

**A genomic revolution**

Within the next year or so, the largest ever international collaboration in biology – the Human Genome Project – will reach its climax. The sequence of the three thousand million chemical coding units in human DNA will be known in its entirety. For the first time ever, we will have an inventory of the mechanisms that permit human life to occur. The completion of the Human Genome Project will be a significant step in our voyage of self discovery.

Genome...

the entire DNA sequence of an organism

We already have the entire list of genes for many viruses and bacteria [[see://five/A microbe's genome/>](#)], for yeast, and for a nematode worm. We will soon have such lists for organisms like the fruit fly, a weed called *Arabidopsis*, and the mouse [[see://four/Of flies, worms, weeds and rodents/>](#)]. The sequence of the smallest human chromosome was completed at the end of 1999. Gene lists for farm animals, crops, and other organisms will be a little longer in coming. Making comparisons between the genomes of these organisms and humans is instructive, since even distantly related species have many very similar genes organised in much the same way [[see://four/Genomes are similarly organised/>](#)].

**Genes behind functions**

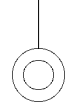
Genome projects aim not merely to discover genes but to explore their functions in living organisms, populations and communities. Researchers can ask questions about biology in a completely different way than in the past. Rather than asking one at a time what particular genes do, they can ask how many genetic factors lie behind a particular phenomenon, what the proteins that the genes code for actually do and to what extent is each gene or protein involved. Such 'functional genomics' will occupy researchers long after the Human Genome Sequence is completed [[see://three/DNA chips/>](#)].

Gene...

a discrete unit of inherited information

Sequence...

the precise linear order of DNA's chemical units



### What drives this endeavour?

Curiosity is one moving force behind these genome projects. However, the knowledge that stems from genomics will almost certainly be useful in addressing some of the severest of humanity's problems: lack of food, pollution, infectious diseases, and the afflictions of old age. Armed with knowledge of the genetic constitution of humans, animals, plants, and other organisms, we can start to define such problems – distinguishing those aspects which are influenced by genes, from those affected by external factors such as economics and politics.

In agriculture, for instance, the improvements made to plants and animals through selective breeding in the past have been on a trial and error basis. Genome studies can reveal what individual genes or combinations of genes do and they will identify in plants and animals variations in traits which have high economic and adaptive value. This will not only make plant and animal breeding more efficient but will also allow breeders to evaluate biodiversity within crops and livestock and within gene banks and other stocks. [[see://seven/Genomics on the farm/>>](#)].

Genomics also changes our understanding of the environment. People are much more environmentally conscious now than 20-30 years ago, when the tools available for studying and understanding the environment were crude. Researchers are now beginning to use genetic markers as a way of following the interactions within a given species, and between that species and any others in its environment [[see://eight/Environmental genomics/>>](#)].

Genomics will also dramatically influence healthcare: it will allow doctors to diagnose disease earlier and more precisely and to prescribe medicines more securely; pharmaceutical companies will develop better and safer drugs; and those who plan and fund health services will be able to assess the relative impacts of medicine, nutrition, and environment/lifestyle on health and disease [[see://six/Human health and disease/>>](#)].

#### Genomics...

acquiring genome knowledge and determining what genes do

### Impacts on society

Some forecasters anticipate that genomics will effect a transformation in the health services. Genomics yields information. Knowledge about our individual genomes will indicate more precisely those diseases to which we are each susceptible and the medicines to which we best respond. Genomics can also help reveal the causes of common killer diseases and has the potential to identify individuals who are particularly susceptible to a given disease long before that disease becomes apparent. Of course, such early warnings of disease possibilities could make people anxious. This is why counselling must be put in place alongside genetic analyses. Given the resources to use the new knowledge, genomics could make medicine much more personalised, holistic, and effective.

Genomics may even change the way we think about ourselves and other living beings on this planet. It may give us a much clearer picture of human kinships and our relatedness to other species. We may have to adjust the ways we conduct our lives to accommodate our new-found capacity for self-knowledge at the genetic level. There may be new responsibilities to bear – the responsibility to adopt a lifestyle that compensates for our genetic frailties, for instance – and we will need to be alert to possible misuses of our new-found knowledge [[see://nine/Living with genomics, and//ten/Genomics in our society/>>](#)]. In many respects, the completion of the Human Genome Project will be only the first step in a much more complex journey.



one

## A genomic revolution



two

## What's in a genome?

A genome is an organism's complete genetic signature; it is the palate of information an organism can call on in order to ensure its own survival and growth. The genome is the collection of information that an organism can pass on to its offspring before birth.

### Genes and genetics

Genes are the units of inherited information; each one contains codes for the production of a different protein. Proteins are the 'activity' molecules in the cell. Thousands (or tens of thousands) of genes come together to constitute an organism's genome. In chemical terms, genes are made of DNA [\[see://DNA\]](#).

Genomes are more than just sets of genes. The entire DNA sequence of an organism contains recognisable genes and other stretches of DNA, including some regions within genes, that do not appear to code for anything. Non-coding DNA accounts for as much as 90-95% of human DNA [\[see://four/Of flies, worms, weeds and rodents/>\]](#).

Genetics is the study of patterns of inheritance. The 'father' of genetics, Gregor Mendel, noticed patterns of inheritance for wrinkliness and colour of peas. The British biologist, J.B.S. Haldane noted that 'hairy ears' ran in certain Indian families. Thus, we have come to relate genes to attributes such as wrinkliness or hairy ears. In these cases, there appeared to be a one-to-one relationship between a gene and a characteristic.

### Transgenic organism...

an organism produced through genetic modification to contain a gene or genes from another species

### Genes are not deterministic

As more and more information on genes emerged, it became clear that simple one-to-one relationships were exceptional. It is quite usual, for instance, for more than one gene to lead to a given trait. Alternatively, genes may need to act in combination before a particular character shows through. Furthermore, environmental factors may influence the trait, sometimes dominating genetic factors. [\[see://six/Associating genes with disease/>>\]](#).

### Junk DNA...

DNA which does not code for proteins and which has no known purpose for the cell

### Is genomics biotechnology?

Genomics is just a part of biotechnology; it is principally about obtaining and dealing with genetic information. That information helps us understand how organisms and ecosystems work, how they malfunction, or how they might be melded to human needs.

