid the diagnosis, treatment and management of symptomatic individuals.

(b) Carrier Testing – to detect individuals who possess a single copy of a gene which follows an autosomal recessive pattern of inheritance. Such an individual will not normally develop any disease or disorder but may pass on the gene to his or her offspring.

(c) Presymptomatic Genetic Testing – to determine whether individuals who have a family history of a disease, but no current symptoms, have the gene mutation.

(d) Predictive Testing – to determine the probability that a healthy individual with or without a family history of a certain disease might develop that disease.\(^6\)

Most of the issues surrounding genetic testing are not related to diagnostic genetic testing in a cancer-affected individual, but instead involve genetic testing when no
cancer has yet been detected. There is also a distinction from detection of changes in cancer cells (somatic mutation) that may guide cancer therapy but are not heritable.

There are limitations to the ability of genetic tests to predict diseases. Besides the quality of the test itself (even for single genes), variable penetrance, expressivity and genetic heterogeneity can compound our interpretation of such tests.\(^7\)

**Issues of Concern in Genetic Testing**

Genetic information can be obtained from a very small amount of material (the DNA in a single cell). It is convenient, and does not require lengthy follow up or history taking.\(^8\)

Genetic information, however, may also be obtained without the knowledge or consent of the person from a sample obtained in the past for another purpose or from cells shed unknowingly. There is concern that third parties such as employers and insurance companies may be interested in the information from genetic testing.

*Predictive Genetic Testing is Different from Conventional Medical Testing*

A conventional medical test provides information about a patient’s current status, which may have implications for the patient’s current care. In contrast, a predictive genetic test informs of a future possibility of disease.\(^9\)

Such results bring an element of uncertainty about not only the timing of illness, should it appear, but also about the severity of the illness and whether present intervention can be effective.

Information pertaining to predictive genetic testing also has implications for other related family members. To some extent, genetic information informs the risk of an unaffected parent, sibling or child when a family member is found to carry a deleterious mutation. On the other hand, when a person has cancer, his immediate relatives are at risk not only because of shared genes but also because of shared environmental influences.

**Clinical Aspects of Cancer Genetic Testing**

*Indications for Genetic Testing for Cancer Susceptibility*

Cancer is not inherited, but the susceptibility to cancer is inherited. In familial cancer syndromes, inherited *germline mutations* are replicated in all cells of an individual. Predictive genetic testing hopes to identify cancer-susceptible individuals early enough to implement cancer screening, surveillance and prevention.

As a general principle, cancer genetic testing\(^10\) should be offered only when:
1. the individual has personal or family history features suggestive of a genetic cancer susceptibility condition;

2. the test can be adequately interpreted; and

3. the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer.

Hereditary cancer syndromes can be well defined and test results can influence subsequent medical care. In some instances, genetic testing has become part of the standard management of these families. (Examples are familial adenomatous polyposis, medullary thyroid cancer)

However, this is not true of all cancer syndromes. New genes are discovered and new tests developed daily. As predisposition testing is an evolving science, a continual assessment of the use of these new tests in clinical practice is needed.

There are many cancer susceptibility genes and syndromes, a possible list of cancer predisposition syndromes where testing could be considered are found at the American Society of Clinical Oncology (ASCO) website (www.asco.org).

It is known that subjects undergoing genetic testing may have a wide range of emotional response from panic to relief. Personal interpretation of results and risks figures can also be coloured by an individual's experiences of cancer within the family and circle of friends. Knowing results can create chain effects and actions for individuals and their families. Uncertain results can create frustrations and a false sense of security. Certain interventions in response to genetic test results have unknown efficacy.

Since not all tests are useful and may cause harm in some situations, the process of cancer genetic testing should only be performed with pre and post-test counselling. There should be a familial risk assessment to identify suitable at-risk individuals, as none of the tests have been recommended as screening tests. Pre- and post-test counselling should be part of the process of genetic testing.

**The Role of Familial Risk Assessment**

Familial risk assessment is practised by centres offering genetic testing and counselling. It involves gathering a detailed family history. The purpose is to compile detailed cancer and non-cancer diagnoses about the family and exposure to carcinogens, and includes up to three generations in the pedigree.

