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HUMAN GENOME RESEARCH

Report 142
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1 INTRODUCTION

On June 26th 2000, scientists in the UK and US announced that they had completed a 'working draft' of the sequence of the human genome (all the DNA contained in the full set of human chromosomes). This consisted of the finished (99.99% accurate) sequence for around one quarter of the total code (including many of the regions of greatest interest) along with a sketchier 'first draft' of most of the remaining sequence. All told, around 85% of the genome has been sequenced in finished or draft form. The current aim is to go back and fill in the gaps over the following two years, so that the entire sequence will be delivered by the year 2003, in time to celebrate the 50th anniversary of Watson and Crick's elucidation of the double helical structure of DNA.

Completion of this project will represent a remarkable achievement, especially considering that the first DNA sequencing methods were not developed until the 1970s. Such detailed knowledge of the human genome will open up new areas of research in basic biology, biomedicine, biotechnology and health care. It will increase our knowledge not just of single gene disorders such as cystic fibrosis, but also of how genes interact with environmental factors and contribute to a range of other diseases including cancers, heart disease, and diabetes. Once the role of gene sequences in these and other types of disease are known, the way will be opened for a new range of DNA-based diagnostics and treatments. Further research on the links between genetic variation and disease risks (e.g. comparison of genomes at an individual or population level) also holds out the promise of new insights into the prevention of some types of common disease.

But the availability of the human genome sequence will also pose a number of challenges for doctors, healthcare systems and policy makers, as well as raising more general ethical, legal and social issues. Some of these have already started to emerge. For instance, the prospect of an increasing range of genetic tests has already led to concerns over how the NHS will cope with the demand for screening, as well as over the potential (e.g. insurance, employment) implications for people taking such tests. Recent years have also seen public disquiet over some of the proposed clinical applications arising from advances in human genetics.

Given the pace of recent developments in genome research and the wide-ranging nature of the issues raised, the POST Board decided that it would be timely to review the area of human genomics. This report thus describes the scientific and technological developments behind efforts to decipher the entire human genetic code and discusses the issues that arise.

2 MAPPING AND SEQUENCING THE HUMAN GENOME

2.1 Historical Perspective

Current efforts to map the human genome represent the culmination of scientific research across a wide range of disciplines stretching back well into the previous Century. Some of the most significant milestones are outlined in **Box 2.1**. These include:

- The concept that traits were passed on to future generations in the form of pairs (one from each parent) of discrete 'hereditary factors' - what we now call genes - was first proposed by Mendel as long ago as 1866.
- The suspicion by the early 1900s that these genes were located on chromosomes (large, thread-like structures made of DNA and protein that appear in cell nuclei immediately prior to cell division).
- Avery and colleagues demonstration in the 1940s that DNA alone is the hereditary material.
- Studies on the chemical composition of DNA had revealed it was made up from 4 different components (nucleotides containing the bases A, T, G and C). These culminated in Watson and Crick's elucidation of the double helical structure of DNA in 1953.
- This structure suggested an obvious means for DNA replication and paved the way for studies of how the DNA base sequence 'codes for' protein structure. A 'central dogma' emerged, whereby (DNA) gene sequences are copied into (RNA) messenger sequences that act as templates for protein synthesis.
- Deciphering the genetic code in the early 1960s. Researchers realised the code was a triplet, with each trio of bases in DNA coding for a single amino acid (the basic building blocks of proteins). By 1966, scientists had worked out what each of the 64 possible triplet combinations coded for.
- Developing the basic tools of biotechnology in the 1970s and early 80s. These include the use of restriction enzymes that allow DNA to be 'cut' and 'pasted' from one location to another, and techniques that allow the sequence of short lengths of DNA to be read.

Such developments enabled whole gene sequences to be deduced, by piecing together the sequences of shorter, overlapping fragments. By the 1980s, researchers had started to think seriously about applying such methods to whole genomes. Initial targets were simple organisms such as bacteria, but even these presented formidable challenges: the first sequences of bacterial genomes were only completed in 1995. However, by the late 1980s and early 90s, a whole series of ambitious collaborative projects were underway, tackling ever bigger and more complex genomes. The first complete sequence of a genome from a higher organism (the single-cell yeast *Saccharomyces cerevisiae*) was published in 1997, followed shortly by the first genome from a multi-cell organism (the nematode *Caenorhabditis elegans*) in December 1998 following a UK research project funded by the Medical Research Council (MRC). The sheer size of the human genome meant that the initial aims of the international Human Genome Project launched in 1990 focused on mapping the positions of genes and other 'landmarks' on chromosomes, rather than trying to read the entire code. But recent developments in sequencing techniques mean that the project now expects to deliver the whole sequence by the end of 2003.

BOX 2.1 SOME SCIENTIFIC MILESTONES UNDERPINNING GENOME RESEARCH

- 1866 - Gregor Mendel published the results of his investigations of the inheritance of 'factors' in pea plants.
- 1900 - Carl Correns, Hugo de Vries and Erich von Tschermak independently discovered and verified Mendel's theory that traits were passed on in the form of pairs of discrete 'hereditary factors'.
- 1902 - Walter Sutton interpreted Mendel's results by proposing that the 'hereditary factors' (genes) were located on chromosomes, with offspring inheriting one complete set from each parent. This was based on observations of chromosomes during cell division.
- 1905 - The link between chromosomes and inherited traits hardened when it was shown that for many species (including humans) an individual's gender was determined by their sex chromosomes. Nettie Stevens and Edmund Wilson independently described how females (XX) inherit an X chromosome from each parent, and males (XY) an X from their mother and a Y from their father.
- 1908 - Archibald Garrod proposed that some human diseases are due to 'inborn errors of metabolism', resulting from the lack of a specific enzyme (protein).
- 1910 - Thomas Hunt Morgan's studies on the fruit fly led to the formulation of some of the basic principles of genetics. These included the principle of genetic linkage, whereby the order of genes along the length of a chromosome can be deduced from the frequency by which they are inherited together (the closer together two genes are the more likely an individual is to inherit both). It was used to construct the first crude genetic map detailing the order of 6 genes along a chromosome in the fruit fly in 1913.
- 1920s - Scientists knew that genes were located on chromosomes, and that chromosomes consisted of nucleic acid (DNA) and protein. But they didn't know much about the structure or function of either. Some clues on the nature of hereditary material began to emerge in 1927, when Hermann Muller showed that x-rays could cause artificial gene mutations in the fruit fly. The following year, Fred Griffith noted that some unknown 'principle' could transform one strain of *Diplococcus* bacterium to another.
- 1940s – In 1941 George Beadle and Edward Tatum proved that genes act by regulating particular enzymes. In 1944, Oswald Avery, Colin MacLeod and Maclyn McCarty reported that they had purified the transforming principle in Griffith's experiment and that it was DNA – this was the first proof that genes are made of DNA.
- 1950s - Scientists began more detailed studies on the structure of DNA, using x-ray diffraction and other techniques. They knew it was made up of 4 different components (nucleotides containing the bases A, T, G and C). In 1950, Erwin Chargaff discovered that DNA always contained the same amount of A as T, and the same amount of G as C. In 1951, Rosalind Franklin obtained X-ray diffraction photographs of DNA. By 1953, using x-ray data from King's College London, Watson and Crick showed that DNA was a double helix, consisting of two intertwined strands linked by weak bonds between the bases (with A binding to T, and G to C). This immediately suggested a way in which DNA could replicate - if the two strands were separated, each could act as a template for making a new strand. This was observed in 1958 by Matthew Meselson and Frank Stahl using radioactive bases. In 1958, Arthur Kornberg purified DNA polymerase I from a bacterium (*E. coli*), an enzyme that allowed researchers to make DNA in a test tube for the first time.
- 1960s - By 1960, the 'central dogma' of how genes code for proteins had been worked out - the gene sequence is copied into RNA (another type of nucleic acid where the base U is substituted for T) in the nucleus. The RNA code then acts as a template for making protein elsewhere in the cell. Scientists knew that the base sequence of DNA/RNA somehow determined the amino acid (the building blocks of proteins) sequence of proteins. They also suspected the code must be read in triplets (3 bases at a time) since this was the most obvious way of getting enough base combinations to account for the 25 or so amino acids found in proteins. In 1961, research showed that the sequence UUU always results in the amino acid phenylalanine being inserted into the growing protein chain. By the time England won the World Cup in 1966, the entire genetic code had been solved by teams led by Marshall Nirenberg and H. Gobind Khorana.
- 1970s – The basic tools of biotechnology were developed. Hamilton Smith and Kent Wilcox isolated the first restriction enzyme (HindII) that could cut DNA molecules within specific recognition sites. Such enzymes are the key tools that allow DNA sequences to be 'cut' from one place and 'pasted' to another. The first such recombinant DNA molecules were produced in 1972 by Paul Berg and Herb Boyer and by 1973, Annie Chang and Stanley Cohen had showed that recombinant DNA can be maintained and replicated in *E. coli.* When Fred Sanger developed a method for sequencing small lengths of DNA in 1977 at the MRC's Laboratory of Molecular Biology, researchers had all the basic tools to start investigating genomes.
- 1980s – Scientists started to track down some of the genes associated with disease. For instance, James Gusella tracked the Huntington's disease gene to chromosome 4 in 1983, and Francis Collins and Lap-Chee Tsui identified the gene involved in cystic fibrosis on chromosome 7 in 1989. Meanwhile, Kary Mullis published a 1985 paper describing polymerase chain reaction (PCR), a DNA amplification technique.

Source: adapted from Genetics Timeline (www.accessexcellence.org/AE/AEPC/WWC/1994/geneticstln.html)

2.2 The Human and Other Genomes

In general, the higher the organism, the larger and more complex its genome (**Table 2.1**). Thus, viruses have very simple genomes, typically encoding some 5 to 30 different genes, while bacteria (the simplest forms of independent life) need thousands of genes encoded in much bigger genomes. The first complete bacterial genome to be published (in 1995) was *M. genitalium*, which consists of some 600,000 base pairs of DNA. Since this time, more than thirty other bacterial genomes have been fully sequenced, as well as a number of higher single celled organisms (e.g. the yeast genome was completed in 1997).

TABLE 2.1 PROPERTIES OF SOME GENOMES FROM DIFFERENT SPECIES

Species	Genome size (Millions of bases Mb)	Estimated no. of genes
Virus (Herpes)	0.25	30
Bacterium (*M. genitalium*)	0.6	470
Bacterium (*E.coli*)	4.6	4,288
Yeast (*S. cerevisiae*)	12.1	6,034
Cress (*Arabidopsis thaliana*)	70	20,000
Nematode worm (*C. elegans*)	97	20,000
Fruitfly (*Drosophila melanogaster*)	165	14,000
Human	3,000	80,000 – 140,000

Such projects have proved to be invaluable in developing the technology required to tackle the larger more complex genomes associated with multi-cellular organisms that have nervous systems, muscles, are capable of sexual reproduction, digestion, etc. Among the most complex genomes to be completely sequenced to date are those of the simple nematode worm (*C. elegans*, consisting of some 20,000 different genes in 97 million bases of DNA), and the fruit fly (*Drosophila melanogaster*, 14,000 genes in 165Mb); considerable progress is also being made on the mouse genome. Efforts are also currently underway to sequence various plant genomes (which generally contain 20,000-30,000 genes in genomes ranging from a few hundred to tens of thousands of Mb).

