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Genetics in general practice

Background

Our improved understanding of the human genome and the genetic contributions to disease have been looming over the horizon for some decades now with great promise of improvements in prevention, prediction and treatment of diseases. Yet, as with many technological revolutions, the real gains on the ground have been much slower to emerge.

Objective

The aim of this paper is to outline some of the common genetic issues that arise in general practice clinical consultations, and the clinical scenarios in which general practitioners (GPs) may suggest genetic testing for patients or referral to one of the various specialist genetics services.

Discussion

GPs will notice that more consultations now involve some discussion of genetic issues and, indeed, there is a range of genetic tests that GPs can request. These issues and tests require detailed explanation to patients and their families.

Keywords

genetic testing; genetics, medical; general practice



With the rapid developments in human genetics in recent years, there have been high expectations about how these scientific discoveries will translate into real benefits for patients.^{1,2} It is clear that these advances are going to filter down to primary care settings and become a significant element of day-to-day clinical care – indeed, there is already a variety of genetic investigations that GPs can request. These genetic tests require detailed explanation to patients and their families to assist them in interpreting what they mean and making informed decisions.^{3,4} The humble family history, often a cursory entry into the medical records, is in fact a powerful tool when undertaken diligently and systematically, and there now exists a validated tool to assist with this process.⁵ Specific genetic tests also now come into play in a wide range of clinical settings: pre-pregnancy and pregnancy counselling in the context of couple carrier screening⁶ or screening the fetus,⁷ newborn screening,⁸ cancer screening,⁹ cardiovascular screening,¹⁰ clotting and bleeding problems,¹¹ and neurological and developmental problems such as fragile X syndrome.¹²

As with so many complex clinical presentations in primary care, there is always tension between those that the GP can manage and those needing specialist management. Over time, clinical practice tends to evolve that defines the line in the sand. There is a level of complexity for many genetics consultations that does require specialised expertise and it is timely, as more genetic testing becomes available, to reflect on how GPs may work with genetics services and genetics counsellors and patients.^{13–16} The aim of this paper is to outline some of the common genetics issues that arise in GP clinical consultations, and the clinical scenarios in which GPs may suggest genetic testing for patients or referral to one of the various specialist genetic services. Prenatal testing is also a rapidly developing field and is dealt with in a separate article¹⁷ in this edition of *AFP* and not addressed specifically in this paper.

The role of GPs

General practitioners are potentially well placed to integrate many genetics issues into routine consultations, although training to date has been limited.^{5,18–20} Much of the day-to-day work of general practice already involves the management of chronic diseases, the prevention of cancer and the management of patients within the context of their



families.²¹ Indeed, much of the interaction between GPs and patients, especially in regard to preventive care, is already fundamentally about risk assessment and management. In addition, as families share genes, GPs working with families are well placed for long term follow up of genetics-based risks.

GPs are also accustomed to communicating test results to patients and managing the subsequent implications of a test.²² But there are significant differences regarding genetic information, compared with the sorts of routine test results that GPs are accustomed to communicating to their patients.²³ Public understanding of genetics is often clouded by overhyped media reports or internet misinformation and there are many common misunderstandings.¹⁶ For example, the presence of a cancer gene often leads some patients to believe that disease is inevitable rather than an increased probability. In addition, genetics tests can have more broad reaching impact than routine investigations for the individual's identity, for their family members and, potentially, for employment and the costs of obtaining life insurance.³ In this context, confidentiality and informed consent are especially pertinent, and particular care is needed in preparing patients for genetic information, to ensure accurate understanding, interpretation and appreciation of the implications.

Raising genetics issues in general practice

GPs are well positioned to determine whether a patient/family might consider pursuing genetic investigation. In considering the value of genetic tests, the GP should be mindful of the possibility of raising anxiety levels unnecessarily, or raising concerns about a disease for which there is no possibility to improve the prognosis.²⁴ There are also familial diseases for

which we do not yet have routine genetic tests, for example schizophrenia or type 2 diabetes, so GPs needs to manage patients' expectations.