The pedigree has to be interpreted with the understanding that reduced gene penetrance and variable phenotype expressivity can occur. A genetic counsellor, physician or nurse counsellor usually does the risk assessment.
In pedigrees where a clear Mendelian pattern of cancer susceptibility is inherited, cancers may exist in every generation of the pedigree. In a cancer predisposition syndrome, multiple cancers can occur in a family.

However, clustering of cancers does not always indicate transmission of a susceptibility gene. Cancers in a family can also arise from shared lifestyle, diet or environmental carcinogens. Examples include tobacco exposure resulting in lung cancers, and hepatitis B carriers with hepatomas.

Sporadic cancers (arising in the absence of heritable susceptibility mutations) common in the population arise from complex interactions between multiple genes and the environment. Sporadic cancers may appear in large families — particularly if they occur at a later age. Risk assessment should provide some guidelines to the subject for individual health decision making.

Several professional societies have recognised the need to improve care in this area. The ASCO has, for example, issued policy and guidelines to cancer specialists in this area \(^{10,13}\) and plan training programs.\(^{14}\)

**Pre-Test and Post-Test Counselling**

Pre-test counselling is a process of communication and is part of the informed consent process for genetic testing. Elements of informed consent\(^{10}\) for cancer genetic testing should cover the topics in Table 1.

**Table 1. Basic elements of informed consent for germline DNA testing**

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<td>1.</td>
<td>Information on the specific test being performed</td>
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<td>2.</td>
<td>Implications of a positive and negative result</td>
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<td>3.</td>
<td>Possibility that the test will not be informative</td>
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<td>4.</td>
<td>Options for risk estimation without genetic testing</td>
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<td>5.</td>
<td>Risk of passing a mutation to children</td>
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<td>6.</td>
<td>Technical accuracy of the test</td>
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<td>7.</td>
<td>Fees involved in testing and counselling</td>
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<td>8.</td>
<td>Risks of psychological distress</td>
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<td>9.</td>
<td>Risks of insurance or employer discrimination</td>
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<td>10.</td>
<td>Confidentiality issues</td>
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<td>11.</td>
<td>Options and limitations of medical surveillance and screening following testing</td>
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Part of the session should be devoted to providing information for individuals who seek genetic counselling. Understanding technical language, the probabilistic nature of risks and cancer information can be difficult even when language is not a barrier.\(^{15}\) In multicultural Singapore, communication of such information can be even more difficult.
Pre-test counselling is best performed by a trained professional who has knowledge of cancer syndrome genetics and is familiar with the proposed test. In Singapore, trained professionals include genetic counsellors, nurse counsellors and doctors.

Post-test counselling helps to place results in perspective for the individual. Results from genetic tests can cause relief or distress in individuals.

Mutation carriers can feel relief at clearing uncertainties\(^{16}\) and begin a discussion of prevention measures. Conversely, non-carriers can experience "survivor guilt" when they realise that they do not share the same risks as affected relatives.\(^{17}\)

Genetic test results can be reported as negative, positive or inconclusive for a suspected mutation. In a report by Giardiello in 1997, almost one third of physicians misinterpreted the results of commercial APC gene testing in familial adenomatous polyposis.\(^{18}\) Given the large number of genes unknown today, a negative result could mean that an inappropriate gene was tested. A true negative result is informative only when the mutation that occurs in affected members of a family is known.

It is clear that genetic tests do not detect all the mutations in affected cases. In addition, some cancer syndromes may have genetic tests available, but the impact on medical management may be uncertain (e.g. TP53).\(^{19}\) Furthermore, inconclusive test results can lead to stress.

Careful handling and counselling after testing is important. There should be a discussion about the possible risks and benefits of early-detection and prevention modalities with a trained professional. Many of these decisions are very personal and may involve handling information for at-risk siblings or even parents.

Maintenance of Genetic Test Information

There is public concern that insurance companies may discriminate against individuals perceived to have an elevated risk of cancer from their genetic test results.

In a paper by Matloff, genetic specialists were posed a hypothetical situation where they had a 50% chance of carrying a mutation for a hereditary cancer.\(^{20}\) Eighty-five percent of respondents said they would undergo genetic testing. However, the majority would not bill their insurance company or would use an alias for fear of discrimination.

In countries such as the United States where health insurance is common and needed to obtain a reasonable level of health care, this issue is especially important. Although Singapore’s health care structure is different, implications for life insurance applications remain.