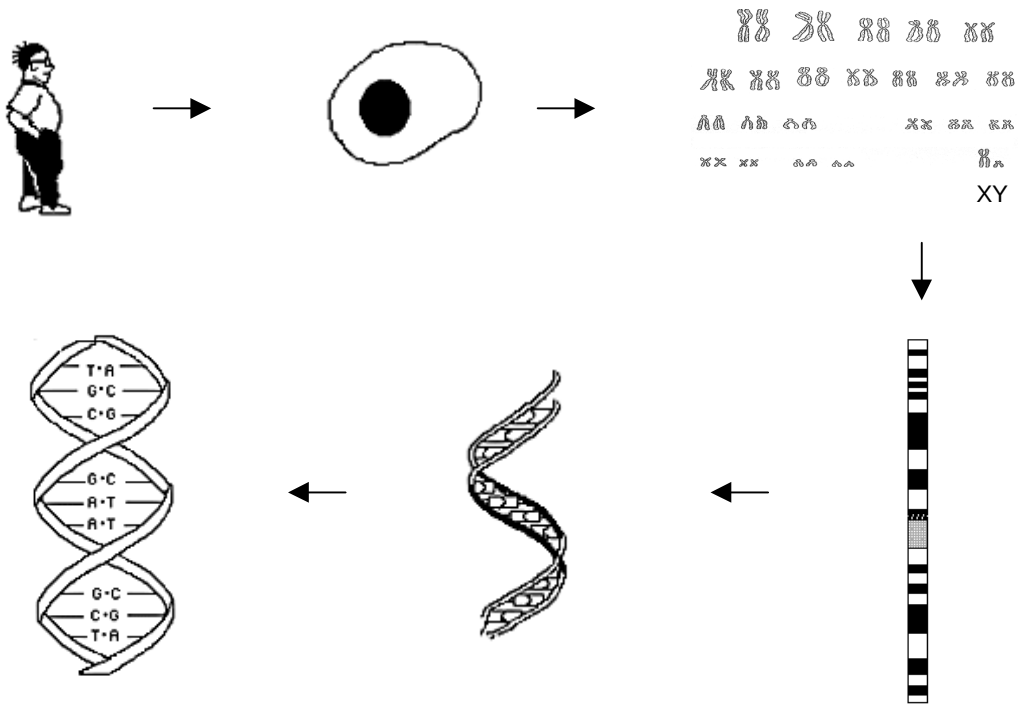
As illustrated in **Figure 2.1**, the human genome is present in nearly all cells in the body, in the form of 23 pairs of chromosomes. For 22 of these, each member of the pair is similar to the other (barring subtle differences), with one chromosome originating from each parent. The remaining pair is the sex chromosomes, where females carry a pair of X chromosomes, and males a single X (from the mother) and a single Y (from the father). In total, the human genome is thus distributed between 24 *different* chromosomes (the 22 chromosomes plus X plus Y) accounting for around 3 billion base pairs (bp) of DNA. Current best estimates are that this includes code for up to 140,000 genes (less than 5% of the total genome). Scientists do not know why the human genome contains 95% more (so-called 'junk') DNA than it appears to need. But they do know that at least part of the excess is accounted for by non-coding regions that occur within (introns) and between genes, by chromosomes containing multiple copies of genes, and by long (non-coding) repeat sequences (the function of which is unknown).

FIGURE 2.1 AN INTRODUCTION TO THE HUMAN GENOME

The human body consists of countless billions of cells.

Each cell contains a full copy of the human genome within its nucleus.

The human genome is contained on 22 'normal' pairs of chromosomes plus 1 pair of sex chromosomes (XX in females, XY in males).



The genetic code is carried by the sequence of 4 bases (A C G and T). This sequence determines the amino acid sequence (and thus also the function) of proteins.

Genes are DNA sequences located on chromosomes. Each codes for a single gene product (usually a protein). There are ~ 100,000 human genes.

Chromosomes are long sequences of DNA wrapped in protein. In total, the human genome consists of 3 billion base pairs of DNA.

2.3 Mapping and Sequencing the Human Genome

The ultimate aim of attempts to characterise the human genome is to obtain the sequence of each of the 3 billion or so bases which it contains. Current sequencing techniques are only capable of reading short stretches of DNA at a time (typically less than 1,000 bases). This means that a '**shotgun**' approach must be used, where the long lengths of DNA that make up the chromosomes are broken down into large numbers of much shorter fragments. While this can be readily achieved using restriction enzymes[1], the problem facing researchers is to deduce the correct order of these short fragments. Two different approaches have evolved:

- A publicly funded international collaborative project coordinated by the Human Genome Organisation (HUGO) involving research groups throughout the world;
- And a privately funded approach, originally pioneered at The Institute for Genomic Research (TIGR) and now applied to the human genome by an American company (Celera).

1 These enzymes are found in bacteria (each snips DNA at a unique base sequence) and scientists can use them to snip DNA into any sized pieces they wish.

2.3.1 The Publicly Funded Human Genome Project

2.3.1.1 Mapping and Sequencing

As outlined in **Box 2.2**, and illustrated in **Figure 2.2**, the main strategy adopted by the publicly funded project involves systematically **mapping** chromosomes by identifying 'landmarks' at intervals along their entire length. These landmarks are simply known features of DNA (genes, polymorphisms, restriction sites, STSs, ESTs, etc. - see Box 2.2) that have been physically located to a particular site on a chromosome. As mapping technology has evolved, then so has the precision with which such features can be located.

The most commonly used mapping techniques involve generating short DNA sequences such as sequence tagged sites (STSs) or expressed sequence tags (ESTs). These are short stretches of known sequence, that have been shown to be unique (i.e. each occurs only once within the genome). Once a sequence is known, it can be mapped to a specific location on a chromosome by using a DNA amplification technique (the polymerase chain reaction - PCR). STS based maps have now been constructed that include markers every 100,000 bases (100 Kb) or so along the length of each chromosome.

BOX 2.2.LANDMARKS COMMONLY USED FOR MAPPING GENOMES

Genetic Maps

Maternal and paternal chromosomes exchange DNA during the process by which sex cells (sperm, eggs) are formed. Genes located very closely to each other are much more likely to be exchanged (and thus inherited) together. It is thus possible to deduce the order of genes along the chromosome from the frequency by which the traits they code for are co-inherited. However, such **gene maps** do not allow researchers to determine the precise physical location of genes on a chromosome (the probability of genes being inherited together depends on the physical properties of the DNA separating them, as well as the distance).

Physical Maps

Show the physical location of landmarks on the chromosome. Among the landmarks most commonly used are:

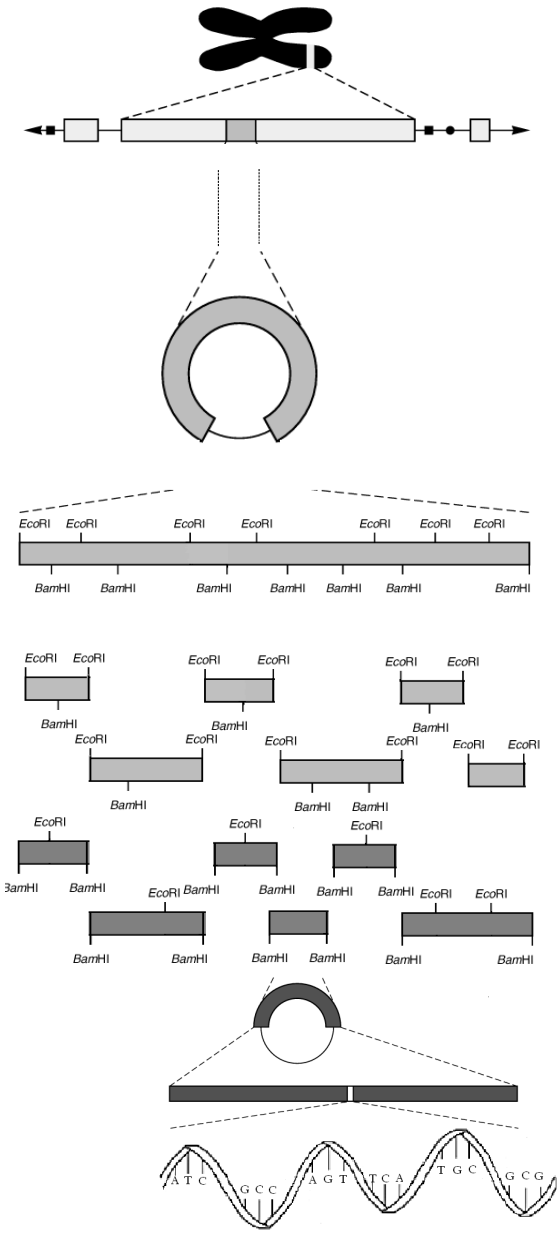
Genes – hybridization techniques can be used to physically locate genes on chromosomes. Such techniques rely on the fact that heating DNA breaks the weak bonds between the two strands; when allowed to cool, the single strand only recombines with a strand with the corresponding sequence. Fluorescent or radio-labeled single stranded sequences are thus used as 'probes' to find the corresponding sequence on the chromosome. Tens of thousands of human genes have now been mapped using such techniques.

Short DNA sequences – typically up to a few hundred bases long are commonly used for creating physical maps. The sequence obtained needs only to be long enough to ensure that it is unique – i.e. occurs only once within the genome. Once such a sequence has been obtained, it is relatively straightforward to pinpoint its precise location within the genome (e.g. using hybridization or PCR-based methods). There are two main approaches to generating such sequences:

- STSs – **sequence tagged sites**. Mixtures of restriction enzymes are used to snip chromosomal DNA up into relatively short (a few thousand bases [kB] long), overlapping, pieces (so-called libraries – see Figure 2.2). These can be separated out and a short section of sequence – an STS – read from each.
- ESTs - **expressed sequence tags (ESTs).** These are derived by isolating a cell's mRNA. In this way scientists can obtain a library of sequences of all the genes that are active in that type of cell at that particular time. Messenger RNA is inherently unstable so researchers have to make stable (c)DNA copies of the sequences; ESTs are obtained simply by reading a short section (e.g. a few hundred base pairs) of each sequence obtained. Because of the manner in which they are derived, scientists know that ESTs come from genes (unlike STSs, which are randomly generated and thus not necessarily gene sequences). They can thus be used to locate the corresponding gene within the genome.

Polymorphisms – are simply hereditary variations in DNA sequence. As described in more detail later, one focus of current research in this area is the identification and mapping of single base pair differences (so-called single nucleotide polymorphisms, or SNPs) between individuals. Eventually it is hoped that such research will lead to a better understanding of why some people are more prone to certain genetic diseases than others, why different people react differently to certain drugs, etc.

FIGURE 2.2 SPLITTING THE GENOME INTO FRAGMENTS FOR SEQUENCING



Human chromosome

Large chromosomal fragments (e.g. up to several 100,000s of bases long) cloned into yeast or bacterial artificial chromosomes (YACs or BACs). Landmarks such as genes or other known sequences are used to establish the order of clones along the chromosome. One BAC library consists of ~25,000 clones, each containing ~150,000 bases.

Smaller fragments (e.g. several 10,000s of bases long) are cloned into large vectors.

Each of these fragments contains multiple restriction sites at which different restriction enzymes will cut the DNA. Sites for two such enzymes – EcoR1 and BamH1 – are shown in the figure.

Cutting these fragments with different restriction enzymes allows a library of contiguous, overlapping, fragments to be obtained. The figure shows the fragments obtained when EcoR1 (top) and BamH1 (bottom) are used.

Each of these fragments may be up to several thousand bases long, and can be cloned into small vectors such as plasmids. These libraries form the source material for sequencing. Further subclones may be prepared for sequencing, with the correct order of the fragments being deduced from the overlapping regions.

Source: adapted from http://www.ornl.gov/hgmis/publicat/primer/fig11.html

As illustrated in Figure 2.2, mapping and sequencing genomes involves successive rounds of splitting a chromosome up into smaller, more manageable fragments, until the pieces are small enough to be individually sequenced. At each stage, the fragments are cloned so that they can be amplified and distributed to laboratories around the world. Detailed maps using the landmarks described in Box 2.2 allow the order of the larger clones along the chromosome to be determined. Ultimately, the process generates libraries of overlapping, contiguous, fragments that are the source material for sequencing. Each of the library fragments still has to be broken down into scores of smaller (overlapping) sequences, short enough (typically <1 Kb) to be read in automated sequencing machines. Sophisticated computer programmes that compare the overlapping regions are then used to reassemble the sequences in the correct order.

The fact that the libraries are mapped to specific chromosome regions makes the process of reconstructing coherent sequences much easier to co-ordinate, and means that any 'problem' fragments or other gaps can be marked, and returned to at a later date. Because the maps include landmarks dotted at regular intervals along the whole length of each and every chromosome, this approach opens up the entire genome for sequencing.

2.3.1.2 Quality Control

All the laboratories involved in the publicly funded project employ similar shotgun approaches to obtain the finished sequences, following guidance on quality control and release of the data published by HUGO (**Box 2.3**). The process was described in the previous Section and involves sequencing overlapping sub-clones of the mapped library fragments, and re-assembling them back into the correct order using sophisticated computer programmes. The first output of this process is a 'rough draft' of (so-called unfinished) sequence between specified markers. Further sequencing is required to fill any gaps, or resolve any problems, and the assembled sequence must then be checked for errors (e.g. using restriction enzymes, see Box 2.3). Once a finished sequence has been obtained, the laboratory must lodge it with a public database within 24 hours. Such procedures are designed to ensure that the finished sequences are 99.99% accurate - i.e. an error rate of 1 base per 10,000 or less. As discussed in more detail later, the strategy is also designed to ensure that the entire genome sequence is accessible to all researchers as soon as it becomes available. This is in contrast to privately funded genome research (see Section 2.3.2) that aims to exploit intellectual property rights before publishing the sequence data.

