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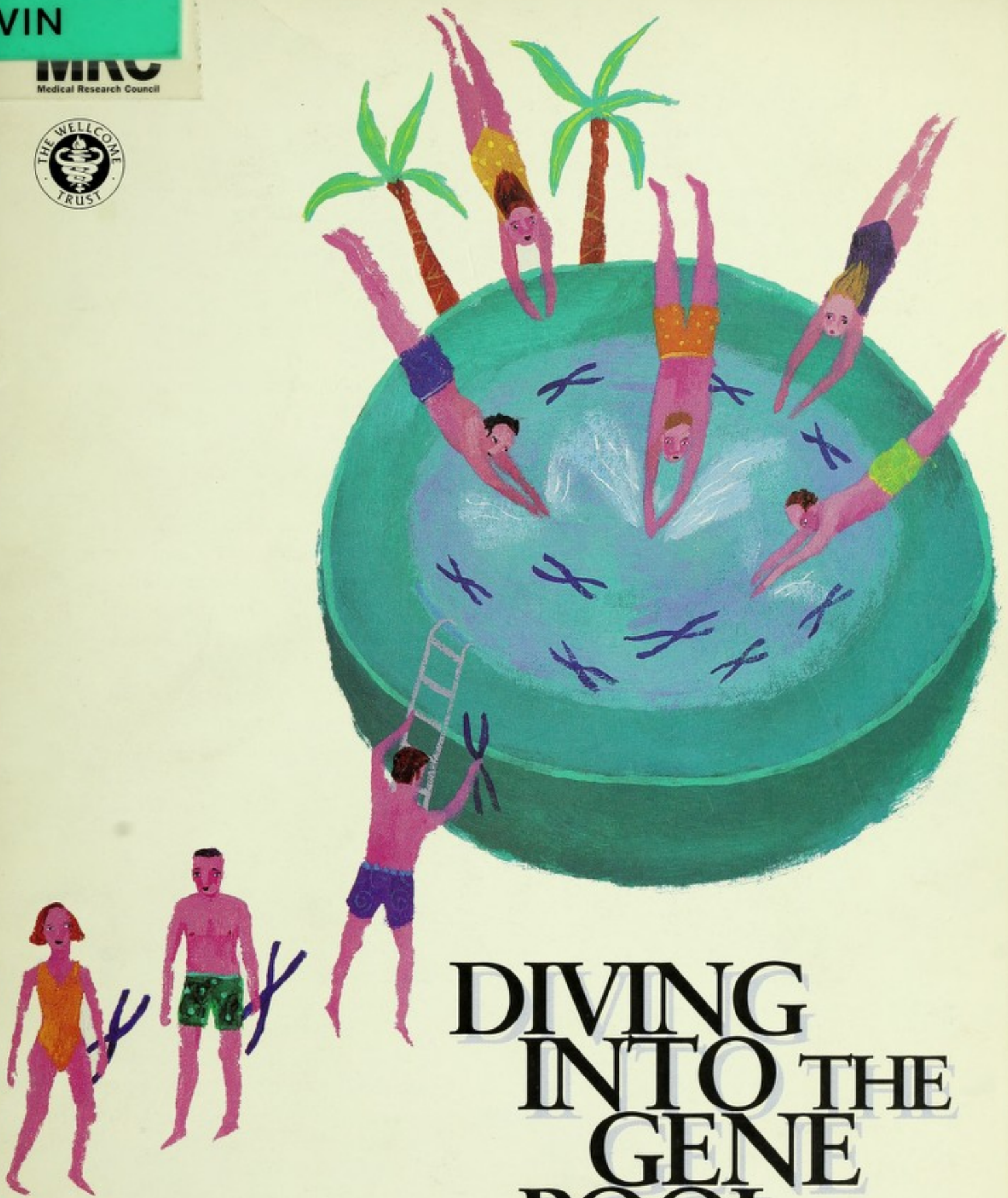


