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Predictive medicine

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Printed and bound in the United Kingdom at the University Press, Cambridge.

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Introduction

In this course you will learn how advances in genetics could change the way in which diseases are diagnosed and managed. The advent of predictive medicine, based on more detailed DNA profiling of individual genotypes using technologies like gene chips, rather than screening for one gene at a time, may shift the relationship between doctor and patient. People will be seeking advice on how to manage their susceptibilities or genetic risks, rather than looking for treatment for an already existing disorder.

This OpenLearn course provides a sample of Level 1 study in Science.

Learning Outcomes

After studying this course, you should be able to:

- understand some of the ways in which genetic knowledge could affect medical practice, in particular in relation to predictive medicine
- understand how populations are screened for conditions such as phenylketonuria and whether screening could be used for carriers of recessive genetic disorders such as cystic fibrosis
- understand how gene chips may be used to screen for large numbers of genes at once, making it possible to predict the likelihood of developing certain diseases and how people may react to such predictions
- understand the implications for the health services.

1 Genetics and healthcare

1.1 What is the future of healthcare?

When someone in the UK visits their GP for a flu jab, to confirm a pregnancy, or to report an unexpected pain, they know that behind him or her stands a vast system for diagnosis, treatment or prevention of disease in the whole population. The details differ from country to country but, like all industrialized countries, the UK has a healthcare system that is one of the largest industries. Tens of thousands of people and tens of billions of pounds a year come together inside a complicated network of institutions to try to achieve what the Americans call 'health maintenance'. The effects of genetic knowledge and the speed with which they come about will be set, in large part, by health services. The new technologies — for genetic testing or screening, pharmacogenetics or gene therapy — will have to be used by health workers. Governments, or health insurers, will have to pay for these new technologies, and answer for their effectiveness. Policy-makers will have to decide not just whether these new technologies can be used, but how they will fit in with existing organizations.

2.1 Predictive medicine?

Some experts now suggest that new knowledge of human genetics is likely to transform medical practice. They propose three main possibilities:

- Genetics will lead to the classification of diseases on the basis of the underlying genetics or biochemistry, rather than by symptoms.
- Genetic information will identify people who are likely to respond to drugs, or to be harmed by them (pharmacogenetics).
- Genetic variation will be a new '*susceptibility factor*', or '*genetic risk factor*', permitting monitoring and early treatment or, perhaps prevention, of an increasing proportion of common, multifactorial diseases, such as coronary heart disease, hypertension, stroke, cancer, diabetes and Alzheimer's disease.

The first two will be important for professionals, but less so for patients' experience of healthcare. The result of a consultation will still be a diagnosis, or a drug prescription. They may be more accurate or more effective than before, but can be dealt with in familiar ways. It is the third, often summed up as the advent of **predictive medicine**, which could imply much greater changes.

Predictive medicine, if it comes, will be based on a much wider use of genetic testing — for more people, and more disorders. At the moment, there is quite a big gap between the scenarios sketched for the future of genetics-based medicine by forecasters and what the health system is geared up to deliver. As with any new technology applied to health in the context of a complex delivery system, implementation is not going to be simple.

SAQ 1

What kinds of thing can you think of that influence whether, and how quickly, a new health technology gets taken up?

Answer

First, of course, there needs to be demand, from doctors, or patients, or both. Then, in the abstract, introduction of new technologies into healthcare also typically need all of the following:

- Demonstration that they work, or are *clinically effective* – through statistically valid trials;
- Demonstration that they are *cost-effective* – through economic analysis of trials and other data;
- Standardization of technology, and *quality control* – through technical definition of standards and, for example, regulation of suppliers or laboratories;
- Allocation of *resources;*
- Recruitment and *education* and *training* (or retraining) for health workers – including specialists, GPs, nurses, counsellors and technicians.

In the case of genetic technologies for predicting common diseases, all this is likely to happen along with a move to rethink public health in terms of genetic information. But before discussing how that might come about, let us consider what we have learnt about implementation from the genetic technologies that have already found widespread use.