BOX 2.3 HUGO QUALITY CONTROL AND DATA RELEASE PRINCIPLES

Data release

- All human genomic sequence information generated by centres funded for large-scale human sequencing should be freely available and in the public domain in order to encourage research and development and to maximise its benefit to society.
- Primary genomic sequence should be released rapidly (e.g. within 24 hours of being finished) to the public databases.

Sequence Quality Standards

- The nucleotide error rate should be 1 error in 10,000 bases or less for most sequence.
- Assemblies should be verified using two or more restriction enzymes. Because these enzymes cut DNA at specific base sequences, researchers can predict the expected fragmentation pattern - if a different pattern is seen, then the assembly contains an error.
- Ideally there should be no gaps in the sequence - where this is not possible, closing the gaps is the responsibility of the original sequencer.

Sequence Submission, Annotation and Claims

- Finished sequence data should be annotated to include details of error estimates, the enzymes used to verify assemblies, methods used to assemble adjacent overlapping clones, the size of any gaps, etc.
- Groups seeking to register claims with HUGO to sequence areas of chromosomes must first prepare a suitable map, resolve any disputes with other sequencing groups, must sequence a minimum of 1 Mb spanning the entire region between recognised markers.

Source: [1st and 2nd International Strategy Meetings on Human Genome Sequencing]

2.3.1.3 Project Goals

Table 2.2 summarises the main goals of the publicly funded human genome project, and illustrates how these have evolved over the years, as mapping and sequencing technologies have developed. More detailed genetic and physical maps were seen as the main initial priority and the 1993 goals for both have been exceeded. For instance, a genetic map was published in 1994 detailing the order of 3,000 genetic markers, exceeding the target of 600 to 1,500[2] set in 1993. Similarly, more than 52,000 STSs had been physically mapped by 1998, compared to the 1993 goal of 30,000 (one every 1,000 Kb).

Other targets such as developing faster and cheaper sequencing technology and obtaining the genome sequence of other model organisms have also been met or exceeded (Table 2.2). For instance, the development of high-throughput capillary sequencers capable of continuous operation means that the sequencing capacity of the publicly funded project has been increased five-fold. This increase in capacity coupled with a decision to focus the sequencing effort at five main centres (see next Section) was one of the reasons why it was possible to announce publication of the 'working draft' in June 2000. It will provide an early view of most (~85%) of the human genome to everyone. Over the following two years or so, it will then be refined, any remaining gaps filled in, etc. and the complete 'finished' sequence will follow by 2003.

TABLE 2.2 HUMAN GENOME PROJECT - SUMMARY OF RECENT GOALS AND PROGRESS

Area	Goals 1993-98	Status (Oct 1998)	Goals 1998-2003
Genetic map	Genetic marker every 2-5cM[1]	1 cM map published 1994	Completed
Physical map	Physical markers (STSs[2] every 100 Kb, 30,000 in total)	52,000 STSs mapped	Completed
DNA sequence	Complete 80Mb of sequence for all organisms by 1998	180Mb human sequence 111Mb non-human	Complete 1/3 human + working draft of other 2/3 by end 2001 Complete human by end 2003
Sequence technology	Improve existing technology Innovative new technology	90Mb/year at ~$0.5/base	Achieve 500Mb/year at <$0.25/base
Sequence variation	Not a goal		100,000 mapped SNPs[3]
Gene identification	Develop technology	30,000 mapped ESTs[4]	Full length gene sequences Identify rarely expressed genes
Functional analysis	Not a goal		Develop genome-scale technologies
Model organisms	*E. coli* complete sequence	Published 1997	
	Yeast complete sequence	Published 1997	
	C.elegans complete sequence	Published 1998	
	Drosophila begin sequencing	~10% completed	Complete sequence by 2002
	Mouse map 10,000 STSs	12,000 STSs mapped	Complete sequence by 2005
Notes	*1 cM is a centiMorgan, a measure of how often genes are inherited together.* *2 STSs are Sequence Tagged Sites, see Box 2.2.* *3 SNPs are Single Nucleotide Polymorphisms, see Box 2.2.* *4 ESTs are Expressed Sequence Tags, see Box 2.2*		
Source:	*www.ornl.gov/hgmis/research.html*		

2 Genetic maps show how likely two genes are to be inherited together. This depends on how close together they are on the chromosome (the closest genes are most likely to be inherited together) and how strong the DNA is between them (if the DNA is easily broken, the genes are less likely to be inherited together). The spacing of genes on such maps is measured in centiMorgans (cM).

2.3.1.4 Who is Doing What?

HUGO has divided the 24 different human chromosomes up between the various international collaborators (**Table 2.3**). UK involvement is through the Sanger Centre, jointly set up and funded by the Medical Research Council (MRC) and the Wellcome Trust. It is funded to sequence around one third (1,000 Mb) of the human genome, mainly on chromosomes 1,6,9,10,13,20,22 and X (Table 2.3). Most of the rest will be sequenced by various laboratories in the US, funded by the National Institutes of Health (NIH) and the Department of Energy (DOE), and by collaborators in Europe, Japan and elsewhere.

TABLE 2.3 WHO IS DOING WHAT IN THE HUMAN GENOME PROJECT

Chromosome	Size (Mb)	Main Institute(s)
1	263 Mb	SC (UK)
2	255 Mb	GSC (US)
3	214 Mb	BCM (US), SC (UK)
4	203 Mb	SHGC (US), JGI (US), SC (UK)
5	194 Mb	JGI (US)
6	183 Mb)	SC (UK), TU (JAP)
7	171 Mb	GSC (US), IMBJ (GER)
8	155 Mb	IMBJ (GER), JFCR (JAP)
9	145 Mb	SC (UK)
10	144 Mb	SC (UK)
11	144 Mb	UTSW (US), UT (JAP), SC (UK)
12	143 Mb	BCM (US)
13	114 Mb	GSC (US), SC (UK)
14	109 Mb	Genoscope (FR), GSC (US)
15	106 Mb	UTSW (US)
16	98 Mb	TIGR (US), CT (US), LANL (US), SC (UK)
17	92 Mb	WIBR/MIT (US)
18	85 Mb	WIBR/MIT (US), RIKEN-(JAP), GSC (US)
19	67 Mb	JGI (US)
20	72 Mb	SC (UK), JGI (US)
21	50 Mb	Chromosome 21 Consortium (US, GER, JAP, ISR, SWZ, FR)
22	56 Mb	SC (UK), PGC (US), UO (US), KU (JAP)
X	164 Mb	SC (UK), BCM (US), MPI (GER), GSC (US), Others
Y	59 Mb	GSC (US)

Abbreviations: SC (UK), Sanger Centre (United Kingdom); GSC (US), Genome Sequencing Centre (United States); BCM, Baylor College of Medicine; SHGC, Stanford Human Genome Centre; JGI, Joint Genome Institute; TU (JAP), Tokai University (Japan); IMBJ (GER), Institute of Molecular Biology Jena (Germany); JFCR, Japanese Foundation for Cancer Research; UTSW, University of Texas Southwestern; UT, University of Tokyo;(FR), (France); TIGR, The Institute of Genome Research; CT, Caltech; LANL, Los Alamos National Laboratory; WIBR/MIT, Whitehead Institute of Biomedical Research/Massachusetts Institute of Technology; (ISR), Israel; (SWZ), Switzerland; PGC, Philadelphia Genome Centre; UO, University of Oklahoma; KU, Keio University; MPI, Max Plank Institute.

Source: adapted from information at http://webace.sanger.ac.uk/HGP/ and www.ebi.ac.uk/~sterkgenome-MOT/

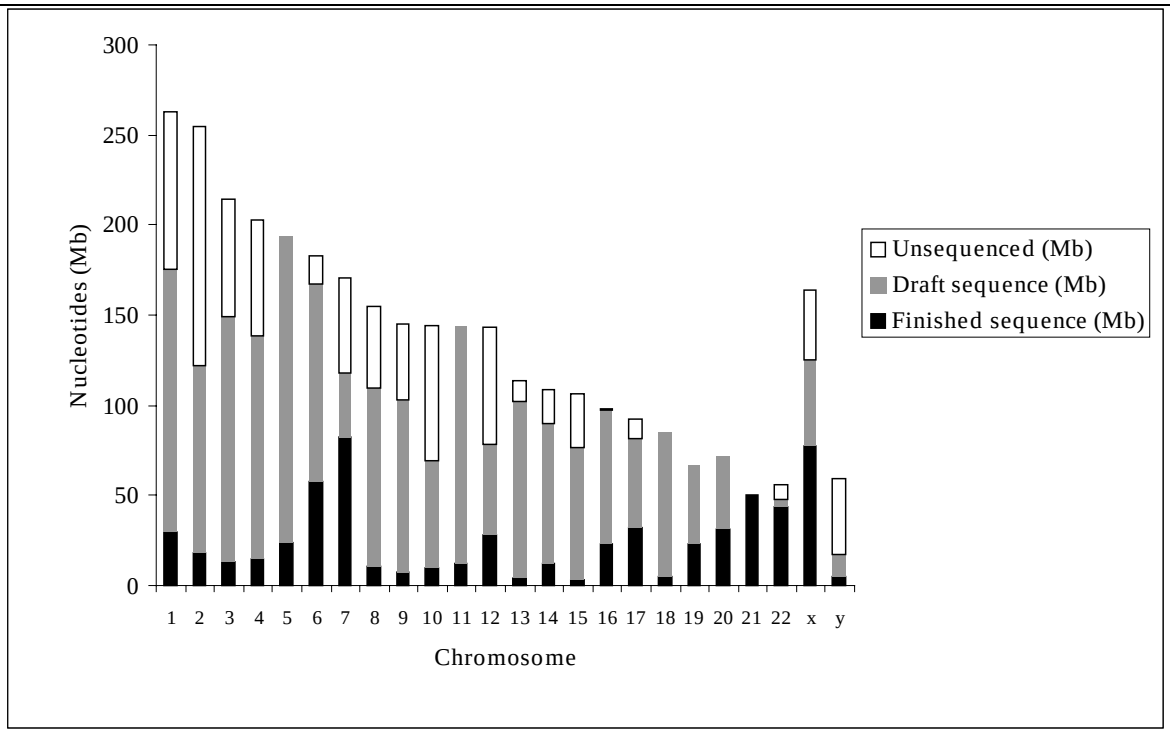
Of the various collaborators listed in Table 2.3, five are chiefly responsible for the large-scale sequencing effort. These are the:

- Sanger Centre, in Cambridge, UK;
- Washington University Genome Sequencing Center (GSC) in St. Louis, US;
- Whitehead Institute in Cambridge, US;
- Baylor College of Medicine in Houston, US;
- and the US DoE's Joint Genome Institute.

2.3.1.5 Progress To Date

Considerable progress has already been made on the project towards the goals outlined previously. More than 30,000 genes have been mapped to locations on specific chromosomes and high-resolution physical maps have been obtained covering the entire genome. Large-scale sequencing efforts are underway for all of the human chromosomes, and some of these are well advanced (**Figure 2.3**). For instance, chromosome 21 is now finished[3], and collaborators from the Sanger Centre and elsewhere have already published the vast majority of chromosome 22's 56Mb total. This spans all the important coding parts of the chromosome. By end June 2000, around 85% of the human genome was available in draft form; about one quarter of the genome had been published as finished sequence.

FIGURE 2.3 PROGRESS IN SEQUENCING THE HUMAN GENOME (AT JUNE 2000)



Source: *http://www.ebi.ac.uk/~sterk/genome-MOT/9606_1000.html*

2.3.2 Privately Funded Human Genome Sequencing

The publicly-funded effort outlined above faces competition in the form of a privately-funded attempt to sequence the human genome. An American company (Celera) aims to employ an entirely different approach in an attempt to sequence the entire human genome. This approach is known as 'whole genome shotgun sequencing', and was originally developed by TIGR to obtain the sequence of smaller and less complex bacterial genomes. It effectively involves skipping the systematic mapping process (that is central to the HGP strategy) and sequencing 'blind'. The process involves several stages:

- Human chromosomes are randomly sheared into millions of (overlapping) pieces 2Kb to 10Kb long.
- Each fragment is cloned into a bacterium for amplification.
- Sections of sequence from both ends of each fragment are read using automated sequencing machines.