Biotechnology is about using living organisms and cells for the benefit of mankind, about the animals and plants on which we depend [\[see://seven/Genomics on the farm/>>\]](#), and about the environment [\[see://eight/Environmental genomics/>>\]](#). Some parts of biotechnology – silage making, dairy production and fermentation, for instance – are traditional practices in agriculture and industry. Others are much more recent; genetic modification for example, emerged only in the mid 1970s.



### Genetic modification

Genetic modification is a way of creating new combinations of DNA codes using the same natural mechanisms by which all organisms cut, copy and mend their own DNA [[see://Genes and genomes change](#)]. One use of genetic modification is to produce proteins as medicines. DNA is, in essence, chemically coded information and the code is the same in all organisms. A piece of DNA that codes for a human protein will direct the production of the same protein in whatever organism it is present. A yeast, or a plant, or an animal could therefore produce large amounts of a protein that is lacking in particular patients. DNA is like the digital code on a music CD: it produces recognisably the same 'song' whether it is played in hi-fi equipment, a Walkman, or an in-car stereo. Very few of the messages written in DNA code are uniquely human: humans and apes share about 98% of their DNA, but human and plants also share over half, and there are many genes that are common to humans and microorganisms.

This means that discoveries made in genomics can rapidly be put into action through genetic modification. If a new gene is discovered, for instance, the protein it codes for may be produced readily in microbes or other organisms in order to understand more precisely what it does.

### Genes and genomes change

Genomes are not static. Genes mutate and, during reproductive processes, genes from parent organisms are shuffled and dealt in new combinations to offspring. Human beings first exploited this genetic variation over 10,000 years ago, encouraging plants and animals that contained combinations of genes that suited their needs as farmers. [[see://seven/Genomics on the farm/>>](#)].

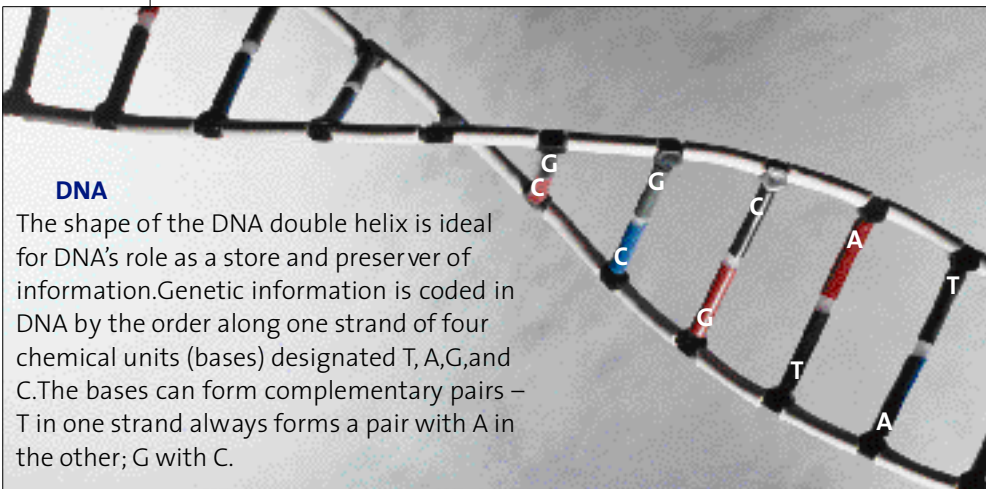
Humans have also domesticated microbial species [[see://five/Domesticated microbes/>](#)] and our intervention has increased over the years. The yeast for the first wines probably came from the bloom on the grape; the microbes that made the original cheeses came from the animals that were milked. Today's beer and bread yeasts, however, are specially selected high performance strains and dairy producers use pure preparations of starter culture.

#### Recombination...

the production  
(natural or artificial)  
of a new assortment  
of genetic information

### DNA

The shape of the DNA double helix is ideal for DNA's role as a store and preserver of information. Genetic information is coded in DNA by the order along one strand of four chemical units (bases) designated T, A, G, and C. The bases can form complementary pairs – T in one strand always forms a pair with A in the other; G with C.





two

What's in a genome?



three

Sequence is just the start



The world-wide effort to produce the complete genome sequences of numerous microorganisms, plants, animals and humans is only the beginning in genomics. There are at least two further levels of complexity: gene activity and gene variation.

### Gene variation

An organism's genome may contain thousands, or even hundreds of thousands of genes. Each gene may vary in DNA terms between individuals. The human genome, for instance, contains around 100,000 genes: there are at least 500,000 common sites of DNA variation within the human genome. At most of these sites, the difference between one person and another is small and, in many cases, may have no effect. Some of these variations will be important, however. They may explain why some people are more susceptible to disease than others [[see://six/Associating genes with disease/>>](#)]. They might account for whether an infectious organism causes a disease or is relatively benign. DNA differences might underlie allergies to nuts or other food, information which could be very useful for food manufacturers, growers, and consumers. Different genetic variants might distinguish animals that produce meat that is lean rather than fat, something that farmers and animal breeders would be interested to know.

Sequencing...

determining the order of DNA's chemical units

### Gene activity

Although every cell of a complex organism such as a plant or animal has an identical genome, not all of the genes in the genome are active in all cells. Different cell types use different sets of genes. Thus some plant genes are active and produce proteins only in the leaves, or in the roots: some animal genes only produce protein in brain cells or liver cells or muscle cells. Similarly, the usage of genes by an organism can change with time or circumstances. For instance, when an organism is under stress, it activates extra genes.

A completed genome sequence is like a 'parts list' for an organism, a catalogue itemising all the molecules an organism can make. Armed with a genome sequence, researchers can ask which proteins or genes an organism uses when it is performing a particular function.

DNA chip or microarray...

a small device for detecting the presence or activity of many genes simultaneously

DNA chip or microarray



**DNA chips**

The activity of a large number of genes can now be measured simultaneously using a device called a DNA microarray or DNA chip. In a microarray, thousands of different DNA sequences are attached to a glass or silicon surface such as a microscope slide or computer chip. Each active gene in a cell produces a large number of temporary mirror images of itself as part of the process of making proteins. These mirror images bind specifically to their corresponding DNA sequence on the DNA chip where they can be detected using fluorescent reagents.