2.2 Population screening for genetic disease: the precedents

Knowing about particular genes, or their effects, also permits screening – the search in a population for persons with certain genotypes that are associated with a particular disease. Thus the test may be offered to one and all. Until now, screening programmes have focused on one gene at a time, or one disease at a time, in cases where a mutated gene poses serious health problems and something can be done for those who are found to carry the mutation. What that something is varies with the disorder. We will look at two different examples, phenylketonuria and cystic fibrosis.

2.2.1 Phenylketonuria

The classic example of population screening is testing new-born babies for phenylketonuria (PKU). Individuals with PKU fail to make a protein, a certain enzyme, and develop mental retardation. The absence of the enzyme results in both an accumulation of phenylalanine, which causes the mental retardation, and a deficiency of tyrosine in the body, as shown in Figure 1.

SAQ 2

Because both phenylalanine and tyrosine are constituents of a normal diet, in what way could mental retardation be prevented in babies born with PKU?

Answer

By restricting the intake of phenylalanine in the diet.

PKU was the first disease for which treatment in the form of dietary restriction was successfully used. Most children are relatively free of symptoms when given such treatment, hence screening of new-born babies. The technique, first used in 1960, is not strictly a genetic test. No fancy DNA technology is involved, just a needle prick on the baby's heel to produce a blood sample (Figure 2). A cheap biochemical test then identifies children who have more phenylalanine than usual in their blood. Only some of these have PKU, and more tests are then needed to identify them more definitely. Babies who do have PKU are put on a phenylalanine-restricted diet, but this is harmful to those without the disorder.

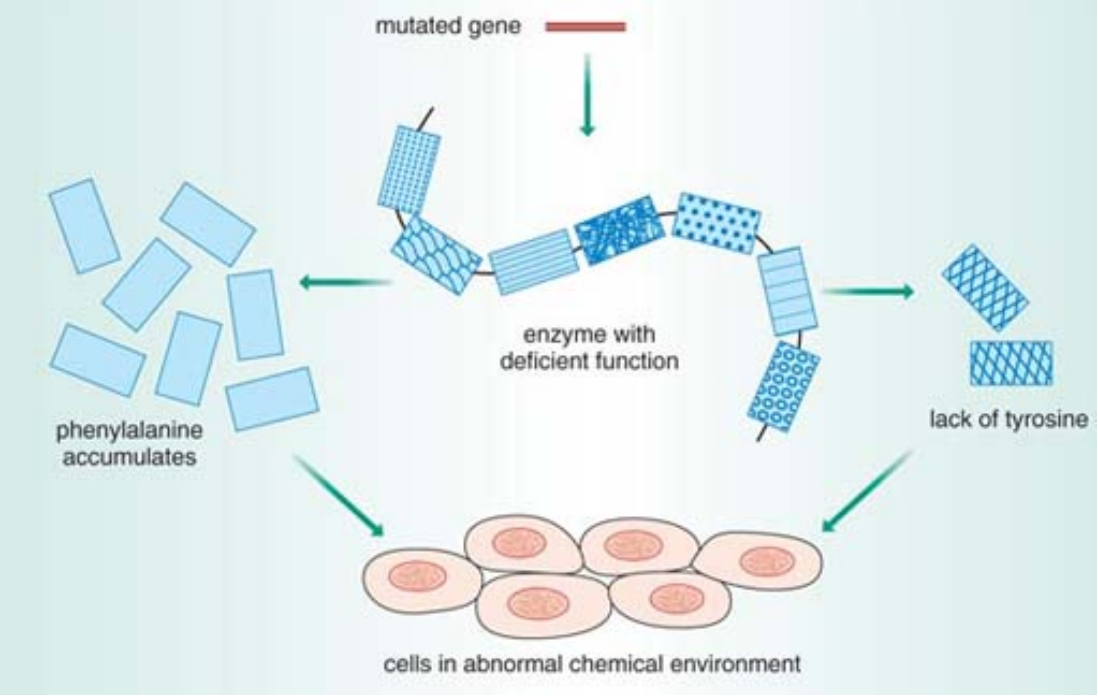

Figure 1 A schematic representation of the biochemical consequences of the deficient gene product (enzyme) associated with phenylketonuria (PKU). This enzyme plays a role in the synthesis of amino acids, the building blocks of proteins. Specifically, the enzyme breaks down the amino acid phenylalanine into another amino acid, tyrosine.