3 M Hattori et al, 2000. 'The DNA Sequence of Human Chromosome 21', Nature, 405, 311-319.

- Computational assembly - sophisticated supercomputers are used to try to deduce the correct order of the fragments from the overlapping sequences.
- Finishing – using special sequencing techniques to fill any gaps in regions of the genome that are not amenable to automated sequencing approaches.

Celera is confident that this approach will deliver an accurate and complete human genome sequence. It has invested some $400M on new sequencing and supercomputer technology. Celera's laboratory outside Washington DC contains 300 of the latest ultra high-throughput automated sequencing machines developed by Perkin Elmer, while the computational power is provided by a supercomputer facility developed in conjunction with Compaq. As outlined in **Box 2.4**, the company has applied the whole genome shotgun approach to obtain the sequence of the fruit fly (Drosophila) genome. The sequencing phase of this project took just 5 months, and the assembly phase a further three months.

BOX 2.4 WHOLE GENOME SHOTGUN SEQUENCING OF THE FRUIT FLY GENOME

To date, the largest genome finished by the whole genome shotgun approach is that of the fruit fly (165 Mb arranged on 4 chromosomes). Celera announced in September 1999 that it had finished the sequencing phase of the project, a process that took just 5 months and generated over 1.8 billion base pairs of code[4]. Assembling the main body of the sequence took a further three months, and the first draft was deposited into public databases[5] in December 1999. The company is currently collaborating with the publicly funded Berkeley Drosophila Genome Project (BDGP) to fill the gaps in the sequence, and published the finished genome in March 2000. Celera sees the Drosophila project as a success, particularly because of its:

- Speed – it is estimated that the whole genome shotgun delivered the sequence two years or so sooner than would otherwise have been the case.
- Accuracy – there was an excellent match between those portions of the genome already obtained by BDGP and other publicly funded groups (more than 20Mb) and the relevant portions of Celera's sequence. Overall, the error rate of the sequence generated by the whole genome shotgun approach matched that obtained by the publicly funded groups (1 error in 10,000 bases on average).
- Completeness – most of the gaps in Celera's sequence are quite small (2,000 bases or less) although genomic repeat sequences (which are notoriously difficult to cope with) are missing. Overall, a total of 14,000 genes were found; the existence of nearly half of these was previously unknown.

Celera regard the successful completion of the Drosophila genome as validating the new sequencing method, and has now turned its attention towards the human genome. It started in September 1999. In January 2000, Celera announced that its database already contained 5.3 billion bases of human genome sequence data. It estimates that this represents around 2.58 billion bases (~80% of the whole genome) of unique sequence, and contains (partial) sequences from more than 97% of all human genes. By April 2000 the company had finished sequencing one individual's genome and was embarking on the computational assembly of the sequence data generated.

2.3.3 The Working Draft

Celera's move into the human genome sequencing arena effectively set up a 'race' between the public and privately funded sectors. While this has created some tension between the two approaches, it has also served to galvanise the whole sequencing effort. One result of

4 The disparity between the size of the genome (165 million bases) and the sequence generated (1.8 billion bases) gives some idea of the complexity involved in the computational assembly.

5 For instance, at http://www.fruitfly.org/

this was a joint announcement on June 26th 2000 of the publication of a working draft of the human genome sequence. Among the key features of the announcement were:

- 97% of the human genome has been mapped;
- 85% of the sequence has now been read in draft form;
- 23% of the sequence has been finished.

2.4 What Happens Next?

As outlined in the previous sections, a combination of the publicly- and privately-funded genome projects has already delivered the majority of the human genome sequence. However, obtaining the finished sequence is by no means the end of the story. Indeed, it is merely the first step towards understanding how genes work, their complex interactions with each other and with the environment, their role in common diseases, etc. Much more research will be needed in order to achieve such understanding, and some of the underlying technologies and research priorities are outlined in **Box 2.5**. These include:

- Bioinformatics – using information technology to store, retrieve and process the huge quantities of genome data. UK bioinformatics initiatives include a new database called Ensembl[6] being set up by groups at the Sanger Centre and the European Bioinformatics Institute (located at Cambridge). It will hold the reference data from the genome project along with a functional annotation of the sequence, and will be freely available to all with an interest in interpreting and exploiting genome data.
- Functional genomics – a name applied to studies aimed at understanding all aspects of genome function. For instance, some parts of the genome will be involved in controlling gene expression, interacting with the environment to switch genes on and off. Other parts may be vital to ensure accurate replication of the chromosome during cell division, or play a more structural role, serving to separate out different domains consisting of clusters of related genes. Developing the tools to allow the study of such aspects of genome function will be a major priority for researchers in the coming years.
- Comparative genomics – identifying the functions of human sequences by comparison with sequences of known function from non-human species. In the UK, the Sanger Centre is involved in a range of genome projects, from bacteria to protozoa and higher organisms such as mouse and chicken. The UK public sector has invested over £7M in mouse genome sequencing and mouse genetics at a number of MRC Units. Such research is seen as being of vital importance to studies aimed at understanding the function of human genes.
- Population studies - linking genetic data to patterns of disease/lifestyle and/or environmental factors. One of the first such studies was announced in Iceland (see **Box 2.6** for details). In the UK, the Wellcome Trust and Medical Research Council (MRC) are exploring the possibility of collecting information on health/disease, genetics and exposure to environmental factors (Box 2.6). Early proposals for this UK Population Biomedical Collection involve collecting data on up to 500,000 people for a period of several years (perhaps even decades). An expert group has been set up to advise on technical (e.g. what information to collect from whom), ethical (e.g. how to ensure informed consent, issues of 'ownership' and confidentiality of the samples and data) and logistical aspects.

6 http://ensembl.ebi.ac.uk/

- Variations in sequence between individuals (e.g. SNPs) which may help explain why people are more or less susceptible to certain diseases, why some drugs work better for some people than for others, etc. One recent UK development is the formation of a consortium to construct a publicly accessible SNP database. It involves the Wellcome Trust and 10 drug companies[7]. The aim is to identify ~300,000 SNPs by April 2001 by comparing DNA taken from 24 individuals from different ethnic groups. Another major UK initiative is a £10 million Cancer Genome Project aimed at identifying the genes that cause cancer. Again funded by the Wellcome Trust, the project will compare DNA sequence from cancer cells with that emerging from the HGP to identify which genes are abnormal.
- Proteomics – the study of all the proteins produced in a cell. Matching this up with genetic data reveals information on the regulation of genes, the roles played by proteins in disease states, etc.

BOX 2.5 MAKING THE BEST USE OF GENOME SEQUENCE DATA

Bioinformatics is the analysis of biological information using advanced information technology. Huge amounts of genome-data (DNA and protein sequences) and related information (e.g. protein structure and function) is now stored on computer databases and accessed throughout the world via the Internet. Researchers can search the databases to see whether newly obtained human sequences match any genes previously isolated from humans or other organisms. Bioinformatics is a key technology underpinning all the main areas of genome research including:

- **Functional Genomics** – studies that aim to understand all aspects of genome function. Among the main goals set by the publicly funded Human Genome Project (HGP) are the generation of complete sets of full-length clones and sequences for human genes, studies into gene expression and control, studies of gene function (e.g. by studying gene mutations in non-human organisms) and developing experimental and computational methods for protein analyses.
- **Comparative Genomics** - gene sequences are largely conserved during evolution, so a gene coding for one enzyme will have a very similar sequence irrespective of the species it is isolated from. This means that information from other genomes is useful in helping interpret human sequences. By comparing 'new' sequence with those of known function already in the databases, researchers may obtain clues about the type of protein it codes for, its function within the body, the biochemical pathways it is involved in, etc.
- **Population Studies** - another big challenge for genome research is to investigate how genetic differences between individuals contribute to patterns of disease at the population level. Such studies are difficult because many different genetic factors may be involved in causing a single disease; the individual effect of each may thus be relatively small. Researchers will also have to disentangle the effects of genes from those of environmental factors such as smoking, drinking, diet, pollutants, etc. Such difficulties mean that studies will have to involve very large numbers of people.
- **Sequence Variation** - each of us possesses our own unique genome, the sequence of which will differ subtly from that described by the HGP. Studying the differences between individual's genomes may help to provide clues as to why certain people are susceptible to some types of disease, whereas others are not. Similar comparisons of genome variations between different human populations may also shed light on the different susceptibilities to disease shown by different ethnic groups. The most common variations in the human genome are single base-pair differences which are thought to occur every 1,000 bases; they are known as single-nucleotide polymorphisms (SNPs). One of the recently announced goals of the HGP is to construct an SNP map of the genome consisting of 100,000 such markers. Such a map of will assist in the tracking down of genetic components of complex diseases such as cancer and diabetes. It may also permit doctors to predict how different individuals will react to various drugs, and tailor therapy accordingly.
- **Proteomics** – studies of proteins being produced in a cell, using two-dimensional separation techniques to produce characteristic protein profiles. These can be used to compare normal and diseased cells, to isolate biochemical markers for diagnostic use, to study gene regulation, etc.

7 AstraZeneca, Bayer, Bristol-Myers Squibb, F Hoffmann-La Roche, Glaxo Wellcome, Hoechst Marion Roussel, Novartis, Pfizer, Searle and SmithKline Beecham

In addition to the research outlined above, privately funded companies will also be looking to exploit genome research. One early example of this was announced in August 1998, when an American company (Incyte Pharmaceuticals Inc.) published plans to spend $200M over 2 years on human genome sequencing. This company intends to focus on individual variations in genome sequence and will start by cataloguing SNPs. It hopes to discover sequence variations in genes that are significant in determining factors such as susceptibility to disease, and to use this knowledge to design more effective drugs. Incyte is seeking patents on some of its sequences; as discussed in more detail in the following Section, the involvement of private ventures in large scale sequencing activities has reawakened the debate on gene patenting in general.

BOX 2.6 POPULATION STUDIES

Iceland

One of the first large-scale population studies attempting to link genetic data with medical records and family background to be announced involves virtually the entire population of Iceland (~270,000 people). One of the attractions of this population is its genetic homogeneity; Iceland's geographical isolation means that the majority of the population is descended from the original Viking settlers. Another is its obsession with genealogy, which means that detailed archives of family lines stretching back to the nation's founding are available. A private biotech company (deCODE Genetics) has computerised these records and struck a deal with the Icelandic government giving it access to a national computer database of health records. This database will be linked to data from research on genetic patterns among Icelanders.

Proposed UK-based Population Biomedical Collection

Proposals for a large UK-based population study are currently being considered by a joint working group chaired by the MRC and consisting of representatives of the Wellcome Trust and NHS. Current proposals are to establish a collection of DNA (blood) samples from half a million adult volunteers recruited via their GPs. Volunteers will also fill in a questionnaire about their lifestyle, environment and current state of health. The aim is to collect follow up information on any diseases the volunteers develop over a period of years. The ethical issues raised by such a collection are discussed in more detail in Section 5.3.6.3.

3 GENETIC TESTING

3.1 What is Genetic Testing?

Advances in human genomics have allowed scientists to identify and isolate an increasing number of gene sequences involved with human disease and drug action / metabolism. This knowledge is being used to develop 'genetic tests' for a variety of different purposes (see **Box 3.1**). These include diagnostic testing, population screening, 'carrier' testing, testing for susceptibility to complex disorders, and pharmacogenetic tests to predict drug action / metabolism.

Strictly speaking, the term 'genetic testing' covers all procedures that yield information on an individual's genetic composition. In addition to the medical applications outlined in Box 3.1, such tests might also be used for 'trivial' purposes such as gender selection, screening for baldness, etc. These and other concerns have led to the various regulatory initiatives outlined in Section 3.3.

BOX 3.1 USES OF GENETIC TESTS

Diagnostic – use of gene tests on individuals displaying symptoms of a particular disease in order to aid diagnosis, treatment and management.

Presymptomatic – testing of healthy (i.e. symptom-free) individuals to provide information on the future risk of developing a specific inherited disease. Such tests are largely used to determine whether an 'at risk' individual has inherited 'late onset' disorders such as Huntington's disease.