Thus DNA microarrays enable researchers to see which genes are active at any particular time and under any specific circumstance. They provide, in effect, a 'snapshot' of gene activity in a cell.

Microarray techniques are very useful in understanding how bacteria behave. DNA corresponding to each of the few thousand genes that bacteria have can be placed on a single microarray in order to show, for instance, which are active during infections. That information could be useful in designing new antibiotics or other treatments. Current microarrays cannot accommodate all the 100,000 or so genes of organisms such as plants, animals or humans. But the use of DNA chips to monitor a subset of genes – say, those that control the human immune response – would be very valuable.

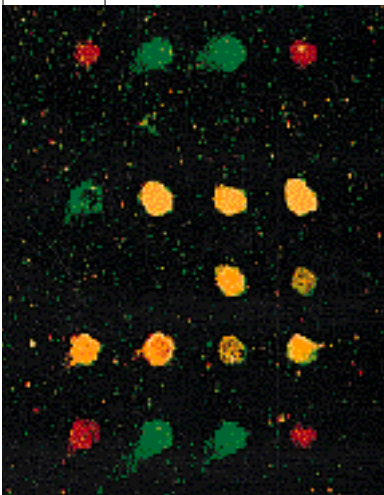
Several companies are working to develop DNA arrays that can be used rapidly and cheaply as routine diagnostic agents [[see://six/Diagnostic techniques/>>](#)]. These will use the same basic principle of detecting DNA or RNA that sticks specifically to the array. However, the binding would be read very rapidly using lasers or detected directly by electrical signalling. A related concept is the 'lab-on-a-chip'; this is a highly miniaturised device being developed for rapid, routine, medical diagnosis. The lab-on-a-chip would contain minute reaction chambers to prepare samples, plus microscopic plumbing and pumps to transport reagents around to detection elements such as DNA arrays.

**Beyond gene activity**

Studying genes and their activity cannot yield a wholly accurate molecular picture of how living organisms work. An activated gene will produce a protein, but that protein may have to be further modified before it is active. It may need to act in tandem with other proteins or with carbohydrates or fats in order to fulfil its role. Ultimately, it will be degraded by enzymes in the cell. Thus a more complete picture of living cells and organisms will necessitate a fuller description of protein function.

**RNA...**

a molecule that carries mirror image copies of DNA information to the cell's protein producing machinery

**Rapid sequencing**

Sequencing methods are now highly automated and miniaturised. Industrial-scale sequencing laboratories house hundreds of robots serviced by teams of technicians.

Most genome sequencing projects are internationally organised and funded because, although they are large, they need to be performed only once. The reams of data they generate – in essence, sequences of millions and millions of 'letters' of coded information – are not published in scientific journals but on the internet so that scientists around the world can have immediate access to them.



three



four

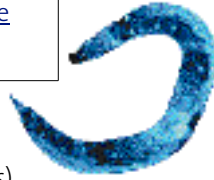
## Sequence is just the start Of flies, worms, weeds and rodents



*Drosophila*

Model systems are important in science. The model organisms used in genomics have, in general, small genomes and short generation times. Investigations into organisms such as the fly and the worm, and the mouse and the rat yield a great deal of information that can be relevant to humans and animals. Often experiments that can be performed on model organisms would be impractical or unethical in higher organisms. For plants, the model organism is a small weed called *Arabidopsis* [[see://Weed power](#)].

Model organisms have a unique value in genomics. Not only are many of the genes from disparate organisms very similar, but their genes are often grouped in the same way on chromosomes. [[see://Genomes are similarly organised](#)].

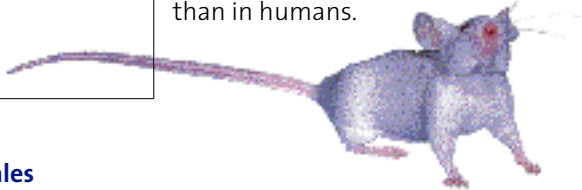


*Caenorhabditis*

### Models of man

The sequence of a nematode worm (*Caenorhabditis elegans*) was completed at the end of 1998 and that of the fruit fly (*Drosophila melanogaster*) in 2000. Their genomes are around 30 and 20 times, respectively, smaller than the human genome. Both organisms are simple and quick to grow, their development is well understood and the existence of completed genome sequences enables the role of particular genes in the growth and behaviour of the organisms to be determined. Most genes seen in these model organisms have direct equivalents in more complex species, such as humans.

A more recent addition to the range of model organisms is the Japanese Puffer fish, or *Fugu*. The *Fugu*'s genome is six or eight times smaller than the human genome, but it probably contains about the same number of genes for similar functions, organised in similar ways. The density of genes in the genome, therefore, will be much higher in *Fugu* than in humans.



### Furry tales

Mice and rats are also models in human genomics. Rodent genomes are not significantly simpler than those of larger animals or man. However, rodents are familiar experimental animals, easy to breed, and widely used to study physiology, behaviour, and the effects of medicines. The rat genome project is not far advanced but significant progress has been made in obtaining physical and genetic maps in mice. A working draft of the mouse genome sequence is expected by 2003. Researchers envisage that when the Human Genome Project is complete, the work of assigning functions to human genes will depend largely on experiments in mice. Some researchers would argue that the most significant advance in understanding the molecular detail of how human beings work will come not with the completion of the human genome sequence but later with the completion of the mouse sequence. Until both genomes are completed, the scope for testing all the hypotheses that stem from human genomic information is very limited.

To find out what a human gene does, researchers will typically disable the comparable gene in one of the model organisms and observe the consequence. It is already possible, for instance, to breed mice with specific genetic deficiencies (knock-out mice) which can be used to simulate human genetic conditions. It would be unethical to do knock-out experiments in human beings, even if it were possible. Genomics will greatly accelerate the speed and fine-tuning of this research.



