Associate Professor Judy Kirk MBBS (Sydney), FRACP, having trained in paediatric oncology in 1987, spent three years from 1991 in Seattle in the field of cancer genetics. In 1995, she set up the Familial Cancer Service at Westmead Hospital. It cares for individuals and their families with concerns about a family history of cancer.

Chromosomes and genes

What we are going to talk about tonight is your genetic material, packaged into chromosomes and packed with about 30,000 different genes. Luckily for you, I won't be talking about all of them. I will take you back to when you were at school and learnt that the genetic material sits inside all of your cells, packaged into chromosomes, and that, if you unwind them, you get strings of DNA. Stretches of DNA code for a specific protein. If there is a problem with the gene, there is likely to be a problem with the protein which that gene makes. That is the underlying basis of all of this, so we will talk about genes and how they impact on us.

Genetic testing

Testing is usually done on blood, or sometimes other samples, to find out about genetic disorders. About 900 genetic tests are available. I am going to talk mainly about the reasons for medical genetic tests, of which there are quite a number – testing unborn babies, sometimes screening embryos for disease. I will talk about the thing I know most about – testing for genetic diseases in adults before they cause symptoms and in particular cancer.

The Familial Cancer Service

We see people worried about their family history of cancer. They might come from a family with generation after generation of young women with breast cancer, where there is a genetic fault that has been passed down and where those who have that fault have a high risk of breast cancer. That can happen on the mother's or the father's side of the family. Similarly with bowel and prostate cancer, although we don't yet know which genes are involved for prostate cancer.

About 900 tests

Listed on the College of Pathologists web site is a catalogue of genetic tests - about 900 of them. The important part about these tests is the warning that comes with this information. People who do these tests should be aware that testing for inherited genetic variants often raises significant issues: medical, ethical, legal, psychosocial and psychological. I am going to talk about a practical case, but raise some of these issues along the way, in the hope that our second speaker, David Weisbrot, will pick up on some of the legal, ethical and social issues which genetic testing takes along with it.

Clinical guidelines

In Australia this sort of genetic testing has, until now, been practised under fairly standard clinical guidelines published by the NHMRC, and there are laboratory guidelines for standards of testing. In, Australia, genetic testing has, to date, been fairly highly regulated and done mainly through genetic services. That might be changing. I will highlight standard medical genetic testing, which is serviceable, useful, has a purpose and gets the job done.

'Designer testing'

I will contrast for you so-called designer genetic testing, which is becoming common. The internet has any number of web sites prepared to take your money if you pop a swab into your mouth and send them your DNA. (See the advertisements on the right side when you Google 'genetic testing'.) They will give you an analysis which sometimes includes fascinating things like your ear wax type, and bits and pieces of information indicating that you might be at increased or decreased risk of something or other, all of this mostly unsupported by the science. This genetic testing is coming to a place near you. We might focus on it later.

I met someone only last week at a function for the National Breast and Ovarian Cancer Centre, a lady who said, "I wanted to meet you. I have had a genetic test – my personal trainer organised it". I thought,

"That's great, I have done thirty years of training and you can have this test done now through your personal trainer." She had paid out $500 for really not much information at all. I might come back to that.

Family histories

We obviously like to deal with family trees. We are interested in them because people nowadays know more about their family history and are a little concerned that perhaps their family history might mean they are at risk of something – or that their own medical history might mean that their kids are at risk of something. Because such people are now attending family cancer clinics, I want you to know what family cancer clinics do. They are at major medical centres throughout Australia.

Family genetic testing

What are these genetic tests and how do they work in these families? Do they actually change anything? Is it important to have this knowledge or is it just a bit of frippery? No. Throughout this, as I go through a practical case, I am going to point out some of the ethical and legal issues on which David Weisbrot might comment later.

A family history of cancer is common

You would be lucky if you didn't have some family history of cancer – because cancer is common. The risk of a woman being diagnosed with breast cancer now in Australia, up to the age of 85, is 1 in 9, and is obviously a lot less common in men – but it does occur. The risk of bowel cancer is equally fairly high. It would be almost amazing to find somebody, if they have a big enough family, who says, "I have absolutely no family history of cancer". In other words, cancer is common and many people will have a family history of cancer just by chance alone.

Not all shared features are genetic

I have a family photo showing two people who seem to have the same condition – missing the same adult teeth. But it is not inherited. One lost his teeth in a knock-up game of AFL many years ago and the other was at an age when she was waiting for her adult teeth to arrive. Just because something occurs twice or more in a family doesn't mean that it is genetic. That often happens, of course, with cancer.