Carriers – people who possess one 'faulty' and one 'good' copy of the gene for a recessively inherited disorder such as cystic fibrosis are known as carriers; they are unaffected by the condition themselves. Genetic testing may be offered to assess carrier status since two carriers are at risk of producing an affected child.

Susceptibility – genetic tests may also be offered to healthy (i.e. symptom-free) individuals to assess their predisposition to developing one or more common complex disorders. As knowledge of the genetic component of such diseases improves, susceptibility tests may become more commonplace.

Screening – the application of genetic tests to populations of people, who are not individually necessarily at high risk. This is in contrast to the testing of individuals selected specifically because they are considered to be at higher than normal risk (see examples above).

Pre-natal Genetic Testing – testing provided to women to investigate individual pregnancies where the foetus is judged to be at an increased risk of a genetic disorder (e.g. because of the mother's age, family history, etc.).

Pre-implantation Genetic Diagnosis – testing of embryos created outside the body to see whether they carry a genetic disorder, before being transferred into the uterus.

Pharmacogenetic Testing – tests designed to optimise drug treatments. Such tests can be used to predict the efficacy of a drug, identify patients at risk of adverse drug reactions, or to optimise drug dosage.

Sources: *HGAC, 1999. "The Implications of Genetic Testing for Employment".*
ACGT, 2000. "Report for Consultation on Prenatal Genetic Testing".
HFEA/ACGT, 2000. "Consultation Document on Pre-implantation Genetic Diagnosis".

3.2 Current UK Genetic Testing

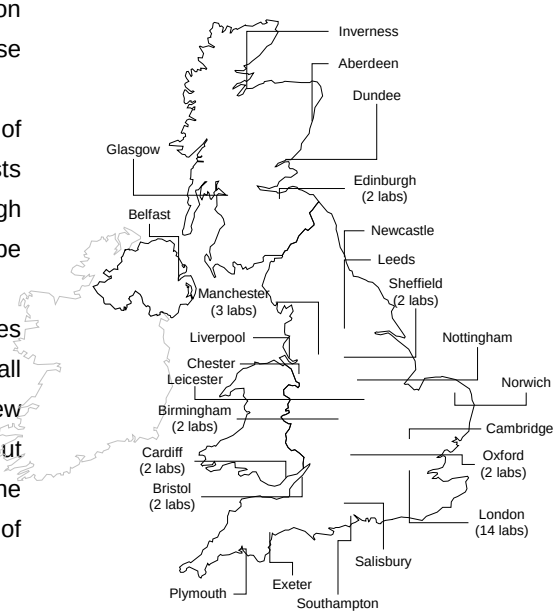
Genetic testing services in the UK are currently offered through NHS Regional Genetics Centres and other clinical laboratories as outlined in **Box 3.2**. The system has historically been geared toward testing for single gene disorders (SGDs, Section 3.2.1), with the bulk of the workload comprising testing for a large number of individually rare disorders. Some of these are so rare that each health district will encounter less than one case per year (Box 3.2).

BOX 3.2 GENETIC TESTING IN THE UK

Genetic testing in the UK is mostly conducted by NHS Regional Genetics Centres, service laboratories and clinical genetics services. There are some 45 such laboratories around the UK, the locations of which are shown in the **Figure** (right). The workload of these laboratories falls broadly into three categories:

- Diagnostic tests for a small number of relatively common single gene disorders such as CF, Huntington's disease and Fragile-X syndrome.
- Diagnostic tests for a larger number (hundreds) of individually rare diseases. Collectively, these tests constitute a substantial part of the workload, although the demand in any one region for any one test may be very low (e.g. see **Table** below).
- Susceptibility tests for common non-inherited diseases that have a genetic component. At present, only a small number of such tests are conducted because few relevant genetic factors have been identified. But genome research is likely to change this and lead to the development of susceptibility tests for a range of common complex disorders.

UK GENE TESTING LABORATORIES



ESTIMATED GENETIC TESTING WORKLOADS FOR SOME INHERITED DISEASES

Condition	Birth frequency	New cases per year per district	Living patients per district
Autosomal dominant disorders			
Familial hypercholesterolemia	1/500	6.0	394
Adult polycystic disease of kidneys	1/1,000	3.0	55
Neurofibromatosis	1/1,250	1.2	69
Huntington's chorea	1/3,000	1.0	18
Retinitis pigmentosa	1/5,000	1.6	36
Familial polyposis coli	1/8,000	0.4	8
Tuberous sclerosis	1/12,000	0.25	19
Autosomal recessive disorders			
Cystic fibrosis	1/2,000	1.5	25
Spinal muscular atrophy	1/10,000	0.3	3
Adrenal hyperplasia	1/10,000	0.3	23
Phenylketonuria	1/13,000	0.2	18
Friedreich's ataxia	1/54,000	0.06	2
X-linked recessive disease			
Fragile-X syndrome	1/4,000	0.75	52
Duchenne/Becker muscular dystrophy	1/9,000	0.3	8
Haemophilia A and B	1/20,000	0.15	11

Source: compiled from information supplied by the British Society for Human Genetics (http://www.bham.ac.uk /BSHG/) and the Clinical Molecular Genetics Society (http://www.leeds.ac.uk/cmgs/).

UK laboratories currently conduct few genetic tests for common non-inherited diseases that have a genetic component, because the genetic factors involved are only now being identified. There is a strong expectation that genome research will identify many more genetic factors relevant to a wide range of common complex disorders (see Section 3.4.3). These are likely to include many cardiovascular diseases, most forms of diabetes, many forms of cancer, Alzheimer's and other conditions of old age, and many other conditions that are of concern from a public health perspective. Any increase in the demand for genetic tests for such conditions would have significant practical implications for the NHS, medical practitioners, etc.; these are discussed in more detail in Sections 5.2 and 5.3. Increases in the availability of pre-natal testing, susceptibility testing, etc. also raise various ethical issues; these too are reviewed in Section 5.3.

3.3 UK Regulation of Genetic Tests

The regulatory and advisory framework for overseeing developments in biotechnology in general was reviewed in 1998/99 by the Government. This review consulted widely with interested parties including a public consultation exercise involving the People's Panel. The review identified a number of concerns over the complexity of the existing framework and the extent to which it was able to address ethical questions and anticipate developments in such a rapidly evolving field. In response to such concerns, the Government proposed a new, strategic, advisory body, the Human Genetics Commission (HGC), with a remit to advise Ministers on all aspects of genetic technologies and their impact on humans.

Details of the HGC's remit, and on the way it will interface with existing regulatory/technical bodies are outlined in **Box 3.3**. The Commission started its activities at end 1999, and will liaise closely with the new Genetics and Insurance Committee (GAIC). Several of the advisory bodies shown in Box 3.3 have been dissolved following the review, with their responsibilities being transferred to the HGC. These include the:

- Human Genetics Advisory Commission (HGAC);
- Advisory Committee on Genetic Testing (ACGT);
- Advisory Group on Scientific Advances in Genetics (AGSAG).

3.4 Genes and Disease

3.4.1 Disease Taxonomy and Classification

Genome research will greatly increase knowledge of the role of genetics in a wide range of diseases. In addition to the clinical benefits such knowledge will bring, it will also have profound implications for the diagnosis and classification of disease in general. The new genetic tests will not only embrace the 'classic' genetic diseases (e.g. single gene disorders, Section 3.4.2), but will also encompass many of the common 'killer' diseases such as cancer, diabetes and heart disease (common complex disorders, see Section 3.4.3). Diagnosis (and treatment) of other diseases (Section 3.4.4) may also be affected; for instance, a person's susceptibility to an infectious disease may be at least partly determined by genetic factors.

BOX 3.3 UK ADVISORY / REGULATORY BODIES RELEVANT TO GENETIC TESTING

GOVERNMENT BODIES

A recent review of the regulatory and advisory framework in biotechnology led to the setting up of the **Human Genetics Commission** (HGC). HGC is a strategic body that advises Ministers on developments in genetic technologies and their impacts on humans. A specific part of its remit is to involve stakeholders and the public through regular consultation exercises. It has taken on the responsibilities of three (dissolved) advisory bodies:

- **Advisory Committee on Genetic Testing** (ACGT) – a body which advised UK Health Ministers on developments in genetic testing, taking into account ethical, social and scientific considerations. ACGT published Guidance on Human Genetic Testing Services Supplied Direct to the Public in 1997, a Report on Genetic Testing for Late Onset Disorders in 1998, and Advice To Research Ethics Committees (points to consider in ethical review of medical research involving genetic testing) in 1998.
- **Advisory Group on Scientific Advances in Genetics** (AGSAG) – a non-statutory advisory body. AGSAG advised the Chief Medical Officer and the Director of Research and Development (Department of Health) on the likely implications of scientific advances in genetics for public health and the NHS.
- **Human Genetics Advisory Commission** (HGAC) **-** Industry and Health Ministers received advice from this body on the wider social, ethical and/or economic issues stemming from advances in human genetics. HGAC published a Report on Insurance and Genetic Testing (1997) and a Report on Employment and Genetic Testing (1999).

HGC will also liaise closely with a wide range of other regulatory and technical bodies as necessary, including:

- **Genetics and Insurance Committee** (GAIC) – a new non-statutory advisory body that will evaluate specific genetic tests (according to criteria that it develops) and assess their application to particular conditions and their reliability and relevance to particular types of insurance. It will advise Health, Treasury and Trade and Industry Ministers on its findings.
- **Gene Therapy Advisory Committee** (GTAC) - a non-statutory advisory body that advises UK Health Ministers on developments in gene therapy research and their implications (see Section 4 for more details).
- **Human Fertilisation and Embryology Authority** (HFEA) – A statutory body set up under the Human Fertilisation and Embryology Act 1990. It monitors scientific developments in its area and considers the safety and ethical implications. HFEA and ACGT published a joint consultation document on preimplantation genetic diagnosis in November 1999.
- **National Screening Committee** (NSC) - advises Ministers on the case for implementing new screening programmes and for continuing, modifying or withdrawing existing ones. Clinical and cost effectiveness, and treatment options are among the main criteria considered.
- **National Institute for Clinical Excellence** (NICE) - a Special Health Authority that assesses clinical benefits and costs of selected (new and established) health interventions.
- **Medicines Control Agency** (MCA) / **Committee on Safety of Medicines** (CSM) – MCA safeguards public health by licensing, inspecting and monitoring medicines intended for human use. CSM is an independent statutory advisory body established under the Medicines Act (Section 4) which advises Government Health Ministers on the quality, efficacy and safety of medicines.

NON-GOVERNMENT BODIES

British Society for Human Genetics (BSHG) – a federated society consisting of the Clinical Genetics Society, Association of Clinical Cytogeneticists, Clinical Molecular Genetics Society, Association of Genetic Nurses and Counsellors and The Cancer Genetics Group. BSHG recently published a paper on Co-ordinated Arrangements for Genetic Testing for Rare Disorders.

UK Clinical Molecular Genetics Society (CMGS) – is part of the BSHG. Its members are largely drawn from within the NHS Regional Clinical Genetics Centres and it is active in the fields of education, training, research and quality assurance. CMGS published a paper on Gene Patents and Clinical Molecular Genetics Testing in the UK in January 1999.

The Royal College of Physicians (RCP) **and Royal College of Pathologists** (RCPath) – are the two professional medical bodies whose members are most affected by developments in clinical molecular genetics. They are active in the formulation of professional guidelines, training, education, quality assurance, etc. The two colleges recently joined with the BSHG to establish a **Joint Committee on Medical Genetics**.

Nuffield Council on Bioethics (NCB) - an independent body established by the Nuffield Foundation in 1991, jointly funded by the Nuffield Foundation, Wellcome Trust and Medical Research Council (MRC). It has published two reports relevant to genetic testing: Genetic Screening (Ethical Issues) in 1993, and Mental Disorders and Genetics: The Ethical Context in 1998.

Sources: Compiled from the Public Health Genetics Unit (www.medinfo.cam.ac.uk/phgu/), CMGS (www.leeds.ac.uk/cmgs/) and HGC (www.hgc.gov.uk).

Of these various different types of conditions, it is the common complex disorders where genetic tests are likely to have the most profound impact. For many such conditions, current diagnostic practice relies upon assessing physical signs and symptoms and somewhat crude biochemical or physiological measures of the biological disturbances that accompany disease. Such approaches result in large, heterogeneous diagnostic groupings such as 'hypertension' or 'diabetes'.