*Arabidopsis*

### Weed power

Some important crop plants such as wheat may have genomes larger than the human genome, so to perform genomic studies on them would be cumbersome. A model organism for genome analysis in plants is *Arabidopsis thaliana*, whose five chromosomes may well contain the smallest amount of genetic information necessary for a flowering plant. The *Arabidopsis* genome is scheduled for completion in 2000 as a result of an international programme of work featuring researchers in the European Union, North America, and Japan. The sequencing of two of its chromosomes was completed in December 1999. The *Arabidopsis* genome will provide a route map of potentially valuable genes that could be used as templates to look for similar genes in other species [\[see://Genomes are similarly organised\]](#), and could be transferred to work in other species. For example, researchers have recently found an *Arabidopsis* gene for dwarfing that can be made to work in rice.

### Model organism...

an organism studied because it can tell researchers about more complex organisms

### Genomes are similarly organised

The most interesting finding to emerge from genetic analysis over the past two decades has been the similarity of genes between different species, and their similar order along the chromosome. Organisational similarities between the human and mouse genomes were confirmed at the end of 1999 when the first complete sequence of a human chromosome, chromosome 22, was published. Over 80% of the human sequence that contains genes includes regions that have direct counterparts on mouse chromosomes. A comparison of wheat and rice genomes also shows relatedness. The two plants last had a common ancestor about 60 million years ago, and today, the genome of wheat is about 40 times the size of that of rice. However, many of the genes and their order on the chromosomes are virtually identical. Plants and animals, too, can have similar genes: a fungal resistance gene in the weed *Arabidopsis* is also used by the fruit fly to combat a fungus.

This conservation of genes and their organisation means that characterisation of a gene, or a whole genome, in one species immediately provides important clues both about gene function in related species, and about the nature and function of individual genes more widely.





four

Of flies, worms, weeds and rodents



five

Model systems and human genetics

### A microbe's genome

Over 30 microbial genomes have been completely sequenced, more than for any other group of organisms. This is partly because microbial genomes, like the organisms themselves, are small. But it is also because microbes are extremely important. Pathogenic bacteria, fungi and viruses are major causes of death and illness for most of the world's human population and are responsible for massive losses of crops and livestock world-wide. Most microorganisms, however, do not cause disease. Organisms on our skin or on the leaves of plants, for instance, help exclude pathogens, and virtually all antibiotics originate in microbes. We rely on microbes to produce much of our food and drink [[see://Domesticated microbes](#)], to maintain the quality of soil [[see://eight/Environmental genomics/>>](#)], and to recycle waste. Furthermore, certain microbes that live in unusual conditions represent life at the extremes.

### Fighting disease

There are two main ways in which microbial genomics will help to improve disease control. First, total sequencing and characterisation of the genes of pathogenic organisms will reveal new ways to attack them, and explain how the organisms resist existing treatments. An example is current research on *Campylobacter jejuni*, one of the world's most successful food poisoning bacteria, probably responsible for more than twice as many reported cases of enteritis as *Salmonella*. Its genome sequence contains about 1700 genes. Over a third of the *Campylobacter* genes appear to have no known counterparts anywhere in nature. On the other hand, the organism seems to have several copies of a gene thought to code for an enzyme that makes changes to the bacterium's surface – a possible clue to *Campylobacter's* ability to evade its host's immune system.

Second, microbial genomics will reveal new antibiotics and other natural therapeutics. In 2000, scientists expect to complete the genome sequence of *Streptomyces coelicolor*, a representative of a bacterial family that has made a major contribution to medicine cabinets over the past fifty years. As well as providing the antibiotics erythromycin, streptomycin, and tetracycline, *Streptomyces* has been the source of antiparasite and antifungal agents, an immunosuppressant, and an anti-cancer drug. *Streptomyces* genes for antibiotic synthesis can be 'mixed and matched.' Once the full complement of genes is known, there will be opportunities to design novel antibiotics and other therapeutics. Understanding the genes that regulate natural biosynthesis will enhance industrial manufacture of natural and semi-synthetic antibiotics.

Genomics will help guide the design of new drugs against specific microbial pathogens, and suggest strategies for minimising the evolution of drug resistance. The complete genomes are, or soon will be, available for many important microorganisms, including those that cause syphilis, tuberculosis, Weil's disease, and some types of food poisoning. Similar data are being generated for other human and animal diseases including anthrax, whooping cough, thrush, gonorrhoea, bubonic plague and malaria.





## Domesticated microbes

People have used domesticated plants and animals since the beginning of farming [\[see://seven/Genomics on the farm/>>\]](#); they have also used microbial species to transform milk into cheese and yoghurt, to soften leather, and to ferment beer and wine [\[see://two/Genes and genomes change/<\]](#). There are over 300 traditional fermented foods world-wide, ranging from the familiar European breads and cheeses to fermented starch crops in Africa and fermented soya beans in Asia.

Genomics yields a much more precise understanding of familiar fermentation organisms. The genome for baker's yeast, *Saccharomyces cerevisiae* was published in 1997 [\[see://What we don't know\]](#). Lactic acid bacteria are major food fermenting bacteria whose genetic characterisation is opening up opportunities for making new and improved foods and, for example, exploiting natural compounds such as nisin for the control of harmful bacteria in foods.

**Microbe, microorganism...**

**organisms such as bacteria, fungi, and viruses that can only be seen with a microscope**

## Extreme genomics

Some of the 100 or so current microbial genome projects are investigating organisms that live under extreme conditions – in highly salty water, hot springs, deep sea volcanic ducts, radioactive environments, or arid deserts. The expectation is that these organisms will have evolved useful and exotic qualities that may be exploited commercially, just as we now use enzymes from heat tolerant organisms in washing powder and food processing. Genomics means that in future such microbial prospecting will be structured and comprehensive, rather than having to rely solely on good fortune.

A better understanding of the relationship between gene sequence, protein sequence and structure, and protein function will also mean that information about natural evolution can be used to underpin 'forced evolution' of microbes, in which scientists drive the production of specific new properties in microorganisms under highly controlled conditions.



## What we don't know

One of the first organisms to be fully sequenced was yeast. Industrially, yeast is important in brewing, winemaking, baking and many other processes. Scientifically, it has been thoroughly studied because it is a primitive representative of higher organisms (such as plants, animals and humans). The yeast genome has over six thousand genes. A function could initially be assigned to only a third of them. The level of human ignorance revealed when the human genome (two hundred times bigger than that of yeast) is sequenced will be similarly humbling.