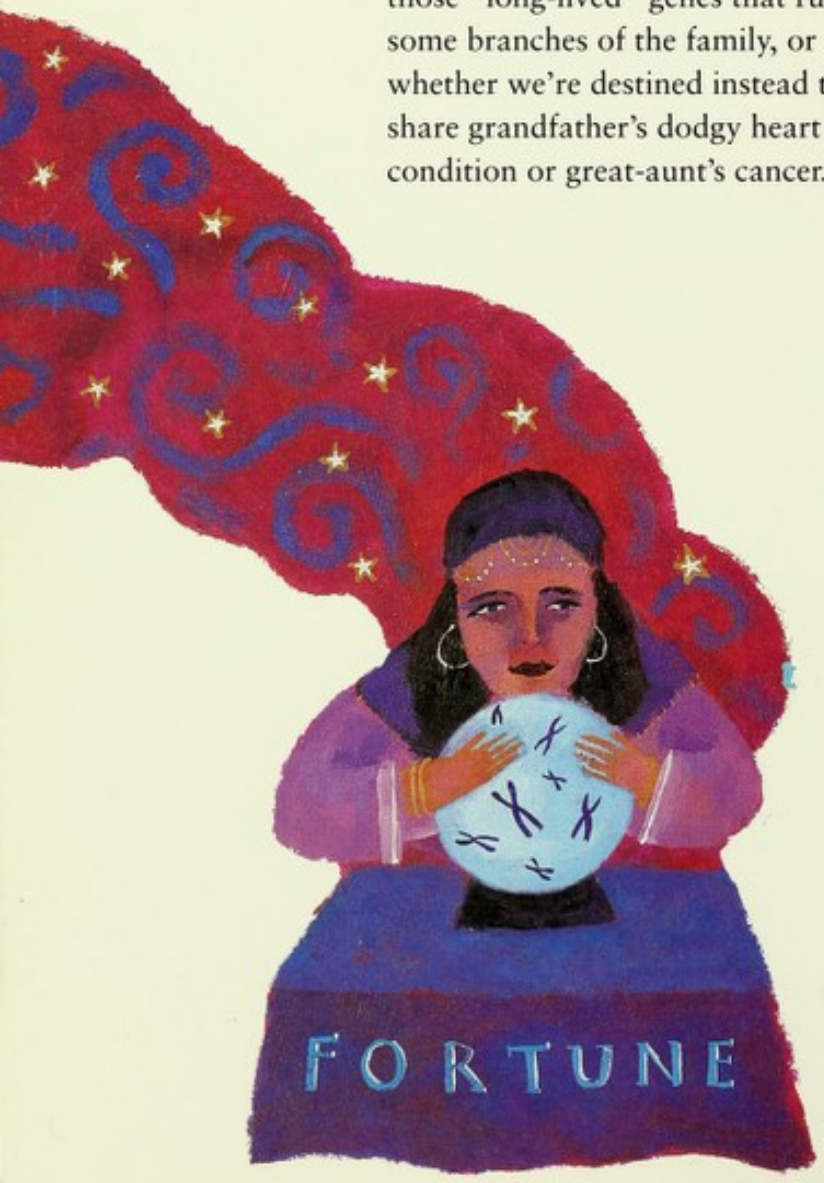
DIVING INTO THE GENE POOL

A user's guide to the new genetic medicine

DIVING INTO THE GENE POOL

Sports scientists joke that – despite everything they know about training and diet – Olympic hopefuls would be best advised to choose their parents carefully. Inheriting a powerful frame and strong lungs gives athletes a built-in advantage for which no amount of pasta loading or workouts at the gym can entirely compensate.

Increasingly, we think of our present and future health in similar terms. We muse about whether we've inherited those "long-lived" genes that run in some branches of the family, or whether we're destined instead to share grandfather's dodgy heart condition or great-aunt's cancer.



ONE DAY, PERHAPS, we won't have to guess. Our children may be able to know for certain how they have fared in the genetic lottery. A quick visit to the local doctor's gene lab may suffice to reveal which disease-causing genes they have had the bad luck to inherit.

Such definitive genetic knowledge is still the stuff of science fiction. Today, our insights into the genetic roots of health and disease are far more limited. Yet knowledge about human genetics is growing rapidly, in the wake of the Human Genome Project – an international programme of biomedical research to map and sequence the entire complement of human genes, in all their variety. Ultimately, we may know all the genes in the "human gene pool". Researchers estimate that humans possess between 60 000 to 100 000 genes; so far, geneticists have isolated about 1000.

This knowledge has led to genetic tests that can tell some people whether they are at high risk of developing one of a handful of inherited disorders, or whether their children are at risk. Year by year, the number of genetic diseases that can be diagnosed in this way is rapidly increasing. What's more, it may eventually become possible to treat, and even cure, genetic disorders such as cystic fibrosis through "gene therapy", and this is now an area of active research.

IN THE BLOOD: WHAT GENES DO

People have always talked about "family resemblances" – as diverse as a Roman nose, slender fingers or a gift for music – that seem to pop up generation after generation. We now know that some – but by no means all – of these recurring traits really are "in the blood": they spring, that is, from shared genes passed down from parents to their children.