Genetics provides information on the underlying mechanisms behind a disease – it can identify the biochemical processes by which a disease starts, progresses, results in complications or responds to treatment. Genetic tests will thus provide doctors with new tools to split existing diagnostic categories down into smaller, more homogenous subgroups. For instance, research on HLA genes[8] revealed an immune mechanism as the basis for some cases of diabetes, leading to the subdivision of this diagnostic category into type I and type II diabetes. Further genetic research has since led to the subdivision of type II diabetes into several other distinct categories, each with a different molecular basis.

As genome research identifies more genetic factors involved in disease, such sub-division will become increasingly common. As outlined in more detail in Section 3.4.3, research has implicated the BRCA1 and 2 genes in a small proportion of cases of breast cancer, and this may change the way that this disease is classified in the future. Other examples of genes implicated in disease that may clarify future diagnostic practice are the Apo E4 gene in Alzheimer's and the angiotensinogen / angiotensin converting enzyme (ACE) genes in cardiovascular disease. Eventually, such developments will lead to an entirely new taxonomy of disease, based on knowledge of the underlying molecular mechanisms. This shift towards diagnosing and classifying disease at a molecular level also raises practical questions over how to ensure that doctors are trained to deal with the new genetic approaches, and how the NHS will cope with the demand for genetic tests and associated counselling (Sections 5.2 and 5.3). It may also mean that doctors will be able to prevent a wider range of diseases; rather than waiting for patients to present with symptoms, individuals and populations can be tested and screened to identify those at increased risk of disease.

3.4.2 Single Gene Disorders

Improvements in the diagnosis (and treatment – see Section 4) of single gene disorders (SGDs) are one of the more immediate likely benefits of genome research. These are the simplest types of genetic disease where a single mutation in a gene leads to a faulty version of a protein being manufactured in the body which in turn causes the disease itself. Several thousand different SGDs have been identified to date, most of which are relatively rare. Examples of some of the more common SGDs include cystic fibrosis, Duchenne muscular dystrophy, Huntington's disease, phenylketonuria and sickle cell anaemia.

The exact nature of the condition caused by a SGD depends on the function of the affected protein. In cystic fibrosis (CF) the gene involved (CFTR) codes for a protein found on the outer membrane of epithelial cells, where it normally acts as a valve, controlling the passage of salts and water into and out of the cell. CF sufferers inherit two copies of a faulty CFTR

8 Human leucocyte antigen genes, a series of genes that code for antigens present on the surface of cell membranes.

gene (one from each parent) and thus manufacture faulty copies of the CFTR protein[9]. This affects the salt / water balance within the cells lining the lungs, pancreas and intestines, causing the build up of the thick, sticky secretions that are characteristic of CF. CF is one of the most common hereditary diseases among Caucasians, affecting around one in every 2,500 babies born in the UK (or ~300 CF babies each year).

Information from the genome project on the sequence and location of the genes involved should allow better diagnostic tests for SGDs to be developed. This has already happened in some cases, where the gene responsible for a disorder has been isolated. For instance, the gene coding for CFTR was isolated as long ago as 1989. The information has already been used to develop improved (genetic) diagnostic tests for CF (see **Box 3.4**). However, this example also illustrates some of the complexities involved in dealing with even apparently straightforward genetic conditions such as single gene disorders.

BOX 3.4 DIAGNOSTIC TESTS FOR CYSTIC FIBROSIS

Biochemical Tests – Prior to the development of genetic tests (see below), diagnosis of CF relied solely on the detection of certain biochemical markers. These included:

- IRT (immunoreactive trypsin test), which measures IRT levels in blood (babies with CF have higher IRT levels than normal). Such tests are still widely used as a precursor to genetic tests.
- Meconium tests – measure levels of albumin (and sometimes also lactase) in mucous. High albumin levels are associated with CF, although meconium tests tend to be somewhat unreliable.
- Sweat tests - measure chloride levels in sweat and are commonly used to confirm CF diagnosis.
- Amniotic fluid enzymes – reduced levels of certain enzymes (e.g. γ-glutamyl transpeptidase and aminopeptidase) in the amniotic fluid are associated with CF. Tests assessing these enzyme levels were widely used in the 1980s, but have now been largely superceded by genetic tests.

Genetic Tests – detect mutations in DNA extracted from blood samples, amniotic fluid, mouthwashes, urine samples, etc. At present, there are three commercially available kits for testing for mutations in the CFTR gene:

- Innogenetics of Belgium markets an INNO-LiPA kit that detects 8 common CFTR mutations. DNA from the individual to be tested is labeled and added to a membrane containing 8 different immobilised probes. If one (or more) of the mutations is present, the labeled DNA will hybridise (bind to) the appropriate probe.
- Zeneca Diagnostics markets a CF20 kit that detects about 90% of common CF mutations in the UK population. It involves a DNA amplification technique – mutations are detected by analysing the amplification products using a separation technique (gel electrophoresis).
- Perkin Elmer markets another DNA amplification-based kit that screens for 31 different CFTR mutations. Following amplification and ligation (where adjacent sequences are joined together), mutations are detected by a fluorescent DNA sequencer.

Screening protocols – very few screening programmes are currently available. Those that are, typically use a mixture of both biochemical and genetic tests. IRT or meconium tests are commonly used as a rapid and cheap first screen. If these prove positive, then genetic tests may be used to confirm the diagnosis and characterise the mutation involved.

The main problem is that while each SGD involves only a single gene, there are very many different ways in which it can 'go wrong'. For instance, researchers have discovered more than 800 different mutations in the CFTR gene in the 10 years since it was first isolated. Each of these can cause CF by manufacturing a faulty version of the CFTR protein. The different mutations may be classified into 5 main groups, some of which prevent the production of CFTR protein completely, others of which result in lower levels of production or activity

9 People with one faulty and one good copy of the CFTR gene are termed 'carriers'; they do not suffer from CF. Children born to parents who are both carriers stand a 1 in 4 chance of having CF.

through various mechanisms. The severity of the CF symptoms and prognosis for the affected individual varies from one class of mutations to another. Another complicating factor is that different types of mutations predominate among different ethnic groups, so that the most common mutations causing CF in Caucasians will be different from those found in Ashkenazi Jews or Asians. Commercially available CF test kits are designed to look for a range (up to 30) of the most common mutations (Box 3.4). Detection rates vary depending on the population screened and the mutations screened for - current tests detect around 80-85% of CF carriers in the UK population, but only around 35% of Asian carriers. Since it is not currently feasible to screen for all (800 or so) possible mutations, an individual receiving a 'negative' result may still carry a rare CFTR mutation that the test was not designed to detect.

However, there is every prospect that this may change in the future with the development of 'gene chips' and micro-arrays (**Box 3.5**). These devices are designed to allow test (i.e. of unknown sequence) DNA to be screened against many thousands of oligonucleotide probes (short lengths of nucleic acids with known sequences) simultaneously. They could thus be used as a means of rapidly sequencing DNA, or as the basis of rapid, high throughput diagnostic tests for mutations associated with genetic disease. The capacity of some of these devices means that a single chip could potentially screen for all the mutations linked with several hundred different SGDs.

While CF is one of the best characterised genetic diseases, genome research should provide similar levels of knowledge for other SGDs. Indeed, many of the genes involved in such conditions have already been mapped to specific chromosomal locations, and are in the process of being sequenced. Researchers suspect that all will turn out to be as complex as CF – for each SGD, any one of hundreds of possible mutations may cause the condition, with the prevalence of mutations varying between different ethnic groups. Technological advances such as gene chips should allow the development of rapid, accurate and cheap genetic tests for SGDs, although this in itself raises a number of issues for the NHS and the medical profession.

3.4.3 Common Complex Disorders

Common complex disorders – including many of the main 'killer' diseases such as cancer, diabetes, certain types of heart disease, etc. - have become a major focus of genome research in recent years. Such conditions are a product of both genetic and environmental factors. Some of the genetic factors involved may be inherited, others acquired from the complex interactions between genes and their environment. As outlined in **Box 3.6**, genome research is already helping to clarify the underlying genetic component of many of these common complex disorders. However, epidemiological research will be needed to reveal information on the nature of the environmental factors that cause mutations, the commonest types of mutation, and their distribution throughout the population.

Breast cancer provides an illustration of some of the difficulties involved in unraveling the underlying causes of common complex disorders. This condition usually arises sporadically, but in a minority (~5%) of cases is inherited (familial breast cancer). It is possible that the same underlying genetic factors operate in both cases, with mutations being acquired in sporadic breast cancer and inherited in familial cases. Studies of families with a history of (familial) breast cancer have identified more than 50 genes that may be implicated in the

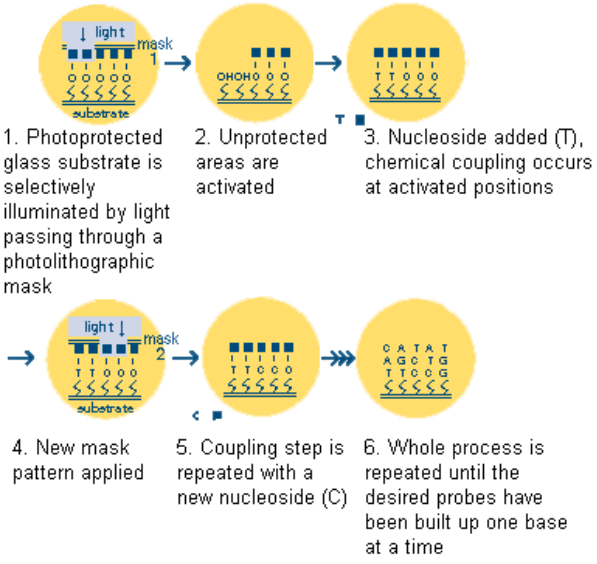
disease. Two of these (the BRCA1 and BRCA2 genes) have attracted particular interest since their discovery in 1994 and 1995 respectively.

BOX 3.5 GENE/BIO CHIPS

Genetic tests rely on hybridisation to detect mutations or other specific sequences. Test DNA (e.g. from a patient) is exposed to short synthetic DNA probes (oligonucleotides) encoding the sequence of interest – if this sequence is present in the test DNA, then it will hybridise (bind) to the probe. This binding may then be detected by the use of (e.g. fluorescent or radioactive) labels, DNA amplification techniques, etc.

The first such tests were essentially sequential: test DNA could only be exposed to one probe at a time. Current tests allow a certain degree of 'multiplexing', screening test DNA against tens of probes in a single test. Gene chips allow test DNA to be exposed to thousands of different probes at a time by using miniaturised, high density arrays of probes immobilised onto a substrate of some description. Two different approaches have emerged to date, and these are described below.

BUILDING A GENE CHIP



- **GeneChip** – this technology has been developed by the US company Affymetrix, and is based on similar techniques to those used in the semiconductor industry. Probes are built up one base at a time on a glass substrate (see **Figure**, left), using a series of photolithographic masks to control where the chemical reactions occur. The end result is a high density array of oligonucleotide probes with each having a predefined position in the array. Fluorescently labeled test DNA is added to the GeneChip cartridge, and incubated to allow hybridisation to occur. Scanning the cartridge in a high resolution scanner reveals which of the probes have bound to the test DNA (and thus encode a sequence found in the test DNA).

The limitation of this technology is not the number of probes squeezed onto a chip but rather the resolution of the fluorescent scanner - the best scanners currently available are capable of reading an array of ~400,000 probes. The first commercially available GeneChip consisted of an array of 16,000 probes targeted at certain HIV genes.

Bio Chips – are currently being developed by the US Argonne National Laboratory in conjunction with the Russian Academy of Sciences' Engelhardt Institute of Molecular Biology, Motorola and Packard Instrument Company. The overall approach is similar to the GeneChip described above - tens of thousands of biological probes are immobilised in a high density array on a substrate, exposed to the test material and hybridisation detected using fluorescent dyes. In this case however, the substrate used is a 'micro-gel' - each position in the array is effectively a miniature test-tube, where known probes (e.g. oligonucleotides, amino acid chains) are screened against the (unknown) target material (e.g. test DNA or protein). As many as 20,000-30,000 probes may be immobilised within an area of one square centimetre. The main technological challenge is to develop accurate liquid handling techniques that allow researchers to load their own probes into the bio chip array, test them against the target material and analyse the results. Similar microarray technology has been developed with MRC support in the UK.