*Streptomyces*





five

## Model systems and human genetics

### Human health and disease

Genomics research will have a major impact on our understanding of human disease. Studying the human genome will improve understanding of how our own genes influence our susceptibility to illnesses (including infectious diseases; [\[see://five/A microbe's genome/<<\]](#). With further research, that knowledge should lead to improvements in diagnosis, prevention and treatment.



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## Implications in health

### Associating genes with disease

Genetic diseases are those where an inborn genetic factor initiates or influences a detrimental effect on human health. Genome studies demonstrate that many disorders have a genetic component even where the dominant influence is external or environmental.

Much of the power of genomics lies in its ability to connect the occurrence of particular variations in DNA with medical disorders. In the simplest cases, just a single gene is involved and the 'misfiring' of that gene almost always results in the disease. Doctors knew long before genomics was conceived that conditions such as Gaucher's disease, Huntington's disease, cystic fibrosis and sickle cell anaemia had a genetic basis because it was clear that they ran in families. There are thousands of such obviously inherited illnesses, many of them severe. Fortunately, most of them are also rare. Modern genetics provides more accurate diagnostic methods for people who are at risk of inheriting these conditions [\[see:// Diagnostic techniques and//nine/Kith and kin/>\]](#) and the prospect of treatment – through techniques such as gene therapy or the use of medicines – for those who have the disease.

Genome studies also reveal, however, that many more common human afflictions such as diabetes, Alzheimer's disease, stroke, heart disease, and asthma may have significant genetic components. Their inherited aspects have previously been obscured because many variants of many different genes may be involved. Environmental factors such as diet and hygiene, and/or social factors such as access to healthcare also influence the occurrence, severity, or detection of such diseases. Doctors and medical researchers plan to conduct large-scale health surveys that aim to correlate genetic variations and environmental factors with the occurrence of common diseases. The world's largest such survey – of half a million people – is already being planned in the UK. In 2000, the first results of a similar European survey on cancer will be known. One of the key tools used in these surveys will be an entirely new kind of one-stop genetic test – a DNA microarray, or DNA chip – that will probe hundreds of genes simultaneously [\[see://three/DNA chips/<<\]](#). Thus genomics will yield a much clearer picture of the causes of human disease.

**Predisposition...**

**the likelihood, determined in advance, of getting a particular condition**

### Diagnostic techniques

Once a disease-associated gene has been identified, DNA-based diagnostic tests can be designed. Most of the tests exploit the double helix nature of DNA [\[see://two/DNA/<<\]](#): in effect, one strand of the double helix is used as a probe to bind to the complementary strand (if it is present) in the sample. The binding is so specific that it is significantly weakened by just a slight mismatch between the two strands of DNA. Coloured or fluorescent reagents, or chemical or physical methods detect the binding reaction.

Traditional DNA-based tests examine one gene variant from one patient at a time. Newer methods – using DNA microarrays – can look at several hundreds of genes at a time. Ultimately, doctors could use large DNA microarrays for genetic profiling, to characterise a patient's risk across a wide range of diseases.

DNA-based tests have several potential advantages. First, they are very sensitive. A simple swab inside the mouth, rather than collecting blood, will provide enough cells for diagnosis.

Second, DNA-based tests are potentially simple and rapid. In the near future, some tests could be performed in doctors' offices, out-patient units, or even at home, rather than in specialist laboratories.

Third – and this is both a strength and a challenge – DNA-based tests can be predictive. Many current diagnostic methods confirm the presence of a disease by, for instance, detecting certain cell types or chemicals produced during illness. However, genetic tests often indicate that there is an increased or decreased likelihood that illness might occur in the future [\[see://nine/Living with genomics/>\]](#). They do not necessarily indicate the timing of the disease, its severity, or, indeed, whether it occurs at all [\[see://nine/What our genes tell us/>\]](#).

#### Genetic profile...

a description of an individual based on a set of their genetic variants

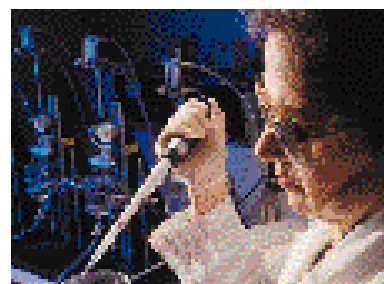
### Treating disease

Exploration of the human genome will identify new opportunities to develop medical drugs. It has been estimated that all the drugs ever developed interact with just 500 molecules in the body. The Human Genome Project is expected to yield a list of around 50-100,000 human genes. By identifying those variants that are associated with disease [\[see://Associating genes with disease\]](#) and understanding how the proteins that they code for act, researchers will be able to design new drugs. There may be only a few thousand or a few hundred such drug targets.

Genetic tests can also improve the use of existing drugs and drugs under development. Genes influence both the positive reactions to drugs (where they work well) and the negative ones (side-effects). Within the next five years, many drugs will be sold in combination with a genetic test of a patient's drug response. Understanding how genes and drugs interact could lead to 'designer' or 'personalised' medicines – drugs or combinations of drugs tailored according to an individual's genetic profile.

#### Complex disease...

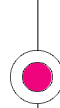
a condition which may have a number of underlying causes – both genetic and environmental





six

## implications in health



seven

## Genomics on the farm

### Genomics on the farm

Farmers from the earliest times have improved animals and plants for their own purposes. In doing so they have favoured some genetic characteristics over others. Cows, for instance, have been bred, amongst other characteristics, for strength, for meat and leather quality, for milk yield, and for docility.

In future, genomics will enable breeders of livestock and plants to make much fuller use of the natural genetic variation available to them, and to introduce specific improvements systematically to meet particular farming or market requirements.

By simply comparing genomes, for example, those of *Arabidopsis* or rice [[see://four/Of flies, worms, weeds and rodents/<](#)] with those of wheat and other cereals, researchers gain clues as to what many individual genes do in crop species. Information from rice, for example is being used to analyse a chromosome in wheat that carries many agronomically important genes, such as those for frost tolerance, plant form and yield. Such comparisons are aided by a UK initiative on plant genome databases (UKCropNet) established in 1996 that encompasses cereals, grasses, the cabbage family (includes oil seed rape), and model organisms.