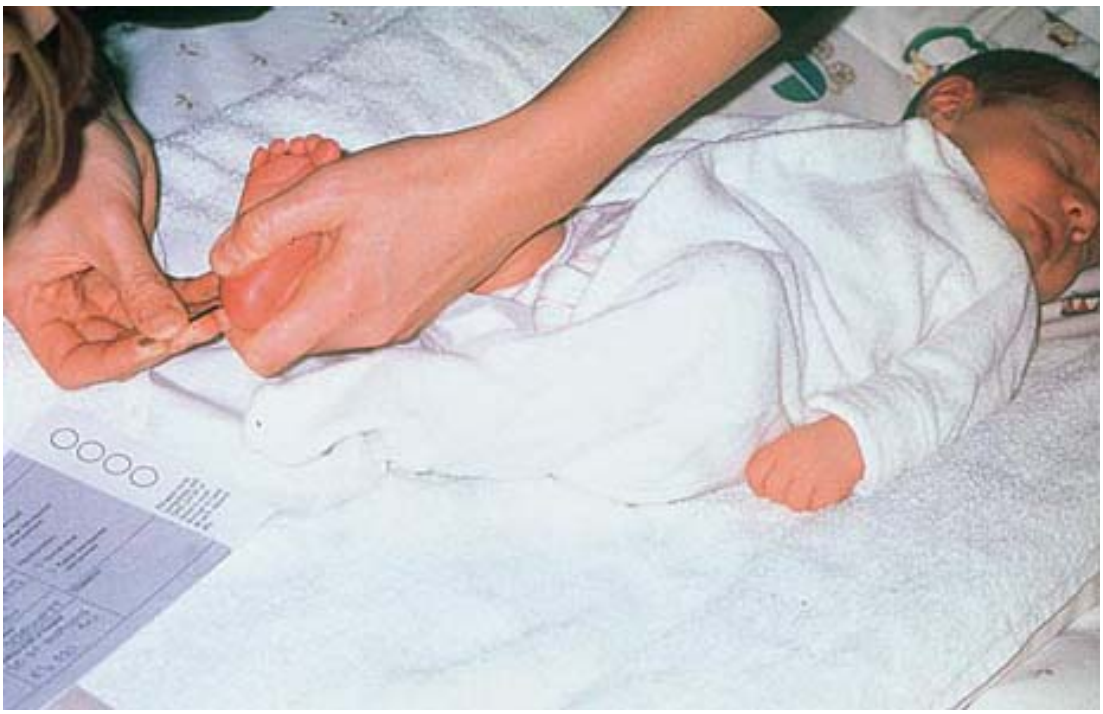

Figure 2 Blood taken by heel-prick, commonly called a Guthrie test, used for screening new-born babies for PKU.

Not completely straightforward, then. As with all tests there is a possibility of misdiagnosis (of *false positive* results) from the heel-prick test. For those correctly diagnosed, the special diet is both expensive and unappetizing – not an ideal combination for child rearing. And a woman with PKU who bears children herself must also adopt a special diet when she is pregnant. On the whole, though, it works. Although PKU is fairly rare (around 1 in 15 000 live births), it used to account for roughly one per cent of profound mental retardation. Screening has practically eliminated this. And as the test is so cheap, and long-term care of the disabled children so costly, universal screening is cost-effective. In the UK, where almost all new-born babies are tested, the money saved is estimated at four times the cost. In 1995, it cost around £800 000 to screen 100 000 babies, but caring for the ones who would have been damaged by excess phenyalanine would have cost over £3 million. The cost saving, of course, goes along with sparing those parents the distress of raising a child with brain damage, but policy-makers like to have both kinds of benefit.