BOX 3.6 GENETIC FACTORS IN SOME COMMON DISEASES

An increasing number of common diseases are being identified which have a genetic component. The list below is not comprehensive; it is a summary based on diseases identified (by the Continued Care Conference) as being of significance to the NHS because they give rise to the need for long-term care.

Alzheimer's disease (AD) – around 2% of cases in the UK take the form of the **familial** disease, characterised by early onset. Mutations in the presenelin-1 (PS1) gene are found in around 40% of people with familial AD. By far the most common form of the disease is **late onset AD**, which is known to be genetically complex. A number of different genetic factors are thought to be involved, along with a range of (unknown) environmental/lifestyle factors. To date, the only gene that has been unambiguously implicated is Apolipoprotein E (ApoE). At least two forms of this gene are known: ApoE4 and ApoE2. The former is linked with an increased risk of developing late onset AD, whereas the latter is though to protect against development of the disease. Both (risk and protective) mechanisms may work through effecting the time of onset. Because ApoE is only one of the factors involved, genetic tests for the different forms of this gene are of only limited predictive/diagnostic value.

Cancer – cancer is now acknowledged as being a genetic (but not necessarily an inherited) disease. Genes are involved in all stages of the development of tumours, from initiation, angiogenesis (growth of new blood vessels to supply the tumour), invasion, progression and eventual metastasis (spreading of the tumour to other parts of the body). Among the genetic factors involved are those that control the cell cycle (e.g. tumour suppresser proteins, cyclins, cyclin-dependent kinases [CDKs] and CDK inhibitors) as well as the Bcl-2 and caspase proteins that are implicated in apoptosis (cell suicide). In addition to this overall picture, certain genes have been implicated in increasing the risk of certain types of cancer:

- Breast cancer – most cases of breast cancer are sporadic, and the genetic factors involved have yet to be identified. Various mutations in the BRCA 1 and 2 genes are linked with increased risk of the rarer, familial form of the disease.
- Colorectal cancer- around 5% of colorectal cancer cases are thought to be inherited. There are two distinct types of the inherited form of the disease. In one type (familial adenomatous polyposis) the cause has been traced to mutation(s) in a gene on chromosome 5 which is involved in cell adhesion. In the other (hereditary nonpolyposis colon cancer) most cases are associated with mutation(s) in one or more of four genes for enzymes involved in repairing mistakes in DNA copying. Researchers are starting to make progress in understanding the acquired genetic changes involved in the development of sporadic colorectal cancer.
- Ovarian cancer – 5-10% of ovarian cancers are familial. Three hereditary patterns have been identified: ovarian cancer alone, ovarian and breast cancers, or ovarian and colon cancers. BRCA1 mutations have been implicated in most families affected by the first two of these.
- Prostate cancer – is a very common disease in elderly men. Recent research has suggested the involvement of susceptibility genes, although no predictive testing is currently available.

Diabetes – both major forms of diabetes (Type 1 which affects young people and Type 2 which mainly affects older people) tend to run in families. They are thought to be the result of complex interactions between genetic and environmental factors. Type 1 diabetes is known to be genetically complex, and several different genes have been implicated in increased risk of this early onset form of the disease. Genetic studies in isolated populations has recently suggested a link between increased risk of Type 2 and a gene or genes located on chromosome 12 involved in insulin secretion.

Heart disease – in addition to its role in AD, ApoE is thought to be implicated in the development of certain types of heart disease and conditions such as stroke through its affects on lipid (fat) metabolism. Other (most notably the angiotensin converting enzyme [ACE] and angiotensinogen) genes have also been implicated in predisposition to hypertension and heart disease.

Source: 'Genetic Tests and Future Need for Long Term Care in the UK', Report of a Work Group of the Continuing Care Conference, CCC, July 1999.

Both BRCA genes code for proteins thought to be involved in tumour suppression; for instance, experiments in mice suggest that the genes may be involved in DNA repair. There is good evidence that both BRCA1 and 2 are implicated in inherited breast cancer, although the level of risk associated with mutations in these genes varies from one population to

another. Early research on families with high rates of (inherited) breast cancer suggested that 85% of women with mutations in one or other of these genes would develop breast cancer by the age of 70. More recent research on Askenazi Jewish women (another group at higher than normal risk of breast cancer) in the US put the lifetime risk of developing breast cancer at around 50% for those with mutations in BRCA1 or 2. In comparison, women in the general UK population have a lifetime risk of around 12.5% of developing breast cancer.

While it is clear that inherited mutations in BRCA1 or 2 increase a woman's risk of developing (familial) breast cancer, the role of these genes in the more common, sporadic form of the disease is unknown. As noted previously, one possibility is that acquired mutations in these genes might be involved in the development of sporadic breast cancer. However, many other factors are also likely to be involved, and these include a combination of complex environmental and genetic interactions. While researchers are still trying to unravel how such factors operate at the molecular level, the main epidemiological risk factors include:

- Age (women over 50 are at greatest risk);
- Previous personal history of breast, colon, uterine or ovarian cancer;
- Previous family history of breast, colon, uterine or ovarian cancer;
- Exposure to female sex hormones (the greater the exposure the higher the risk, so that factors such as age of onset of menstruation, age at menopause, exposure to hormone therapy, etc. can all influence breast cancer risk);
- Lifestyle factors (e.g. low levels of physical activity, high alcohol intake, smoking);
- Ethnic origin (e.g. Ashkenazi Jewish women are at higher than normal risk of developing breast cancer);
- Mutations in the BRCA1 and / or 2 genes;
- Confirmed diagnosis of atypical hyperplasia (a non-cancerous cluster of breast cells).

Of these various risk factors, only a few per cent of all breast cancer cases can be accounted for in terms of mutations in the BRCA genes. Because of this, genetic testing for mutations in these genes is not an appropriate tool for screening the general population; it may however benefit those women identified as being at particularly high risk. Hundreds of different mutations in the BRCA1 and 2 genes have been identified to date, and tests screening for them are commercially available. As with single gene disorders such as CF, the advent of gene chip technology (Box 3.5) is leading to the development of faster, cheaper and more comprehensive (i.e. testing for more mutations) genetic tests for breast cancer.

The development of genetic tests for breast cancer and other common complex disorders raises a number of issues. Unlike SGDs (where genetic tests often unequivocally confirm the presence of a disease), detecting mutations in genes implicated in common complex disorders merely indicates an (unquantifiable) increase in risk of developing that condition at some (unknown) point in the future. This means that it is possible to screen for genetic faults before scientists understand the exact consequences of carrying those mutations. Or before doctors are in a position to offer effective treatments (the development of new therapies takes longer than new diagnostic tests). The practical implications of such tests for the NHS and the ethical, legal and social issues surrounding their use are discussed in Section 5.

3.4.4 Other Diseases Involving Genetics

Much of the focus of genome research has fallen on the common complex disorders because these are the diseases of greatest concern to public health. But there are also a number of other diseases where genome research may reveal a larger role for genes than was hitherto thought likely. Examples include:

- **Infectious disease** – it has been suggested that genetics may be one of the factors that determines a person's susceptibility to certain bacterial or viral diseases. This could work in a number of different ways. For instance, genetics is likely to be a factor determining the nature and strength of the immune response elicited by exposure to an infectious agent. Or small variations in the sequence (e.g. SNPs) of genes coding for cell surface proteins such as receptors may affect whether viruses gain access to cells 'displaying' such proteins. Initiatives such as the plan to map human SNPs should help clarify the role of genetics in such conditions.
- **Behavioural disorders** – evidence from linkage studies (comparing disorder rates in identical and non-identical twins, adoption studies, etc.) has long suggested that a range of behavioural disorders have a small genetic component. The evidence is strongest for conditions such as manic depression and schizophrenia, although genetics has also been implicated in Alzheimer's and personality disorders. It is hoped that genome research will lead to the identification of the genes involved, and the way in which they interact with environmental factors. Researchers in this area expect environmental factors to play a very large role in the development of such conditions, but hope that understanding the (albeit small) genetic component will provide a basis for improved diagnosis and treatment.

In addition to these conditions, it is hoped that genome research will clarify the underlying mechanisms by which chromosomal disorders cause conditions such as **Down's syndrome** (see **Box 3.7**). This syndrome occurs in individuals who have extra chromosome 21 material present in the cells of their body (in most cases, individuals carry an extra copy - i.e. three instead of two - of chromosome 21). The characteristic symptoms (which may include learning difficulties, heart defects, epilepsy, hypothyroidism and celiac disease) are thought to result from over-expression of some of the (so-called 'critical') genes on chromosome 21. Researchers hope that pinpointing the critical genes, and understanding the processes by which the over-expressed gene products interact with other genetic and metabolic factors may result in more effective treatments for Down's syndrome. It is also possible that such research will allow the development of more sophisticated pre-natal tests, that can predict the likely severity of the syndrome from the genetic profile of the extra chromosome 21 material.

BOX 3.7 DOWN'S SYNDROME

Causes

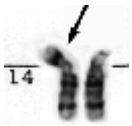
Down's syndrome is a chromosomal disorder, which affects around one in 800 live births. All individuals with Down's have extra chromosome 21 material in their cells, although this can occur by one of three main routes.

Trisomy 21 - in the most common form, affected individuals posses an extra (i.e. a third) copy of chromosome 21 in each of their cells (see Figure, right). This results from unequal chromosome division, usually during the mothers production of eggs. It is this form of Down's that increases in frequency with maternal age.

Trisomy 21

Mosaic trisomy 21 - the second form of Down's accounts for ~2-4% of cases of Down's. It is a variation on trisomy 21, where affected individuals have three copies of chromosome 21, but only in certain cell types. This form may arise from some (trisomy 21) cell types losing their extra chromosome. Alternatively, the unequal division of chromosomes at cell division may occur shortly after fertilisation, thus only affecting certain cell types.

21



Translocation trisomy 21

Translocation trisomy 21 – in some 3-4% of Down's cases, the extra chromosome 21 material does not 'stand alone', but is rather attached to another chromosome. The most common translocation occurs when the extra chromosome 21 material attaches to chromosome 14 (see Figure, above).

Pre-natal testing

Tests for Down's fall into two categories: screening tests and diagnostic tests. Screening tests are used to identify 'high risk' pregnancies, and involve checking the mother's blood for a number of different factors:

- Alpha fetoprotein (AFP), which is made in the yolk sac and in the foetal liver. In Down's syndrome both of these are smaller than usual, and so decreased levels of AFP are detected in the mother's blood.
- Estriol, a hormone produced in the placenta from metabolites supplied by the foetal liver and adrenal gland. Again, levels of estriol detected in maternal blood are lower than normal in Down's pregnancies.
- Human chorionic gonadotrophin (hCG) is a hormone produced by the placenta. High levels of one of the subunits (the β subunit) are detected in the mother's blood in Down's syndrome pregnancies.

Women identified by the screening tests as being at 'high risk' (maternal age is also factored into the risk assessment) may be offered diagnostic tests that directly examine foetal cells for the chromosomal disorders that cause Down's. Such cells may be collected by amniocentesis, where liquid from the womb (containing foetal cells) is collected by inserting a needle through the mother's abdominal wall. Or such tests can be conducted on material collected by chorionic villus sampling (where foetal cells are removed from the placenta). Both methods carry a slightly increased risk (~0.5-2%) of miscarriage.

4 GENOME RESEARCH AND NEW TREATMENTS

Improved understanding of how genes and the products they code for are implicated in disease will open up new horizons for improved treatments. Such developments are likely to occur in three main areas:

- gene therapy – treatments involving transfer of nucleic acid sequences to human cells;
- existing drugs – information about an individual's genome should allow existing drugs to be used more effectively (pharmacogenetics);
- new drugs – improved understanding of disease mechanisms, basic cell processes, etc. will provide new targets for the development of novel treatments.

4.1 Gene Therapy

Gene therapy describes any procedure where beneficial genetic material is transferred into the cells of patients. As described in more detail in **Box 4.1**, genetic material can be transferred directly into cells in the body, or the cells can be removed from the body, modified and transplanted back into the patient (*ex vivo* therapy). Gene therapy was originally envisaged mainly as a cure for single gene disorders such as CF. The main approach was augmentation – using gene transfer to augment cells defective in a particular gene product (such as the CFTR protein). However, more recently the focus has shifted towards developing treatments for more common diseases. These include cancer, infectious diseases such as HIV and acquired conditions such as heart disease.