In order to make agriculture sustainable, farming practices will increasingly have to be tailored to meet particular market needs, and environmental and other constraints. In part, at least, this means making crops more suitable for particular end uses, for example, in food, or as renewable feedstock for industrial manufacturing. Genomics can help greatly here, both through traditional plant breeding technology and genetic modification.

### Crops

Many modern crops have been bred to produce high yields under intensive farming conditions such as high fertiliser use. In focusing upon genetic combinations for these traits, genes such as those responsible for tolerance to extremes of temperature or product texture, may have been relatively ignored. Genomics lets plant breeders examine the panoply of genes (and their functions) present in cultivated varieties, in wild plants and in seedbanks. Breeders could, if they wish, introduce or re-introduce genes that may be missing simply because they had little immediate value in intensively farmed modern crops.

Identifying the genetic factors that regulate plant growth, development and flowering time, and the ways these interact with environmental influences will enable plant breeders to introduce genes that will increase crop yields and reduce harvesting costs. Importantly, genomics could allow farmers to use crops that are adapted to their environments rather than those that demand that the environment is changed (by chemical treatments) to suit them. New varieties that are able to tolerate drought, heat, cold or salty conditions could enable food production to be increased, particularly in developing countries, without taking more land under cultivation. Salt tolerance is also important in the developed world where irrigation has reduced soil quality.

Genomics will reveal the genes that are important for nutrient production, flavour or texture. It will pinpoint genes that are responsible for some food allergens or the production of natural plant toxins, such as those in potatoes, beans, and cassava. Such discoveries, when combined with modern breeding methods and genetic modification, could improve the safety and nutritional value of foods.

Agriculture's environmental impact and farming costs could both be reduced by crops that have enhanced resistance to disease and, therefore, require less fungicide and other chemical treatments. More than 40 genes coding for resistance to disease have been found in *Arabidopsis* [[see://four/Weed power/<](#)]. Genomics is also revealing how genes equip plants to scavenge for nutrients in the soil, possibly paving the way to varieties that require less fertiliser.



### Animals

In livestock, including cattle, pigs and chickens, genomics will accelerate the use of information on gene function for breeding purposes. For example, some cattle genome studies are characterising the genetic contribution to complex traits such as fertility and carcass composition, helping breeders to identify the cattle most suitable for breeding.

Disease resistance is important for animal health and welfare. Genomics will accelerate the understanding of its genetic basis and this will help in breeding resistant animals and in designing new veterinary drugs. For example, genes in chickens that make them more resistant to *Salmonella* and Marek's disease have been found recently.

Understanding the genes that govern the immune response will enable researchers to design better vaccines and to tailor specific vaccines to different breeds.



### Agricultural communities

Genomics could bring new employment to rural areas. As scientists find out how individual genes contribute to a particular end product, it will become increasingly feasible to alter existing products or, through genetic modification, to develop new products. For example, crops such as oil seed rape might be modified to produce high value speciality chemicals or industrial lubricants, replacing petrochemical products. Trees that grow straighter or that are easier to process into paper are also in development, as are plants or animals that yield vaccines and other medicines. Such products would be processed in agricultural refineries which, like the windmills of bygone eras, would be low-energy rural producers of industrial raw materials.



### GM controversies

Some pressure groups and consumer rights organisations are concerned that the use of genetically modified organisms may have adverse environmental impacts. One of the concerns surrounds the consequences of the possible spread of modified genes.

Researchers can monitor the genes that have been added to GM organisms. Detailed knowledge of plant genomes will mean that the environmental impacts of non-GM, organic, or wild plants could also be readily studied.



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## Genomics on the farm



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## Environmental genomics

### Environmental genomics

Genomics can address some fundamental and difficult environmental and ecological questions such as ‘how do ecosystems function?’; ‘what is biodiversity and how might it be changing?’; and ‘how do organisms really behave in natural environments?’ Genomics can also be applied to help monitor, treat or prevent environmental pollution.



### Ecosystem function

Microorganisms such as bacteria and fungi are central to the behaviour of many ecosystems: they play crucial roles in nutrient cycling and determine the resilience of systems to changes and stresses, such as those caused by pollution. There are about a million microbes in every gram of soil, but we know little about soil organisms and only one in a hundred will grow under laboratory conditions. Knowledge of microbial genomes [\[see://five/A microbe’s genome/<\]](#), however, enables researchers to detect and analyse microbial activities even when that activity is due to unknown species.

For instance, genetic information from one member of a group of related organisms allows researchers to detect, enumerate, or assess the activity of others in the group. Using DNA microarrays [\[see://three/DNA chips/<\]](#), researchers can assess which genes are switched on inside organisms at different times or under different environmental conditions. Thus they can study phenomena such as the capture of nitrogen from the atmosphere where the genes involved are very similar wherever the process occurs. Microbial genome projects will help work out how microbial communities in soil, water or on plant surfaces are affected by weather and climate change, or by human interventions such as fertilisation or pollution.

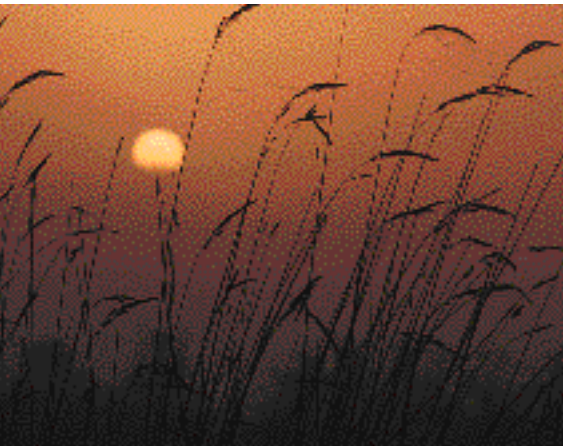
### Biodiversity

There is broad agreement that biodiversity should be maintained; it is the subject of international political agreements. Yet we simply do not know how much diversity we have, let alone how much is sufficient. Assessment of genetic variability can provide one measure of biodiversity. Ecologists using genomic tools can start to describe the evolutionary tree of life. They can also address previously intractable questions about the origins and maintenance of biodiversity. For instance, genetic data could help distinguish whether the tropical areas are more diverse than temperate zones as a result of evolutionary history, or whether the variation is due to ecological factors such as primary productivity. Genomics thus helps resolve biodiversity debates and influences conservation policy.

