TESTING FOR FAMILIAL CANCER SUSCEPTIBILITY GENE MUTATIONS

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Abstract

Genetic testing is a useful means of identifying individuals who are at an increased risk of developing familial cancer. This information assists such individuals to make lifestyle alterations and consider surgical intervention to minimise their risk of developing cancer. In WA, genetic testing is conducted free of charge to the public through Genetic Services of WA who provide an integrated service. This includes pre- and post-test counselling, testing, family support and a surveillance registry. However, the recent granting of an exclusive gene patent licensing agreement for familial breast cancer susceptibility genes threatens free of charge public testing services Australia-wide. Exclusive licensing effectively creates a monopoly on the testing services available, and accordingly there has been a great deal of controversy over the breast cancer gene patent and licensing agreements internationally. This article explores aspects of testing for familial cancer susceptibility gene mutations, focusing on experiences with familial breast cancer.

Genetic technology is revolutionising the way in which diseases are diagnosed and managed. An important outcome of the increasing application of genetic technology to health services has been the introduction of genetic testing, which has had particular relevance for cancer treatment. In recent times testing has been successfully utilised for detecting familial mutations in the breast and ovarian cancer susceptibility genes.

Breast cancer is the most common form of cancer among Australian women, and it is estimated that it will affect approximately one in 12 women in their lifetime[1]. While fewer than five per cent of all cases of breast cancer in Australia may be attributed to familial links, the risk of developing the cancer for potentially high-risk persons (less than one per cent of the population) is six to 10 times higher than the population average[1]. The causes of breast cancer are complicated by interactions between environmental factors such as diet, and genetic factors. In regard to familial breast cancer, currently identified environmental risk factors are thought to explain less than 10 per cent of breast cancers. This indicates there is still much to learn about why breast cancer runs in families more often than would be predicted by chance alone[2]. Genes associated with inherited risk of breast cancer other than BRCA1 and BRCA2 are likely to be discovered in the next few years[2].

The BRCA genes act as tumour suppressors. Mutations in these genes lead to increased susceptibility to uncontrolled cell replication, thereby resulting in cancer. These mutations, largely specific to a family, may be passed through several members, male and female. Population-based studies conducted internationally indicate that individuals who have inherited (deleterious) BRCA mutations have an elevated lifetime risk of both breast and ovarian cancer[3]. For those individuals at increased risk of developing familial breast and ovarian cancer, genetic testing may be an appropriate option to refine actual risk as a component of their risk management.

Genetic testing for familial breast cancer

Genetic testing is a complex process and involves searching for a gene mutation in an affected family member. Should such a mutation be found, predictive genetic testing may be offered to other family members who currently have no symptoms but are also at risk of carrying the same mutation. Even if a mutation is located, this only indicates that person has a higher risk of developing the disease – there is no certainty they will actually go on to develop breast or ovarian cancer. Moreover, there is no completely effective means of preventing either breast or ovarian cancer once a mutation is discovered. However, recommended screening and prophylactic strategies might reduce the morbidity and mortality from breast cancer in family members ascertained to be at "high risk" through genetic testing.

In WA genetic testing is conducted through Genetic Services of WA (GSWA), which is a multidisciplinary, state-wide service based at King Edward Memorial Hospital. GSWA has a long-established Familial Cancer Program that provides a comprehensive service to families with a history of breast, bowel and ovarian cancers, other less common cancers and related syndromes. The service incorporates important pre- and post-test counselling, family support, education, genetic testing and liaison with clinical specialists where relevant, for individuals or families with a history of cancer.

Comprehensive DNA-based testing for cancer susceptibility gene mutations has been offered through the Familial Cancer Program at GSWA since 1995. This testing detected most sequence variations, but until recently testing only detected specific known deletions or duplications. These sort of mutations are believed to be common in familial breast and bowel cancer and are now tested for in the GSWA laboratory with a novel test, the Multiplex Ligation-dependent Probe Amplification (MLPA), which identifies any exon deletions or duplications[4]. The GSWA laboratory stores DNA and RNA from family members and when new tests appear the stored material is re-analysed. The laboratory is currently using these improved technologies to investigate for mutations in stored specimens, in which previous studies were inconclusive.

In calculating an individual's estimated risk of developing cancer, based on mutations in the cancer susceptibility genes, a multitude of complex issues arise. Mutations in these genes increase an individual's risk for both breast and ovarian cancer, however the estimated risk is different. For example, in BRCA1 mutation carriers the estimated risk (to age 75 years) of developing breast cancer is 40-80% and the risk of ovarian cancer is 10-60%. Male carriers of the BRCA1 mutation also have a slightly higher lifetime risk of developing cancer of the prostate[1].

In BRCA2 mutation carriers the estimated risk (to age 75 years) of developing breast cancer is 40-80% and the risk of ovarian cancer is 10-40%. Carriers of mutations in the BRCA2 gene also have a slightly higher lifetime risk of developing cancer of the pancreas, male breast and prostate[4].

Despite these complexities, there are numerous benefits of cancer susceptibility gene mutation testing. These include early detection, appropriate surveillance and sometimes the option of preventative surgery. Through the course of genetic testing an individual is often alerted to other possible lifestyle changes that may keep cancer at bay[5].