I am going to focus on bowel cancer. I often talk about breast and ovarian cancer about which there is a lot of interest, and which is a lot of my work. The other half is hereditary bowel cancer. I raise this because there are, unusually for one of my talks, many Y chromosomes in the room. I thought I probably shouldn't mention the fact that the Y chromosome has been found to be composed of a lot of junk DNA and to not contain much of substance. I go back, however, to bowel cancer.

Bowel (colonic) cancer

Because bowel cancer is common, many people will have a family history just by chance alone. I am going to talk about how bowel cancer develops. All of our cells are dividing and dividing and dividing all the time. Sometimes the divisions result in mistakes in some genes. In fact, this is happening all the time. Sometimes the mistakes are repaired and sometimes they are not. It is never just one genetic fault which causes this problem, but rather an accumulation of faults which happen in the bowel cells through our life.

For 95% of people with bowel cancer this is what has happened. The faults have accumulated as we age. They are sitting there in the bowel tissue. They are nowhere else in your body, so you can't pass on those sorts of genetic faults. That is the usual type of bowel cancer, due to an accumulation of what we call 'somatic faults' in these genes – things which happen in the tissue as we go through life. That is normal.

Errors when cells divide

If you think about the complex process of cell division – that every time a cell divides and makes a couple of cells, it has to copy the whole genetic code out and then divide. In fact, we have some special genes which code the proteins which run along and proof-read each new strand of DNA and correct any

mistakes before the cell is allowed to divide; these are called 'mismatch repair genes'. We will talk about those a little later, because they are responsible for some family's problems. When you think about the complexity of a cell dividing, which is happening all day, it is no wonder that things occasionally go wrong.

Normal colonic tissue may have a little bit of overgrowth of tissue, but then as faults in these various growth control genes occur, the overgrowth becomes a small polyp – an adenoma. With further genetic changes, the polyp becomes bigger, and finally rather nasty and ugly, eventually a cancer – all due to the accumulation of genetic faults in cells as we go through life. Unfortunately, this is going to happen to some of us which is why we should have a screening test (for occult blood in the faeces) over the age of 50, to try to detect that sort of change early.

Inherited errors

The problems that I deal with are rather different from that. The people I see are from families who tend to have started off life with a mistake already in one of these important genes. Something is wrong in every single cell right from the very start - in every single cell of the body at birth. They have inherited that fault either from their mother or their father. People like this have that first step already in the important areas where these genes would normally protect us – in all the lining cells of the bowel. They have a much higher chance of developing adenomas and bowel cancer, and some other cancers as well. This is different. This is an inherited genetic problem which carried a very high risk – an 80% risk of bowel cancer. It would be good if we could find these people and provide appropriate screening and protection. This can be passed on – something that really would have an impact on the rest of the family.

This particular syndrome that I am going to talk about was described by Henry Lynch some years ago. Lynch described families with generation after generation of young people with bowel cancer – often under the age of 50. Over the years, he noticed that they had other cancers occurring in various parts of the body, most particularly cancer of the uterus in the females. He searched for the genetic fault causing this problem.

The 'Lynch syndrome'

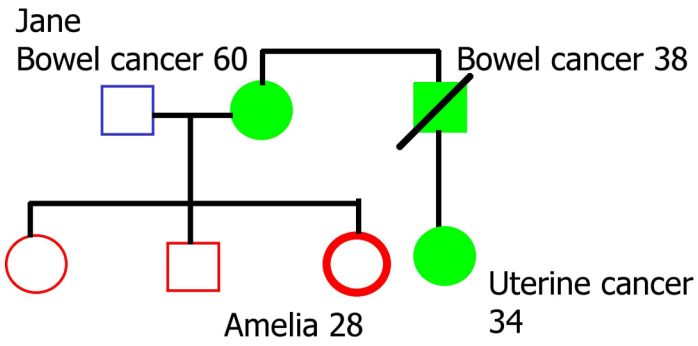
Initially we all called it the Lynch Syndrome. Then people started to think that it was a bit much his calling it after himself, so we changed it to the ridiculous name 'hereditary non-polyposis colon cancer' (HNPCC) a little bit more difficult to say. Funnily enough, the literature has kind of turned. Henry Lynch is now in his 90s. Perhaps people are just being nice, but the whole world has turned to calling it the 'Lynch Syndrome', which is ever so much easier to tell patients.

The Lynch Syndrome is due to an inherited fault in one of those repair genes I told you about – the proof-reading genes which make sure that cells haven't made mistakes before they divide. If you don't have that working properly, you have a much higher risk of cancers in many sites. Lynch determined that there was a very high risk of bowel cancer if you didn't do anything about it, probably an 80% risk of bowel cancer, and perhaps 40% of the women with these gene faults developed cancer of the uterus, as well as some small increased risk of other cancers.