By looking back at DNA in preserved specimens of ancient animals and plants, it is possible to get some idea of how biodiversity has changed over time, particularly with respect to times when drastically different global climates would have restricted the genetic diversity.

Genetics, archaeology and palaeontology are now being combined to help discover the origins of domestic horses. Comparing DNA sequences from modern horses allows scientists to draw up a family tree of their relationships and to estimate the age of their common ancestors.

Studies of ancient DNA can lead unexpectedly to modern applications. For example, a new DNA-based test can distinguish durum wheat from cheaper varieties which may be added to pasta; the test can thus protect consumers against unscrupulous producers.



**What organisms really do**

Genetic methods can be used to give researchers a much deeper level of understanding of organisms in their environments. Molecular approaches can be used, for instance, to help track the movements of individual organisms: ecologists have distinguished over 2,000 individual humpback whales using genetic fingerprints obtained from skin scrapes and can consequently monitor whale movements over long distances in great detail. Similar techniques can establish how or even whether different populations of species interact: the survival of small isolated populations of water voles in Scotland was thought to be threatened by mink until DNA studies showed high levels of genetic mixing with nearby vole populations. DNA studies also confirmed that pipistrelle bats in the UK are not just one species, but two.

**Bioremediation...**  
cleaning up waste or pollution using a biological approach

Seaweed



**Environmental biotechnology**

Knowledge of microorganisms derived from genomics research can contribute to developments in environmental biotechnology. Naturally occurring soil bacteria can clean up land that is contaminated with chemicals and heavy metals because they produce detoxifying enzymes. However, these bugs are not very efficient. Consequently, the most economical way of cleaning up 'brown field' sites is simply to remove the soil and take it elsewhere – digging and dumping, not an environmentally friendly solution. Small-scale trials show that genetically modified bacteria containing extra copies of the gene that produces the detoxifying enzyme can process more noxious substances in less time; fast enough, perhaps, to make microbial clean-up a more economically attractive process. Genetically modified plants also have a role in pollution treatment; they can remove toxic heavy metals from contaminated soil.

Genomic studies in marine organisms may have practical value. For instance, researchers have identified some of the genes that make bladderwrack seaweed tolerant of heavy metal pollution. These genes could help in environmental monitoring at sea and on the land by guiding the design of genetic probes. They might also be useful in efforts to clean up polluted land. Other studies – on the genetic changes in certain flounder genes – will help in identifying the environmental causes of cancers in the fish.

Biotechnology can also be used to prevent pollution in the first place. For instance, microorganisms and their enzymes can replace highly toxic chemicals in the bleaching of paper or the 'stone-washing' of blue jeans. Biotechnology can also provide biological alternatives to pesticides, fertilisers, or industrial solvents and lubricants. In addition, environmental biotechnologies are being used to clean up gaseous, liquid and solid wastes before these leave factories and to reduce the use of pesticides and weed-killers in agriculture [\[see://seven/Crops/\]](#).



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## Environmental genomics



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## Living with genomics

As the Human Genome Project and other genome projects progress, we as individuals will be confronted by many ethical and social issues. In democracies, the way that people address those issues will shape the response of governments and will mould any laws they introduce [\[see://ten/Genomics in our society/>\]](#).

### What our genes tell us

While our bodies age and the spectrum of illnesses we encounter changes throughout our lifetime, our genome does not alter. It follows, therefore, that medical or other tests based on genes do not tell us that we are ill. Neither do they indicate that something will go wrong. They indicate only that an individual has a higher (or lower) chance of something going wrong in the future.

For instance, there are two genes – BRCA1 and BRCA2 – that have been implicated in increased susceptibility to breast cancer. Women who inherit the disease-associated variants of these genes have a much higher risk than normal of early breast cancer. However, the presence even of these strongly-acting genes is not an absolute predictor of breast cancer: 20-40% of women with disease-associated gene variations escape the disease. Furthermore, these two genes together account for only 5-10% of breast cancer cases. The vast majority of breast cancers have other causes, some of which may be genetic.

Similarly, research into the genetics of childhood diabetes shows that a gene variant that is present in every single case of the disease is also present in over half the population of the UK. The presence of this gene alone is clearly not a good predictor that diabetes will occur: several other gene variants and environmental factors have to combine before the disease becomes manifest.



### Acting on inside information

Many diseases respond best to treatment – through medicines, surgery, or changes to diet and lifestyle – if they are detected as early as possible. Thus predictive tests based on DNA could have clear medical value. If you knew, for instance, that your genes predisposed you to, say, cardiovascular disease, then you could improve your chances of not having a heart attack in a number of ways: by sticking to a sensible diet, by taking regular exercise, by not smoking, or by seeking pre-emptive medical treatment.

On the other hand, a bad prognosis may itself be a psychological burden to a patient, especially one unprepared for the information. Consequently, genetic testing must go hand in hand with counselling; diagnostic tests are rarely performed (even when technically possible) before treatments are available.

As researchers compile a more complete list of human genes, and as they start to understand what each of them does, it may become possible to increase the predictive power of genetic tests. Even then, great care needs to be taken in interpreting test results.

Genes can have a major effect in many diseases but the view that genes determine health outcomes is simplistic and wrong. Educators, medical professionals, politicians, as well as the general public will need to address any such misconceptions if genetic testing is to fulfil its potential in healthcare.



### Kith and kin

Genetic information often has direct implications for more than one person. Each of us shares many genes with our relations. Thus if one person in a family finds out they have a particular genetic condition or predisposition, then they also know that there is an increased chance of it in their blood relations.