But shared histories are influential too. Sorting out which of these features can be put down to the genes, and which to the "environment", is no easy matter. In fact, most human characteristics – even such basic things as the shade of your skin – are the result of a complex interaction between genes and life experiences.

Genes are microscopic molecules packed away in every cell in our bodies. They carry the coded instructions cells need to make the right protein in the right place at the right time.

Some proteins build the body's structural framework, such as muscle, bone and teeth. Others are enzymes, which orchestrate living processes to keep the metabolism ticking over nicely. So a "mistake" in a gene that results in a malformed protein can have all sorts of consequences.

You could say that genes – those spiral strands of DNA – are relatively simple-minded cogs in the incredibly sophisticated machinery of our bodies. Yet when one of these cogs goes wrong, it can have far-reaching effects.

BUT FINDING OUT what's gone wrong can be tricky. Part of the problem is that genes don't work in isolation. So to understand the function of any one gene, scientists have to unravel all the complex interactions between genes and the hundreds of other sorts of biomolecules in cells. For a start, researchers need to discover which protein a gene normally produces when "switched on", and what turns on the "switch". Only then can they begin to work out what goes wrong when that gene goes awry, and to search for ways of correcting the fault.

WHEN IS A GENE 'BAD'?

Humans have 99.98 per cent of their genetic material in common, but minute genetic variations persist. Many genes exist in the human gene pool in scores or even hundreds of variants, each only slightly different from the next in its sequence of chemical building blocks. Most of the time we are oblivious of such trivial differences. They matter only when they happen to lead to disease.

Researchers have now tracked a few hundred, mostly very rare, inherited diseases to single genes. In most cases, a disease actually develops only if an individual inherits two copies of the same faulty gene variant, one from each parent. Some of the more common conditions – such as cystic fibrosis, thalassaemia and sickle cell disease – are inherited in this way. Geneticists call this "recessive" inheritance. A child has a 1 in 4 chance of being born with the disease if both parents are healthy "carriers". The parents have just one copy of the disease gene and suffer no ill effects from it.

But in some genetic diseases, inheriting just one copy of a particular gene is enough to cause the full-blown disease. These are the "dominant" genetic disorders, such as Huntington's disease – which is characterised by a gradual loss of control over movement and mental deterioration in middle age. Each child has a one in two chance of having inherited the disease from a parent who has the Huntington's gene, and who will also eventually develop the disease.

Serious genetic diseases can also result from a genetic mishap during the formation of the sperm or egg. About a third of the children born with Duchenne muscular dystrophy fall into this camp. For reasons that are still unclear, some genes seem particularly prone to these spontaneous changes, or mutations.

GENES ALSO PLAY an important role in the development of the major killers in the West. The so-called chronic diseases of coronary heart disease, stroke, diabetes and most forms of cancer take years to develop, and are heavily influenced by an individual's diet, body weight, smoking habits and penchant for exercise. But perhaps as many as a dozen genes may also influence our susceptibility to each of these diseases. Most of us know an Uncle Fred who led a dissolute life and lived to a ripe old age, while Aunty Mabel, who did all the right things, was struck down in mid-life. Some of this patent unfairness could well be the result of good or bad luck in the genetic lottery.