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The Familial Cancer Program also operates a cancer registry that provides surveillance for women identified as being at increased risk of developing various familial cancers, including breast or ovarian cancer. If no mutation is found in the family, members are still encouraged to follow screening measures due to their strong family history of disease. The Familial Cancer Program also invites such individuals to join the registry in the event that a new genetic mutation is identified in the course of future research or technological development. In addition, the service provides opportunities for individuals to participate in approved clinical trials and research projects conducted through the Familial Cancer Program and the Breast Cancer Risk Assessment Clinic at Royal Perth Hospital.

The holistic and multidisciplinary service in WA provides counselling and information to individuals considering undertaking genetic testing. The pre- and post-test counselling component of the program allows for the mechanisms of genetic transmission to be explained, and the likelihood that a mutation is present in a family being assessed. It also provides counsellors with an opportunity to clarify the advantages and limitations of genetic testing, as well as possible options for risk management[3]. A recent study of women tested for mutations in the BRCA genes suggested that counselling is effective in helping women throughout the genetic testing process, highlighting the need for a comprehensive genetic service[6].

An experience of genetic testing

Genetic testing for familial breast cancer mutations raises a multitude of psychosocial issues, which need to be considered before an individual undertakes testing. For example, in deciding whether or not to undertake testing the individual needs to consider the impact of the information on their own psychosocial coping, family dynamics and issues such as life insurance and employment. Ultimately, the choice is a personal one but genetics professionals can ease the decision-making process by equipping individuals with the best information about the issues involved so they can make the best choice for themselves and their family.

In response to the high prevalence of breast cancer in her family, one woman underwent a double mastectomy in order to minimise her risk of developing breast cancer. This woman states that "breast cancer has been casting a long shadow over the women in my family, it seems as if part of our family is devoid of women" and is therefore also currently considering genetic testing in order to add to the genetic knowledge in her family.

In another family, both mother and daughter undertook genetic testing through GSWA two years ago. Breast cancer has affected three generations of their family. They heard about the services offered by GSWA through a family member who is a GP and who felt that given their strong family history of breast cancer, there might be genetic factors involved. Both women were found to carry mutations in breast cancer susceptibility genes, but so far only the mother has developed ovarian cancer. Other family members have also undergone genetic testing, however some have elected not to receive this predictive information.

The daughter states that she was apprehensive about having the testing done, but the counselling support she received from the genetic counsellors and valuable written information assisted her in making the decision. She also noted that the explanation of the information by the clinical geneticists was most important in assisting her decision-making. Receiving the results that she carried a mutation was "frightening but you learn to live with it". Knowledge of the mutation has enabled her to be vigilant and prepared. The daughter states that "we're luckier than most people because we know what we're facing and we are watched closely". Both women are undergoing regular surveillance and have been encouraged to join the Familial Cancer Registry.

Gene patents

Despite the benefits clients derive through familial cancer services such as that offered by GSWA, the ability of public hospitals to provide free-of-charge genetic testing services to the public is threatened by the implications of gene patenting[7]. Recently a US-based biotechnology company, Myriad Genetics Inc, has taken out a broad patent for the BRCA genes in numerous countries, including Australia. Myriad has used the framework of exclusively licensing the use of its test to a very limited number of commercial genetic laboratories in specific locations[7].

Broad-based gene patents raise the controversial issue of whether or not it is ethical to patent a naturally occurring substance[8], and further to make a commodity out of it. Extending beyond this ethical issue is perhaps the more critical question of whether it is in the interests of public health and research to allow gene patents, and evidence increasingly suggests it may not be[9]. While it is acknowledged that patents support the protection of corporate interests and are a central tenant of international trade agreements between industrialised nations[10], these corporate interests need to be weighed against the public good. The exercise of exclusive and monopolistic gene patents will interfere with patient care by disrupting the integrated testing, clinical and counselling services already offered throughout Australia. It may also compromise the viability and expertise of publicly-funded genetic testing services, and divert testing services away from established Australian best practice guidelines[7] which serve to ensure the medical and psychological wellbeing of individuals undertaking testing.

Gene patents also have the potential to compromise public health by inhibiting biomedical research that could prevent an alternative genetic test from being developed. A researcher wanting to find a cure for breast cancer would have to negotiate with the patent holder for access to the BRCA1 and BRCA2 genes. In addition, they must also negotiate with all the other patent holders who have discovered and patented any of the hundreds of other mutations in these genes. The stimulus to patent genes in the last decade has been likened to a "genetic gold rush"[10]. A Victorian-based company, Genetic Technologies Limited, has patented 95% of all intronic DNA (also known as 'junk DNA') in the likelihood that this material may be found to be important[11].

Internationally, there have been very few legal challenges launched against gene patents, and there certainly have been no decisive legal moves to address directly whether human genes are even an appropriate substance to patent[9]. In the US, moves to reform legislation on gene patents have been introduced by Senator Lynn Rivers. The Rivers Bills aim to grant medical researchers and clinical geneticists protection from patent infringement, in an effort to minimise negative impact of gene patenting on health services. In Australia, a similar course of legislative action is yet to be undertaken, and in the interim gene patents remain a very real threat to the delivery of genetic testing as a component of our public health service.

Conclusion

It is currently known that a small number of cases of breast and ovarian cancer may be attributed to mutations in various genes, including BRCA1 and BRCA2. It is expected many more

genes that contribute to cancer will be identified as research advances. In order to provide the highest standard of health service for individuals identified as being genetically at risk of developing familial breast or ovarian cancer, it is essential that a holistic service continues to be provided with equitable access at an affordable cost for all Australians.

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