Most of us have two healthy copies of these repair genes when we are born, one from each parent. People with the Lynch Syndrome have started off life with one good copy and one faulty copy, which could be from either parent. As they have that in every single cell when they are born, they have already taken that first step and are more likely to develop other gene faults, which can be passed on. When this person makes their eggs or sperm, half the eggs or sperm will have the good copy, half the faulty copy, so that means each child, male or female, has a 50% chance of having this gene fault.

The same applies for breast and prostate cancer families. It is not a 100% thing where everybody gets it. It is what is called a dominantly inherited condition, with a 50% chance for each child.

A typical family tree



Verification of family history

Amelia is a bit worried about her family history because her mother, Jane aged 60, has bowel cancer. That is not unremarkable. However, Jane's brother developed bowel cancer at 38, and she tells us that her cousin, aged 34, had cancer of the uterus. This is very young for uterine cancer.

This history looks like genetic testing for Lynch Syndrome might be helpful. In order to really know whether or not we should test this family, we first need to verify the family history. That is the first ethical and legal problem I am going to throw to David Weisbrot, because, as you can imagine in a family like this, it is sometimes a little bit complicated. People will occasionally say they have had cancer when they haven't, or people will think it was cancer of the uterus when it was cancer of the cervix, which has nothing to do with this.

Genetic counselling

In order for us to spend money wisely, we really need the genetic counsellor to verify this family history. In NSW that involves sending a consent form to Amelia, who sends it to her cousin, who signs – giving us permision to have access to the pathology report. We then approach the pathologists at the hospital she was at, obtain the report, and sometimes do special tests on the tumour, using special stains. You can imagine how hard this would be without the cooperation of the family.

What if that cousin were dead? Do I just march in and take the tissue, or would her husband give consent for that, given that it could be an issue for the children? It is quite different in Victoria, where they collect a family history, send it off to the cancer registry *holus bolus* and the cancer registry says verified or not verified. They have the family history which is much easier to verify, but a lot of information has been looked at for people (so far) the service has never met. We are rather more careful in NSW. It probably costs us more money and time to do this but no privacy, I don't think, is breached in this process if you have the appropriate consent, and that's what you do.

Lack of cooperation

That is the first tricky thing which comes up in cancer genetics. Some people don't want to cooperate. Some don't want it revealed that in fact they *never* had cancer. In fact, we recently came across a lady who has lived all her life worrying because she had breast cancer and is worried about her daughter. Once we got the pathology reports (with her consent), I unfortunately had to tell her that she hadn't had breast cancer. The diagnosis was made many years ago, with some nice surgeon patting her on the head

and saying, “It’s all right, dear, we have got it early, don’t worry”, and sending her on her way. In fact, the pathology report was benign.

The risk of developing cancer

For any of you who are worried about their family history as I talk about all of this, I can reassure you that most people would fall into what I call the ‘average risk’ category –people who have no family history of bowel cancer, or who have just one close relative who was diagnosed over the age of 55. That is a common history and doesn’t affect anybody’s risk.

The next category, according to NHMRC guidelines, would be people with a little more family history. We have just seen a family where there is really more than that; there are a number of affected relatives. There have been young people with cancers. This places Amelia at potentially high risk, not definitely high risk. We think that there is a faulty gene in the family. We don’t yet know whether or not she has the faulty gene.

Finding the gene fault

Our job now is to find the gene fault causing the problem in the family. I wish it were as easy as it is just to say it. Genetic testing, the way we go about it, is to first test someone with that problem. At this point, we can’t test Amelia. We have to test one of the affected family members, either her mother or cousin, whoever is willing to have this test. This testing takes quite some time to do.

Again, people are occasionally not cooperative. If they do agree, we take blood from an affected family member first and search for the relevant genes. Unfortunately, they are whopping great genes, which are quite difficult to test and this takes quite some time; and it is quite expensive for us to do. There is no Medicare item number, so the system pays for this genetic testing. We search up and down; quite often, even in a family where we know there must be a faulty gene, we can’t find the specific mistake in the gene that is causing that family’s problem – so we can go no further. That is what I call an inconclusive test. We still think that there is a genetic problem in this family, but we have not yet identified it.

In other families – and this is rather gratifying when it happens – we can identify the exact mutation or fault in a particular gene which is causing the problem. Then, and only then, can we test other family members – a very simple test which tells us whether or not they have that gene fault, whether or not they are at high risk, and whether or not they can pass it on to their children. This ‘predictive test’ is done quickly and easily once we know what we are looking for.