A systematic approach to family history is more accurate than an ad hoc approach. One tool, the Family History Questionnaire (*Table 1*) is a validated questionnaire for primary care assessment of some of the common diseases: diabetes, ischaemic heart disease, melanoma, breast, ovarian, colorectal and prostate cancer.²⁵ It can be used as a paper-based questionnaire for patients or integrated as a template into medical software, or undertaken with the GP or in the practice waiting room.

There are some particular clinical scenarios that may prompt the GP to consider genetic testing. These scenarios and the sorts of tests that might be considered are listed in *Table 2* (available online only). This table has been developed using the NHMRC's Genetics at a Glance summary,²⁶ which is underpinned by an extensive resource, *Genetics in Family Medicine: The Australian Handbook for General Practitioners*.³ Although published in 2007 and requiring updating in parts, it is still relevant to general practice and the GP's role in genetics medicine. The table has also been heavily informed by the *Guidelines for preventive activities in general practice* (the Red book).²⁷ It presents the common genetics issues encountered in general practice including: hereditary haemochromatosis, neurofibromatosis, skin cancer, prostate cancer, breast cancer, colorectal cancer, type 2 diabetes, familial hypercholesterolaemia, fragile x and other causes of developmental delay, hereditary thrombophilias and haemoglobinopathies.

There are some important clinical and ethical considerations that should be addressed before offering patients genetic tests.²⁶ The patient should be fully informed about the purpose and personal/family implications of a genetic test before obtaining consent. One key issue is to explain to patients who have had a predictive or pre-symptomatic genetic test, that

Table 1. Family health questionnaire: 9 items

This risk assessment focuses on your close relatives including parents, children, brothers and sisters who are either living or dead.	Yes	No
Have any of your close relatives had heart disease before the age of 60? 'Heart disease' includes cardiovascular disease, heart attack, angina and bypass surgery.		
Have any of your close relatives had diabetes? 'Diabetes' is also known as type 2 diabetes or non-insulin dependent diabetes		
Do you have any close relatives who have had melanoma?		
Have any of your close relatives had bowel cancer before the age of 55?		
Do you have more than one relative on the same side of the family who has had bowel cancer at any age? Please think about your parents, children, brothers, sisters, grandparents, aunts, uncles, nieces, nephews and grandchildren.		
Have any of your close male relatives had prostate cancer before the age of 60?		
Have any of your close female relatives had ovarian cancer?		
Have any of your close relatives had breast cancer before the age of 50?		
Do you have more than one relative on the same side of your family who has had breast cancer at any age? Please think about your parents, children, brothers, sisters, grandparents, aunts, uncles, nieces, nephews and grandchildren.		
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they have a duty to inform life insurers of the test result when applying for a new policy or altering an existing policy.²⁶ Also, although the GP has no duty per se to inform the relatives of a patient about a positive genetic test result, the patient should be encouraged and supported to share the information with their relatives, and it may be worth discussing in advance how the test results are to be communicated.

Some genetic tests may be available in Australia at no cost to the patient through genetics services funded by state or territory governments, whereas other genetic tests may be available only at out-of-pocket costs to the patient, sometimes at a cost of hundreds to thousands of dollars. In Australia, the following DNA tests are available on the federal Medicare Benefits Schedule (MBS) for specific indications: haemochromatosis (HFE), fragile X syndrome, Factor V Leiden and some other inherited thrombophilias.²⁶ In addition, various tests for chromosomal analysis are also available on the MBS, for example, karyotyping and chromosomal microarrays for investigation of developmental delay.

Case 1. Breast cancer risk

A woman aged 25 years comes in for her routine Pap smear in a country town in rural Western Australia. In discussion with the GP she mentions that two of her aunts, her father's sisters, had breast cancer at the ages of 38 and 42 years respectively. She wonders if it is actually possible 'to get the cancer gene through her dad's side'. She is otherwise well and healthy and is wondering if she should be having some further tests to see if she has an increased risk of breast cancer. The GP explains that it is indeed possible to have increased breast cancer risk through the paternal side of the family and that her family history puts her in a potentially high risk category for breast cancer. Given her complex history, the GP suggests referral to a familial cancer clinic or genetics service to further explore her risk of breast cancer.