2.2.3 Cystic fibrosis

A different model for the genetic tests of the future is screening for cystic fibrosis (CF). This is a DNA-based test, which became possible after the gene involved in CF was identified in 1989. CF is a recessive disease, and it should be easy to test to see if prospective parents carry a mutated allele. A simple mouthwash yields enough cells for DNA extraction. If both partners are carriers, they can consider further counselling before conception, and/or pre-natal testing of any potentially affected fetus.

Even simple disorders are turning out to be not so simple. There are now known to be more than 900 different mutations in the gene for CF. Many are rare, but even the best (and most expensive) testing currently envisaged would identify only about 85% of couples at risk. Even so, CF screening would probably be cost-effective, too. But the situation is complicated by the fact that the only way to ‘prevent’ the disorder is for two

carriers to avoid having children, or to be prepared for an abortion if a pregnancy turns out to be the one in four that has two mutated copies of the gene for CF. At the same time, treatment for children with CF (Figure 3), more and more of whom now live well into adulthood, is getting better, but also more expensive. And prospective parents may, of course, hope that forecasts about gene therapy come true in time to help their child. So once again a potentially straightforward test leads to decisions that are anything but straightforward.

2.2.4 Longer-term considerations

Something else to ponder is the effect that screening might have on the longer-term incidence of disease and (not the same thing) on the incidence of gene variants linked to disease. Sometimes, the impact on a disease can be dramatic. Take thalassaemia, a haemoglobin disorder similar to sickle cell disease, in which premature destruction of haemoglobin-containing red blood cells leads to anaemia. It is relatively common in some Mediterranean countries. Like sickle cell disease, it is understood in great detail at the molecular level, but this has produced little in the way of effective treatment. So screening may be offered to adults to identify carriers. In Cyprus, where there was such a high incidence that the Church endorsed screening before marriage in what are typically close-knit communities, thalassaemia has all but disappeared. In the UK, by contrast, medical services find it harder to reach those at risk, who are scattered among a community of largely low-risk families. As a result, the incidence of thalassemia has only fallen by around 40 per cent.

However, even if marriage avoidance or pre-natal diagnosis and abortion were more common, what effect would this have on the frequency of a disease *allele*, as opposed to the incidence of the disease? If the disorder results from a dominant gene, as in Huntington's disease (HD), then testing and termination tend to eliminate the allele from the population. But then there is no point in mass screening for dominant disorders, such as HD, as families involved already know that the disease is in the family – that is what dominance means. An affected person has an affected parent who in turn had an affected parent. But most of the simple genetic diseases are due to inheritance of two recessive alleles.

Figure 3 A father giving physiotherapy to his son with CF to remove the build-up of mucus from the lungs.

SAQ 3

In recessive disorders, what effect might pre-natal diagnosis and selective abortion have on the frequency of the allele in the population?

Answer

Not much, since only fetuses with two mutated alleles will be eliminated. Heterozygotes will be spared and, as adults, may pass the mutant allele on to their children.

In fact, the availability of pre-natal testing may encourage some couples to have more children than they would have had previously. Similarly, preventing PKU by altering the diet may increase the frequency of the allele concerned, as many of the children who used to be damaged would not have reproduced.

2.3 Scaling up

They may look at dozens of alleles, and involve thousands of people, but existing screening programmes have been concerned with *individual* genes. But the technologies now being developed will soon permit the recording of hundreds of genes at a time. So-called *gene chips* combine the skills of microchip designers with DNA sequence information to offer rapid, easy-to-read results for an individual covering hundreds of genetic variants. A gene chip is a thin slice of glass about the size of a postage stamp. Stuck to the surface is a grid, each line the width of a human hair and each containing a small sequence of single-stranded DNA, a gene variant. The total DNA can represent either hundreds of gene variants for just one gene, for a number of genes or even a gene set for the entire genome. When a patient's DNA is added to the chip, pieces stick to matching sequences and the rest are washed away. The results are read by means of an electronic scanner and analysed by a computer software program, which identifies the matches within a matter of hours. Gene chips are already in use; for example, the one used for detecting variants in the breast cancer gene *BRCA1* can detect any nucleotide change in any position in that gene.