There is concern that genomics could fuel human tendencies to discrimination. Discrimination still affects employment, access to education, and to justice. Genetic inheritance is already on the list of possible sources of bias, along with sex, race, sexuality, educational background, income, age, appearance, disability, and religion. In advance of the completion of the Human Genome Project, researchers, medical professionals, and ethicists together with representatives of the lay public need to address the issues that attend access to personal genetic information.

The Advisory Committee on Genetic Testing, which gives advice to government and is now part of the Human Genetics Commission [[see://ten//Genetic testing/>](#)], has issued guidelines that address many of the issues around genetic testing.



### Ethics...

**the code (often unwritten) of personal and societal principles that define acceptable behaviour**

### Making treatment effective

Genetic testing could be a tremendous boon for health care, allowing individuals to avoid or reduce the impact of genetic diseases. It might prove possible to shift the balance of health care expenditure in the country from expensive late-stage treatment of diseases to earlier diagnosis and prevention, and to provide better treatments earlier in a patient's disease when efficacy could be higher.

The medical profession and the general public must have realistic expectations of genomics. The development time scales for genetic tests are much shorter than those for treatments. New drugs, for instance, can take over a decade to develop whereas new diagnostic tests can be ready in a matter of months.

The extended availability of genetic testing also begs the question whether individuals can choose to remain ignorant about their individual genetic heritage. Some people may wish to live their lives unfettered by knowledge of their genetic risk. However, in doing so they may place avoidable burdens of care on health services or on their carers. It could be argued, therefore, that it is antisocial to remain ignorant.



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## Living with genomics

The UK framework of rules that encompasses biotechnology and genomics includes comprehensive legal provisions regulating experimentation on and application of genetically modified organisms. These are designed to ensure human health and protect the environment. In addition, to keep abreast of rapidly advancing areas such as genomics, successive governments have established a network of advisors including both specialists and lay people. Advisory and regulatory groups focus on issues such as genetic testing, gene therapy, food, release of genetically engineered organisms to the environment [[</a>\], animal to human transplantation, and \*in vitro\* fertilisation. In 1999, the government established the Human Genetics Commission and the Agriculture and Environment Biotechnology Commission, thereby boosting lay input to the developing regulatory framework. These bodies will work alongside the newly established Food Standards Agency.](http://seven/GMcontroversies/)



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## Genomics in our society

### Genetic testing

Under its remit in genetic testing, the Human Genetics Commission has issued specific guidelines and codes of practice. For instance, guidelines suggest that although organisations outside the National Health Service and the UK's Regional Genetics Centres can perform genetic tests, these should be restricted to tests that detect carriers of particular genetic traits. There are guidelines for genetic disorders that affect people later in life and guidelines which recommend that children should not be tested for conditions where there is no treatment, even when there is a family history of disease. The question of testing in the workplace was considered in a report issued in 1999; that report stopped short of proposing a ban on genetic tests for employment purposes but it did conclude that it would be unacceptable to exclude people from employment (or promotion) simply because they had a predisposition to future illness.



### Insurance

A recent UK survey of over 7000 people revealed that even the "possibility" that a person has a genetic condition can affect their ability to obtain life insurance. Carriers of particular genes who have adverse risk of disease themselves have also experienced difficulties. The insurance industry's code of practice declares that, for the time being, companies will not ask people who apply for insurance to undergo genetic tests. Insurers can, however, ask if people have taken certain genetic tests and they may use information from reliable tests to justify increases in premiums. The Human Genetics Commission is monitoring this situation.





## Demystifying genomics

### People and training

Genome-based information is of little use if people do not know how to use it properly. In healthcare, the interpretation and explanation of genetic test results will require increased numbers of trained genetic counsellors [[see://nine/Acting on inside information/<](#)]. Doctors and other health care professionals, who have already expressed apprehension about handling genetic information, would benefit from additional training, while human resources professionals and those in the insurance industry [[see://Insurance](#)] will need to understand the meaning of genetic information.

Even in research and development, there is a dearth of people who combine an understanding both of biology and the computational and mathematical methods needed to interpret all the data that genomics generates. Cross-disciplinary collaboration and multi-skilled researchers will be important in ensuring that genome information provides appropriate economic and social benefits.

### Patents

Corporate activity in genomics is dependent, to a large degree, on patents. Living matter has been patentable since 1975 when the US Supreme Court allowed a patent on a group of oil-digesting microorganisms. Individual plants and animals (as opposed to varieties and breeds) are patentable, too, a position confirmed by European Union legislation passed in 1998. Humans are not patentable, however, and neither are body parts.

A patent is, in effect, a deal between the law and an inventor. The inventor gains the right to profit exclusively from his or her invention in return for describing it completely so that others can build on it. A patent thus safeguards against secrecy by ensuring that scientific and technical data circulate freely.

In Europe, the discovery of genetic sequences is not patentable. The European Patent Office concluded that simply discovering genes was not useful and, therefore, not patentable. However, if a genetic sequence codes for, say, a medically useful protein, then a patent claim on the sequence would be allowed.

In the US, however, many patents have been filed by companies and other organisations [[see://Genomics Incorporated](#)] covering huge numbers of partial genes. The US Patent and Trademark Office has granted some of these despite being opposed by science funding bodies, the Human Genome Organisation, many European governments and leading politicians.

### Genomics Incorporated

The involvement of companies, small and large, impacts significantly on genomics. For example, funding for the public sector Human Genome Project increased significantly in 1999 following the announcement by a private US company that it aimed to completely sequence the human genome by 2001. In the US, investment by private companies in genomics far exceeds that of the public sector. Private companies have sequenced several microbial species and are generating other genomic information on behalf of pharmaceutical clients.

In many areas of genomics, publicly-funded and private research and development efforts run in parallel. These include genomic mapping in crops, sequencing of microbial pathogens, mapping genes related to human diseases, mapping person-to-person variations in the human genome, and the establishment of databases of genetic and health information.

### End note

**Data generated from the various genome projects and from studies of gene function add a new layer of detail to our knowledge of living organisms and life processes. Used properly, this knowledge can contribute to rapid improvements in health care, agriculture and our stewardship of the environment. Public and professional appreciation of the broader implications of such research, along with informed debate will shape the benefits that society ultimately derives from it; this booklet hopefully contributes to promoting such awareness.**