Case 2. Thrombophilia

Jane is a 32 years of age and goes to the GP complaining of a left lower leg pain, which seems to have come on spontaneously. The GP examines her and notices that the calf is warm and tender and suspects a deep venous thrombosis (DVT), which is confirmed on Doppler ultrasound later that day. Looking back through Jane's medical history on the medical software summary, the GP also notices that Jane had an unexplained late miscarriage at the age of 28 years. On further questioning about her family, Jane explains that her father had an unusual arm thrombosis during his university days and spent some time in hospital on a blood thinning medication. The GP suggests that although the immediate issue is to manage the DVT, it would be a good idea to be screened for thrombophilia.

Case 3. Fragile X syndrome

Justin is 5 years of age and is brought in by his mother Cynthia for a routine vaccination. During the consultation, Cynthia explains that Justin has been having a very hard time

since starting school, struggling to keep up with the other children. Indeed, the teacher has raised the possibility of a learning disability. Cynthia also mentions that her 8-year-old daughter is only just coping at school as she is very shy and finds mathematics really challenging. The GP is aware that Cynthia has recently had her intrauterine device removed and is planning to have a third child. The family is well known to the GP, who is aware that Cynthia's father, Michael, has a recent history of intention tremor of the hands, two recent unexplained falls, and had been referred to a neurologist. The GP explains that it would be a good idea to get Justin assessed by a paediatrician in the first instance, and advises that it might be worthwhile for Cynthia and her husband to come and have a chat about their plans to get pregnant again, and consider seeing a genetics counsellor. The GP also makes a note to book an appointment for Michael, to discuss the possibility of fragile X tremor ataxia syndrome (FXTAS), which is a possible explanation for his neurological presentation.

Genetic services in Australia

There are state- and territory-based clinical genetics services throughout Australia. These services provide specialist risk assessment, diagnosis, testing and counselling services, which might include outreach services in some regions. Familial cancer and prenatal testing services may be offered through these clinics or through separate specialist centres. GPs can refer patients directly to clinical genetics services or may wish to contact the service themselves first to discuss genetic issues, risk assessment and management.

A recent phenomenon for GPs to be aware of is the marketing of direct-to-consumer genetic testing (also known as genetic profiling). A number of companies have been offering testing where the consumer mails in a sample, for example a saliva sample, and receives a detailed report outlining their personal genetic risks for a long list of diseases. At this stage, however, the accuracy and interpretation of these reports is uncertain and the NHMRC has warned consumers to carefully consider the unintended consequences for insurance, privacy and emotional health from such tests.²⁸ Direct-to-consumer genetic testing is dealt with in more detail in a separate article in this edition of *AFP*.²⁹

Over time genome-wide sequencing will become increasingly available for patients with suspected genetic conditions, but as yet this is not offered routinely in diagnostics. This type of sequencing uses technology known as 'next generation' or 'massively parallel' sequencing, which involves very fast, high-throughput sequencing of DNA fragments generating millions of 'reads'. Using this technology it is possible to sequence a panel of selected or targeted genes, whole exomes (all of the protein coding sequences in a genome) or whole genomes (the entire 6 billion base pairs of DNA in a person's 46 chromosomes), at much reduced costs, compared with sequencing each gene separately. Note that the new noninvasive prenatal tests (NIPT) now available for prenatal screening are based on this technology. However, one of the challenges associated with these genome-wide technologies is interpreting the enormous amount of information generated, particularly when the sequence variants identified are not



clearly pathogenic, a challenge already faced with the introduction of chromosomal microarrays.³⁰ It remains to be seen how this new sequencing technology will become integrated into diagnostics and influence GP practice but, given the pace at which these technologies develop and how quickly they can enter healthcare (such as has happened with chromosomal microarrays and NIPT), GPs need to be aware of these developments.

Conclusion

Genetic testing offers patients the opportunity to better understand their health risks. At the same time the sensitive new information that can be obtained from genetic testing has broad implications for emotional wellbeing, privacy and insurance. The GP can assist patients by being informed about the genetic testing that is available and being alert for clinical scenarios where genetic testing may be appropriate. As with other fields in primary healthcare, GPs can work with specialist health professionals such as geneticists and genetics counsellors to ensure patients receive the best advice and care.

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