Checking the relatives

This can be a prolonged process in these families. In Amelia’s family, we would take blood from either Jane, her mum, or Jenny, her cousin, but occasionally we would have families where the affected family member simply does not want to be involved or we cannot drag anyone in to have a genetic test. For that sort of family, Amelia would be left in the potentially high risk situation. We would have to look after her as if she *did* have the condition, since we can’t clarify it for her.

Who should be testing these genes?

Then it comes to the question of who should be doing this testing. At the moment, it is done in some public laboratories. But there are also some private laboratories. This has become very topical recently in relation to the two known breast cancer susceptibility genes, BRCA1 and BRCA2. An American company, Myriad Genetics, holds the patent on these genes. The work, up to the finding of these genes in about 1995, was many, many years of intensive, mostly public, research which lead to the discovery of these genes, and the isolation of these gene sequences. Then, at the last minute, Myriad Genetics put in a huge injection of investment, won the race to find the gene sequence and patented the genes. They have the complete and utter monopoly on genetic testing in the United States and have tried to have a monopoly here, where they have given an exclusive licence for testing these genes to a company in Melbourne – Genetic Technologies – who, claiming their right to exclusive testing, have now twice tried to shut down the public laboratories.

Gene patents

There has been a Senate inquiry into gene patents. We will probably hear a little bit about that from David Weisbrot. In 2009, the American Civil Liberties Union – you've got to love them – brought an action challenging the validity of those patents. In March 2010, a US Federal Court judge invalidated many of Myriad's patent claims. We have our own expert here, Dr Luigi Palombi, at the ANU, who has really pushed this issue in the press for some time.

Judge Sweet said, "The products of nature do not constitute patentable subject matter." So there has always been this question of whether this is simply a discovery or an invention which would be patentable.

Watson and Crick, of course, discovered DNA. Since then, the discovery of various genes has been made. This new court case points, I suggest, to a major challenge of the patenting of genes.

The results for Amelia's family

Back to our family: Jenny, the cousin, does agree to have blood taken for a mutation search. She waits about six months for the results - that's how long it take. As we do find a mutation in one of these repair genes, we can now test other family members, including Amelia, now desperate to know whether or not she has this problem. There would be little point to genetic testing if there were absolutely nothing we could do about this disease. If Amelia has this gene fault, she is at very, very high risk of bowel cancer. For such families, we start screening colonoscopies at about age 25 and do them every one to two years. Doing that and removing polyps has been shown to reduce mortality from bowel cancer in these families.

Also, women with this faulty gene, once they have finished having their family, may have a hysterectomy to prevent ovarian cancer and cancer of the uterus – cancers for which we have very little screening. So something can be done about those.

Some people choose to have pre-natal testing – pre-implantation genetic diagnosis – which is not common. On the other hand, if we find that Amelia doesn't have this gene fault, she can forego all this expensive and unnecessary screening. She will be at average risk and so will her kids. If she doesn't have it, her kids can't have it.

Questions arising

That is the good way in which genetic testing works. We know the risks. We know what to do about it. Otherwise, there would be little point in this sort of testing. In the end, Amelia, fortunately, was found not to carry this gene fault. There are some other questions we needed to answer before she had that genetic test and they relate to some of the things David Weisbrot might talk about:

- How does this impact on my life insurance or my health insurance?
- What is the privacy of this sort of test?
- Who is going to know about it?
- Can an insurance company call me and get the result?
- Should my children be tested for an adult onset disease? The answer is no.
- Should I have any more children?
- What if I become pregnant?
- Can I have a test which will tell me if my child has this condition?

There are a number of issues that arise for a family as a result of all of this genetic information.

Conclusion

I hope that I have shown you the differences between what I think are serviceable and useful medical genetic tests and 'designer tests', which I will cover very briefly. Only a couple of weeks ago, Walgreens, a pharmacy chain in the United States, were about to launch, with great fanfare, an at-home genetic test which allowed you to assess your risk for cancer, Alzheimer's, etc. Luckily the FDA put a stop to that. This is the sort of thing that is happening. I've told you about the lady who had a test done

through a personal trainer. There is an increasing number of people who think they can make money from the worried-well by looking at your genes and giving you really very little clinical information which is, at the moment, of any relevance. There is one particular one available through a Sydney GP at a cost of $4,150, which 'enables them to look at circulating tumour cells'. Really, there is not much science behind this to justify spending that amount of money. Family members, worried about whether or not they have cancer, can pay $900 for this test which has no scientific support.