SAQ 4

If such a DNA chip was developed for cystic fibrosis, what would be the consequences for screening for this disease?

Answer

Since at least 900 variants are known, this technology could identify all variants or alleles of the gene and not just the common ones, making screening much more exact, and eventually foolproof.

When devices like this come into wider medical use, potentially as desktop boxes in the doctor's surgery, then more general DNA profiling of individuals, i.e. identifying variants for many hundreds of genes simultaneously, becomes possible. In 2005, the UK Human Genetics Commission recognized that DNA profiling is likely to become feasible in less than 20 years time. There will be no problem handling all the data, according to the forecasters: ‘assuming that there are about 1000 clinically relevant genotypic markers [variants] per person, then genotyping one billion people would result in about 10 terabytes of data, an amount that would fit on a mere 1000 DVD optical discs’, says a writer in the journal *Science*. But what will we do with all this information?

In general, it will not be the kind of information derived from earlier screening programmes, which has been used to choose specific treatments for one known disease,

or to offer advice about the chance of a pregnancy producing a child with a particular, usually not very common, disorder. Instead, it will add up to a catalogue of individual **susceptibility factors**, or genetic risk factors, or alleles, for the most common, multifactorial diseases – like cancer, heart disease, stroke, diabetes, hypertension or Alzheimer's disease. (The term 'genetic risk factor' refers to a susceptible disease allele and should not be confused with 'risk factor', meaning an 'environmental factor'. Both genetic risk factors and risk factors increase the risk of an individual developing a particular disease.)

And while it will help doctors make predictions, they will be statistical predictions, telling people they are more likely to develop this disease, less likely to develop that, than the population at large. This will pose quite different problems of counselling and decision-making than those seen with the single-gene disorders – like CF or HD, for example – which make up the bulk of our experience of genetic testing so far.

The complexities of hereditary influences on breast cancer hint at some of these problems. Spend a few minutes thinking about what might be some of the main problems of counselling and decision-making posed by the discovery of the two genes – *BRCA1* and *BRCA2* – strongly associated with breast cancer, before reading on.

There are a number of features of the link between certain alleles of the two genes and breast cancer that may be hard to convey clearly, to health professionals as well as patients. They include:

- Most breast cancer is *not* associated with either of these two genes – each of which accounts for perhaps 2.5 per cent of the total incidence of the disease.
- Although certain alleles of the genes concerned are associated with an enhanced risk of breast cancer, testing for them does not give a clear-cut result. A positive test does not mean that a woman will definitely get breast cancer. A negative test does not mean that she will definitely not. This is *not* related to inaccuracies in the test – false positive or false negative – it is simply a property of the genetic information. The development of cancer is a multi-step process and involves mutations in at least five or six genes. An individual who inherits a recessive, mutant allele in either the *BRCA1* or *BRCA2* gene is one step nearer to developing cancer than an individual who inherits two normal alleles of both of these genes. The absence of a clear-cut result contrasts testing for a single gene disorder such as HD, where a positive test for a mutant allele means a certainty of developing the disease.
- If a test result is positive, there is no certain route to prevention. Options include so-called prophylactic mastectomy, or breast amputation, along with hysterectomy of womb and ovaries to reduce the risk of ovarian cancer associated with the same genes. Less drastically, regular monitoring may be recommended, but if this is done using X-ray mammography, it may itself increase cancer risks (X-rays are mutagenics).

Cancer is a source of particular anxiety to many, so it would probably be wrong to suggest that testing positive increases the numbers of the 'worried well'. They may already have been concerned about breast cancer, especially as many will have seen a high incidence of the disease in their families. What is clear is that publicity about 'cancer genes' increases demand for testing (in contrast with the experience of HD), and that responsible management of the tests demands a great deal of explanation and counselling. One result has been that some doctors in cancer clinics have had to become genetic counsellors.