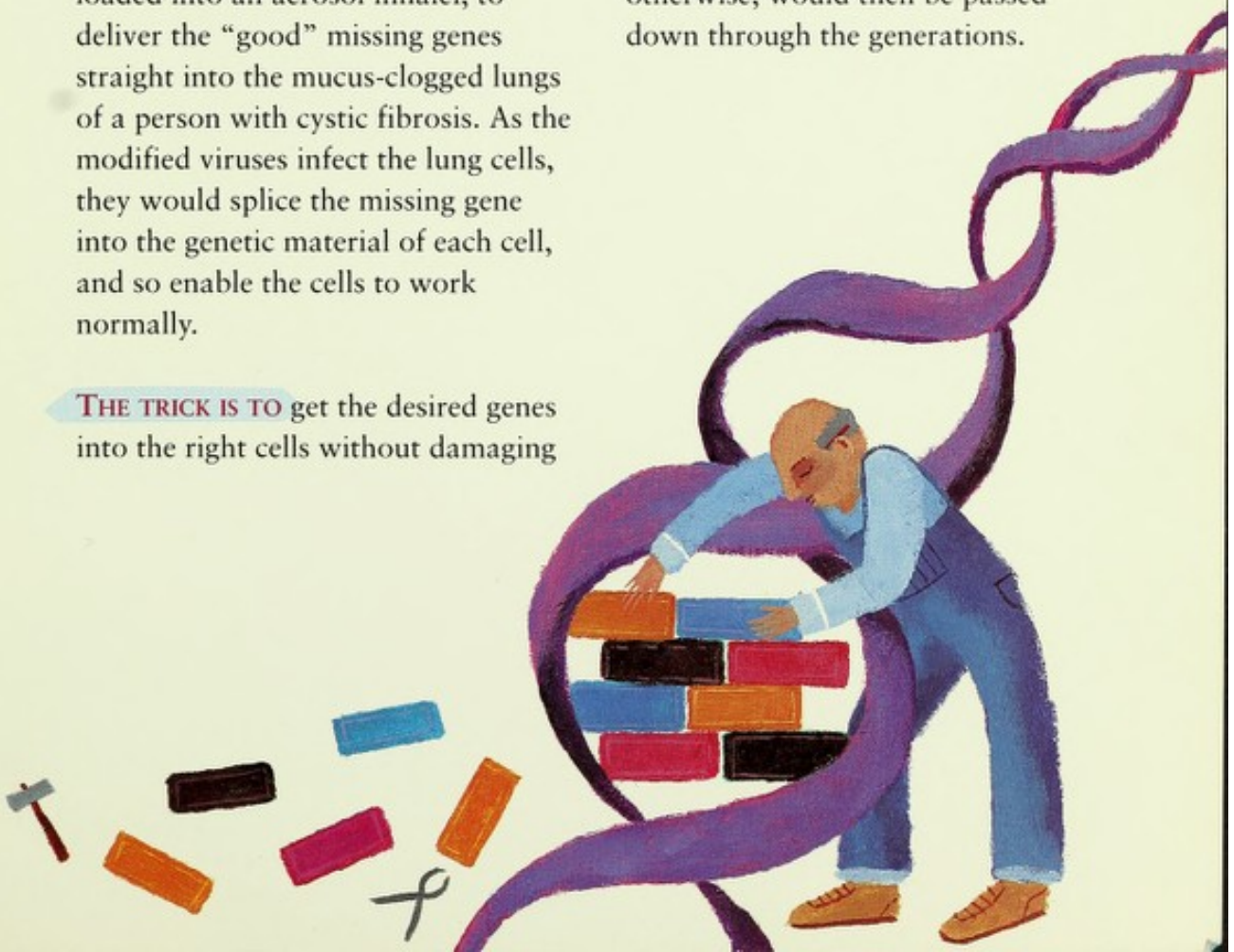
REBUILDING GENES

Gene therapy – treating or preventing disease by manipulating an individual's genetic material – is now moving out of the realms of fantasy and into the clinic. The idea is to ferry into a patient's body copies of the desired gene, which will produce the missing protein or the missing genetic "switch".

Progress is being made using specially "disabled" viruses and other gene-carriers such as liposomes (fatty particles) to ferry healthy human genes into the relevant cells: say, the lung cells of people with cystic fibrosis, or the muscle cells of boys with Duchenne muscular dystrophy. For instance, these viruses could be loaded into an aerosol inhaler, to deliver the "good" missing genes straight into the mucus-clogged lungs of a person with cystic fibrosis. As the modified viruses infect the lung cells, they would splice the missing gene into the genetic material of each cell, and so enable the cells to work normally.

THE TRICK IS TO get the desired genes into the right cells without damaging the cells' genes. What's more, researchers need to ensure that the new gene works properly once in position, and continues to function normally for as long as possible. Overcoming these problems remain a considerable technical challenge, and gene therapy is unlikely to become a routine treatment during the next ten years.

More controversial is the concept of "germ-line gene therapy", in which the sperm, egg or embryo itself is genetically modified to alter a disease-causing gene. But most researchers and ethical bodies consider this form of manipulation to be unacceptable. Any modifications, intentional or otherwise, would then be passed down through the generations.



SCREENING FOR GENES

Clinical geneticists in major UK hospitals can now offer genetic tests and counselling to individuals or couples who realise that a known genetic disorder runs in their family. Affected children can be given the best care available, and parents advised of their risk of having further affected children. The couple may choose to have prenatal tests during subsequent pregnancies and to terminate the pregnancy if the fetus is found to have inherited the disease.

Sometimes it is also feasible to search more or less at random for people with a particular faulty gene. For instance every hospital screens newborn babies for an inherited metabolic disorder called PKU, which can be treated by diet. More controversial are proposals to screen adults of child-bearing age to detect healthy carriers of disease genes such as cystic fibrosis. The idea would be to inform individuals or couples of their risks of having an affected child.