Historically, family histories of cancers have long been used clinically for assessing a person’s risk. Insurance premiums are increased for those at risk of inherited diseases. In some situations, it may also be possible for a genetic test to inform that a person who
has a family history of cancer actually does not carry the susceptibility gene. Genetic tests are heterogeneous and the accuracy, reliability and predictive value for risk need to be evaluated for their use.

The indiscriminate use of genetic tests is of concern. The United Kingdom Human Genetics Commission publication discusses some of the issues related to insurance and employer use of personal information.\(^8\)

Genetic information is privileged, confidential, medical information. There are standard safeguards in hospitals regarding access to and use of medical information that includes computerised medical records. No information should be released without the patients’ consent.

Although discrimination based on genetic information has not been reported in Singapore, fear of discrimination may prevent people who might benefit from genetic testing from doing so.\(^{21}\)

While the UK Human Genetics Commission (http://www.hgc.gov.uk/business_publications.htm) and the American Society of Clinical Oncology have recognised that this is an area of concern, different countries approach the subject differently.\(^{10}\) In the UK, a Genetics and Insurance Committee\(^8\) has been set up to oversee and discuss the issues with the industry and independent experts.

**Research Genetic Testing**

While researchers are interested in the academic aspects of cancer causation and in discovering which genes are important in making some individuals susceptible, subjects may not directly benefit from knowing these findings.

Much of what we have learnt about cancer genetics is from high-risk individuals and families who have selflessly provided information and samples for research. There should be scrupulous ethical and legal safeguards for research participants. On the other hand, these safeguards should not stifle research efforts.

Improving technologies and powerful biotechnological tools creates enormous potential to form large databases of genetic information. Even with minuscule samples, a den of information can be mined and stored. The information can also be mined from archival samples.


Use of information from subjects tested on research protocols should be based on institutional guidelines with ethics committee oversight and approval.
Consent for genetic testing research should require careful explanation of the nature of the study supplemented with written information.

The difference between clinical and research testing should be made clear to participants. For example, clinical genetic testing in the United States means that the laboratory has to follow certain (Clinical Laboratory Improvement Amendments, CLIA) guidelines (http://www.cms.hhs.gov/clia/). Guidelines ensure quality assurance and quality control methods in molecular diagnostics. Research laboratories may not follow stringent guidelines for collecting, transport and storage of biological materials.

In clinical testing, an individual chooses to undergo genetic testing wishing to know the outcome. In research testing, the individual may choose not to find out anything about his/her genetic status. The handling of research testing results should be made known to the subject before participation in the protocol.

For protocols in which the subjects find out their cancer predisposition status, pre- and post-test genetic counselling should be provided to help them understand the implications of the results.

Guidelines are available for research involving genetic testing (UK Advisory Committee on Genetic Testing October 1998).22

**Testing Children for Cancer Susceptibility**

In general, genetic testing for adult onset disorders is not undertaken if the child is healthy and the test result has no direct medical application. Children may have difficulty understanding the information on genetic testing, although this may vary depending on maturity and age. Children may also have a different view of testing from their parents or surrogate decision-maker. Genetic testing in children is a complex subject and several societies have addressed it.10, 23-26

When the genetic test may detect conditions for which treatment or preventive measures are available (e.g. FAP), testing of minors should proceed according to established consent guidelines for other necessary medical treatments in children.

**Economics of Genetic Testing**

Newer and novel oncology drugs for the treatment of advance cancer are expensive. This contrasts the cost of gene identification and prevention of common cancers. True negatives identified on genetic testing may also avoid costs of unnecessarily early screening. In our current healthcare system, genetic testing is not recognised as reimbursable by Medisave.

However, there should be an ongoing review as new studies showing cost effectiveness27 and efficacy28-31 in cancer prevention have emerged.
The whole framework of regulation should encompass judicious testing of high-risk individuals in a system of risk assessment. Audits and studies of these efforts should be undertaken. Given that cancer risk and attitudes towards prevention can be different for our population in Singapore, we also need to address these with further research to integrate genetic testing into cancer prevention services.\textsuperscript{32}

**Conclusions**

Genetic testing in oncology practice is a tool that needs to be wielded with care. Providing information in the form of genetic counselling has become a standard of care for individuals undergoing genetic testing for cancer predisposition.

A framework to develop and deliver these services would allay public anxiety over abuse of genetic information and discrimination by employers and insurers. Proper implementation could lead to better prevention for cancer.

**References**