This begins to suggest some of the demands that would be produced by more widespread genetic screening that yielded information about health risks and disease probabilities.

Another difficulty is that, although more health workers can be trained to help people to deal with information like this, not too much is known about how their customers will respond. We know a certain amount about how people understand probabilities (not too well, on the whole), but much less about how they may react to specific predictions.

SAQ 5

Can you think of different ways in which people might deal with a genetically-based prediction that they were at high risk, or genetically susceptible, for heart disease in middle age?

Answer

Research suggests there are two broad classes of reaction: activism and fatalism. Activists try and take control, and strive to minimise their risk by diet, exercise or drugs, and by avoiding smoking. Fatalists, on the other hand, hear the prediction as something they can do little about, and decide they will indulge freely in all the things health-educators say are bad for you – because they are going to get sick anyway.

The trouble is, it is hard to know who will react which way. There are similar uncertainties about other common disorders that are often suggested as candidates for susceptibility, or genetic risk, prediction. If a gene of major effect in the development of schizophrenia is ever identified, for example, some families may feel they are relieved of blame or guilt for the occurrence of the disorder, while others may interpret a test that shows the presence of the gene as showing that they are to blame after all. Again, we do not really know which is more likely.

Click below to view the video sequence.

Video content is not available in this format.

Now would be a good time to view this video sequence, which requires you to consider some medical benefits arising from knowledge about our genes.

2.4 Current UK provision

One way of describing the organizational shift that the advent of predictive medicine would demand is to suggest that genetics would become a general, rather than a specialist service. But it is much easier to say that than to explain how it will happen. For all the publicity about genes, genomes and genetic information, medical genetics is a very small part of current health services.

In the UK, an indication that a patient or a family has a genetic problem will lead to a referral to a regional genetics centre. There are just 25 of them, each catering for a population of between one and five million people. Between them, they dealt with 37 000 amniotic fluid samples from pre-natal testing in 1997–98, of which just 4.1% were abnormal. In the same year, a mere 769 DNA tests on adult cells for individual genetic variants, such as those linked with cystic fibrosis or breast cancer, were carried out in UK molecular genetics laboratories.

Even at this level, the regional genetics centres are already stretched. Their workload increased by between 50 and 100% between 1991 and 1997, and has gone on increasing since. For example, the number of genetic tests available for use rose from 41 diseases in 1991 to 178 diseases by 1998. As a specialist service, regional genetics centres are widely regarded as a model of organization, with specialist doctors typically working alongside counsellors and nurses trained in genetics, and often keeping close links with laboratory researchers. But it is an organization that has grown up catering for rare disorders such as CF and HD, and not common, multifactorial diseases with a genetic component, which may affect the whole population.

So far, policy-makers have tended to assume that the obvious way to bridge this gap is to update GPs on the new knowledge of human genetics, and get them to advise people about what any new tests might mean. But ask GPs, and most say they are already much too hard-pressed to take on this work. When you recall that the average consultation with a GP lasts a little over five minutes, this is not surprising.

Another answer may be to train more nurses to communicate about genetics, or to integrate genetics with wider health education and public health programmes. Of course, the latter might simply increase demand for genetic advice, and make it harder for the health service to keep pace. Either way, expect to read a good deal more about the need to adapt the health service to make the most of new genetic knowledge, alongside the much more familiar debates about NHS funding and staff recruitment and training.

Conclusion

When we read about genetics and the future of medicine, we should also think about genetics and the future of health services that have to deliver medical care. The advent of predictive medicine, based on more detailed DNA profiling of individual genotypes using technologies like gene chips, rather than screening for one gene at a time, may shift the relationship between doctor and patient. People will be seeking advice on how to manage their susceptibilities or genetic risks, rather than looking for treatment for an already existing disorder.

This will have implications for how healthcare is organized — in terms of standardizing technologies, informing clients, and training staff. We know little as yet about how this transition will need to be managed.

All these changes will occur against a backcloth of public debate and government consultation and decision-making about new genetic technologies. The best ways to involve ordinary citizens in this discussion are still being worked out.

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