A FEW GENETIC TESTS now available are a form of "genetic forecasting". These attempt to reveal the risk that an individual will later develop a serious disease, such as Huntington's disease.

In the future, scores of diseases that strike only in later life may become amenable to this novel form of fortune-telling, although diagnosing susceptibility to chronic diseases such as coronary heart disease is likely to be some years distant.

Whatever the future holds, it is important to keep in mind that, today, most genetic tests give ambiguous, uncertain results. Usually, no one can say for certain whether a person who has inherited a suspect gene will in fact ever develop the disease. Conversely, **not** having the gene in question does not guarantee you won't get the disease.

So even though genetic tests are now becoming available for men and women who have a "family history" of ovarian or breast cancer, Alzheimer's disease and some kinds of bowel cancer, these tests cannot as yet give definitive predictions. What's more, in many cases little can be done to prevent the condition developing. But in some circumstances, knowledge of a genetic risk to health enables people to take preventive action. For instance, individuals discovered to have a genetic condition that leads to very high levels of cholesterol in their blood may be able to reduce their future risk of heart disease by changing their diet or taking cholesterol-lowering drugs.

WHO SHOULD KNOW WHAT ABOUT WHOM?

The uncertainty of today's genetic tests creates hidden complexities. Genetic testing of any kind needs to be accompanied by extensive genetic counselling and social support in screening programmes, so that people can fully take on board what the test can tell them, and what it can't.

More research is needed to discover what people want to know, and with what kinds of support. A landmark screening programme in Wales for newborn children with Duchenne muscular dystrophy has proved popular even though there is no effective treatment for this muscle-wasting disease. The key is to give "bad news" in the best possible way, say the researchers – backed up by counselling, expert medical attention and social support. There is a danger that cheap and cheerful screening tests with no face-to-face social support may proliferate: already, a commercial enterprise offers carrier testing for cystic fibrosis through the post.

DO MOST PEOPLE want genetic tests? The evidence is equivocal to date. Before a test for Huntington's became available, many people at risk said they would want to know. But in the event, remarkably few have taken up the offer. On the other hand, women with a family history of ovarian or breast cancer seem to welcome genetic tests. Each disease may present a different picture, as the complexities of genetic medicine become apparent.

As all forms of genetic testing become more widespread, there are real fears that discrimination against the "genetically stigmatised" may surface. Already, insurance companies have refused to rule out the possibility that they would penalise, or even refuse to insure, people found to harbour genetic defects that might make them ill in the future. The issue of privacy and access to medical records is also a matter of heated debate. Legislation may be needed to safeguard human rights in an era of genetic diagnosis.

The genetic lottery is an apt metaphor: each of us inherits a unique complement of genes, on loan from the human gene pool. Increasingly, we are in the novel position of seeing just how we have fared in this game of chance. In the future, medical research may find ways of altering our genetic makeup, or the ways our genes work, to make us all healthier. But other scenarios are also imaginable. We need to act now to ensure that our growing knowledge of genetic mischance does not fuel new forms of social discrimination.

If we can tackle these important issues head on, and use the information wisely, then advances in genetics have the potential to improve both our understanding of what causes disease and our ability to develop new therapies.

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You can visit an exhibition "Science for Life" at the Wellcome Centre for Biomedical Science at 183 Euston Road, and read the souvenir guide *Science for Life*

For more information on charities working for families with genetic diseases contact:
GENETIC INTEREST GROUP
Farringdon Road
London EC1M 3JB
tel: 0171 430 0090
fax: 0171 430 0092

For more information on all childhood disorders and to be put in touch with local support groups:
CONTACT A FAMILY
170 Tottenham Court Road
London W1P 0HA
tel: 0171 383 3555
fax: 0171 383 0259

For medical help:
If you seek genetic counselling for yourself or your family contact your GP, who should be able to refer you to a regional clinical genetics clinic

For more information on ethical issues in genetic medicine contact:
NUFFIELD COUNCIL FOR BIOETHICS
28 Bedford Square, London WC1B 3EG
tel: 0171 631 0566 fax: 0171 323 4877
for a copy of
Genetic Screening: Ethical Issues
Published by the Nuffield Council for Bioethics (see above), December 1993, price £6 inc p+p

FURTHER READING

Assessing Genetic Risks: Implications for health and social policy edited by Lori B Andrews et al, National Academy Press, Washington DC 1994.

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