In principle, genes can be transferred into any type of human cell, including sex cells. However, this type of gene therapy (called **germ line therapy**) is not permitted because of concerns over the ethical implications of introducing genetic characteristics that will be passed on to future generations. Gene therapy involving non-sex (autosomal) cells is permitted in the UK (and elsewhere) and is regulated by the Gene Therapy Advisory Committee (GTAC). This Committee considers that such therapy has not yet developed to the stage where it can be considered a treatment. Rather, it regards all gene therapy as research, with trials taking place under strict rules laid out by GTAC[10] and only after this Committee has approved the proposed clinical protocols. Since 1992, GTAC has approved more than 40 such research protocols (**Table 4.1**) in the UK, most (35) of which have been trials involving various types of cancer. World wide, more than 400 gene therapy trials (involving more than 3,500 people) have been approved, mostly (~80%) in the US.

What impact will genome research have on gene therapy approaches in the future? In theory, the number of single gene disorders and common complex disorders treatable by such approaches should increase significantly in the coming months and years. Despite initial high expectations, results of the first trials conducted were generally disappointing. Researchers found it difficult to achieve high levels of therapeutic gene expression in targeted cells for sustained periods of time. However, recent trials have given more encouraging results. For instance, gene therapy has been used to activate the immune system to act against prostate cancer in trials in the US. Other recent encouraging results include treatment of children suffering from an inherited immune disorder (SCID) in trials in France, and trials involving haemophilia in the US.

10 GTAC, "Guidance on Making Proposals to Current Gene Therapy Research in Human Subjects", 1994.

BOX 4.1 GENE THERAPY

Gene therapy involves the transfer of beneficial genetic material into human cells. This may be accomplished in one of two main ways:

- direct introduction of genes into cells in the patient;
- removing cells from the patient, modifying them and then returning them to the patient (*ex vivo* therapy).

Transfer of genetic material into human cells is achieved using a vector. To date, two main approaches have been developed:

- Viral Vectors - using viruses as a means of transferring gene sequences into human cells. Viral vectors may be specific to certain types of cell, are highly efficient at transferring DNA, and may (depending on the type of virus) integrate the gene sequence directly into the cell's chromosome. However, researchers have to 'disarm' viruses used in such protocols by removing potentially harmful viral sequences. Among the most common viral vectors are adenoviruses, retroviruses, and adeno-associated virus (AAV).
- Non-viral vectors - various non-viral strategies have also been developed for transferring genetic material into human cells. One such approach has been to package therapeutic sequences up in liposomes – small parcels of lipid (fat) that can fuse with cell membranes. Genes wrapped up in this way are transferred into cells during the fusion process, although only a small proportion of the sequences end up in the cell nucleus. Other approaches currently under development include human artificial chromosomes, wrapping DNA up in various novel polymers, and modifying endothelial (lining) cells to act as vectors.

Originally, gene therapy was envisaged mainly as a cure for single gene disorders such as cystic fibrosis. The main approach was one of augmentation – using gene transfer as a means of augmenting cells defective in a particular gene product (such as the CFTR protein). Another approach to treating single gene disorders is gene correction, where the cell's own repair mechanisms are used to correct 'faulty' gene sequences. More recently however, gene therapy trials have focused on developing treatments for a wider range of disorders. While these include acquired disorders (e.g. heart disease) and infectious diseases (e.g. HIV), much of the current focus is on developing gene therapies for the treatment of cancer. Approaches include:

- Transferring drug sensitivity genes (i.e. that make cancer cells more susceptible to anti-cancer drugs) or 'suicide genes' (e.g. that render cancer cells susceptible to a drug that has no effect on unaltered cells).
- Immunotherapeutic approaches, where the genes transferred stimulate the immune system to recognise and destroy cancer cells.
- Augmentation of defective genes in cancer cells – e.g. transferring 'good' copies of defective genes that are involved in cell division.

Gene therapy trials in the future may also benefit from the development of better vectors. Approaches will include refining current viral and non-viral vectors and developing entirely new systems that transfer DNA more efficiently to target cells, utilise more powerful regulatory sequences and maintain expression of the therapeutic gene over longer periods. Many such vectors are being developed in the laboratory, to the point where there is a bottleneck awaiting assessment in clinical trials. One issue discussed in more detail in Section 5.4 concerns the safety of adenovirus, one of the most widely used gene therapy vectors. While this vector has been safely used in gene therapy trials throughout the world, concerns were raised following the death of a patient enrolled in a gene therapy trial in the US[11]. It has been suggested that the death may have been linked to an immune response (shock and respiratory distress) to the adenovirus vector used in the trial.

11 see Nature **401**, 517, 1999

TABLE 4.1 UK GENE THERAPY RESEARCH PROTOCOLS APPROVED BY GTAC

DISEASE	CENTRE / DATES	DATE APPROVED (No. PATIENTS)
Severe Combined Immune Deficiency	Institute of Child Health / Gt Ormond St Hospital	1/93 (1)
Cystic Fibrosis (nasal)	Royal Brompton Hospital	3/93 (15)
B cell lymphoma	MRC Cambridge	7/93 (7)
Neuroblastoma	Imperial Cancer Research Fund (ICRF) Bristol	2/94 (withdrawn)
Metastatic melanoma	ICRF Oxford	5/94 (13)
Metastatic melanoma	Institute of Cancer Research / Royal Marsden Hospital	2/94 (12)
Cystic Fibrosis (nasal)	Oxford / Cambridge	2/94 (12)
Cystic Fibrosis (nasal)	Edinburgh	5/94 (16)
Cystic Fibrosis (lung)	Royal Brompton Hospital	9/94
Lymphoma	University College London	12/94 (3)
Breast cancer	Hammersmith Hospital	10/95 (12)
Cervical carcinoma	University of Wales, Cardiff	6/95 (9)
Cervical intraepithelial neoplasia III	University of Wales, Cardiff	5/96 (12)
Cervical cancer	University of Wales, Cardiff / University of Manchester	8/97 (8)
Hurler's Syndrome	Royal Manchester Children's Hospital	12/95 (3)
Head / neck cancer	Beatson Oncology Centre, Glasgow	1/96 (30) 7/97 (30) 3/97 (12)
Cystic Fibrosis (nasal)	Oxford / Cambridge / Leeds / Manchester consortium	5/96 (11)
Head / neck cancer	Institute of Cancer Research / Royal Marsden Hospital	9/96
Cystic Fibrosis (nasal and lung)	Royal Brompton Hospital	12/96 (16)
Glioblastoma	Beatson Oncology Centre, Glasgow	12/96 (9) 7/99
Glioblastoma	Beatson Oncology Centre, Glasgow / Institute of Neurological Sciences, Glasgow	3/97 (withdrawn)
Gastrointestinal cancer	Royal Marsden Hospital	4/97 (1)
Breast cancer	Guy's Hospital	11/97 (11)
Ovarian cancer	The John Radcliffe Hospital (Oxford), Guy's and St Thomas's Cancer Centre, Royal Marsden Hospital, St George's Medical School (London)	9/97 (22)
Colorectal cancer	Queen Elizabeth Hospital, Birmingham	3/98
Ovarian cancer	City Hospital/University Hospital Birmingham	3/98
Head and neck cancer	Royal London Hospital/Charing Cross Hospital	Withdrawn
Malignant melanoma	Southern General Hospital/Western Infirmary Glasgow	9/98 (5)
Breast cancer	Churchill Hospital Oxford	10/98
Metastatic malignant liver tumours	Hammersmith Hospital	UC (Under Consideration)
B cell lyphoma	Royal Bournemouth/Royal Hampshire Hospitals	5/99
Ovarian cancer	Northern General Hospital Sheffield	2/00
Head and neck cancer	CRC Institute for Cancer Studies, University of Birmingham	7/99
Liver cancer	CRC Institute for Cancer Studies, University of Birmingham	7/99
Malignant melanoma	St George's Hospital	7/99
Ovarian cancer	Royal Marsden, Christie, John Radcliffe Hospitals and CRC Institute for Cancer Studies	7/99
Head and neck cancer	Beatson Oncology Centre Glasgow	7/99
Peripheral arterial occlusive disease	St George's Hospital London	UC
HIV	Chelsea & Westminster, Royal Free, Brighton and Cardiff	5/00 (conditional)
Malignant melanoma	Churchill Hospital Oxford, Royal Marsden Hospital	5/00
Colorectal cancer	Christie Hospital Manchester	UC
Bladder cancer	St James's University Hospital Leeds	UC
Breast cancer	Guy's Hospital, London	UC
Melanoma	Churchill Hospital Oxford	UC
Breast cancer	St James's University Hospital Leeds	UC

4.2 Better targeting of Existing Drugs (Pharmacogenetics)

It has long been recognised that different people can experience widely different reactions to any given medicine. Indeed, a 'rule of thumb' has evolved within the pharmaceutical industry that only around one in three people given a drug benefit from it. This may be in part due to environmental factors, since the action of a drug may be influenced by the patient's diet, whether they are taking other drugs, their general state of health, etc. But genetic factors are also involved, and advances here are expected to lead to personalised medicine, allowing doctors to more accurately match drugs with individuals based on improved knowledge of:

- what is actually wrong with the patient;
- how they are likely to react to a given drug.

As far as the first of these is concerned, better knowledge of the underlying mechanisms of disease should lead to improvements in diagnostic precision (see Section 3.4.1). This will result in the current diagnostic categories for many common disorders becoming fragmented into an increasing number of sub-categories based on genetic or other biomedical tests. This trend towards molecular diagnosis should allow doctors to distinguish patients with similar symptoms but different underlying causes and to choose treatments accordingly.

Turning to variations in the way that people respond to drugs (pharmacogenetics), genetics may be involved in two main ways. Firstly, genetic variations cause differences in drug targets – the receptors, transporters, cell signalling pathways and other biological molecules that drugs bind to in the body to exert their therapeutic effects. This means that a given drug may be more effective in some people than in others.

Secondly, and more immediately exploitable, genetic variations exert a considerable influence on the rate and manner in which people metabolise drugs. As outlined in **Box 4.2, t**he body has evolved many different enzymes capable of breaking down a wide range of potentially harmful substances. Levels of these enzymes can vary considerably from one person to another affecting the rate at which a drug is broken down, the route by which it is metabolised, and the type (and toxicity) of the metabolites. Pharmacogenetic tests that predict individual variations in drug metabolism can potentially allow prediction of:

- the extent to which a patient will benefit from a drug (efficacy);
- whether a patient will react adversely to a drug;
- the likely toxicity of a drug to the patient in question;
- whether a patient can produce an active version of the drug[12];
- the optimum dose required to give the desired effect in a particular individual;
- the potential for interactions between different drugs (or their metabolites).

4.3 Drug Discovery and Development

Genome research will also revolutionise the way in which new drugs are discovered and developed. As illustrated in **Figure 4.1**, drug discovery and development is a long and complex process, and recent developments in human genetics and genome research may impact at every point in the chain. The first main impact will be a big increase in the number of potential 'targets' – new ways to treat or prevent disease - for drug development.

12 Some drugs are given as inactive (prodrug) forms that require enzyme action at the target site to produce an active therapeutic effect.

These targets will be derived from the identification of genes that are associated with disease. Two main approaches are being used to identify such genes: the human genome project and genetics research linking information on disease with gene sequence variations (Figure 4.1).

BOX 4.2 GENETIC VARIANCE IN DRUG METABOLISING ENZYMES

Genetic variations have been identified in the genes coding for more than 20 enzymes involved in drug metabolism. Many of these are cytochrome P450s, a family of enzymes responsible for the breakdown of most of the drugs used in modern medicine. Genetic variations in the level of these enzymes affect the way in which individual patients metabolise drugs. Some examples of the consequences of such variation are given below.

Efficacy / dose – the rate at which people metabolise drugs is one of the factors determining the dose required to achieve the desired therapeutic effect. For instance, some people carry inactivating mutations in the gene coding for cytochrome P450 CYP2C9, an enzyme that normally breaks down the anticoagulant drug warfarin. Such people metabolise this drug very slowly, and thus need lower doses than those given to people who metabolise the drug at a 'normal' rate. Other genetic variations can cause people to metabolise drugs very rapidly. For example, some individuals inherit multiple copies of the gene coding for another cytochrome P450 enzyme, CYP2D6 that metabolises (*inter alia*) the tricyclic antidepressant nortriptyline. Such individuals break down the drug so quickly that it is virtually impossible to achieve a therapeutic effect with normal doses.

Drug activation – some drugs are delivered in an inactive (prodrug) form that are then converted into the active form by enzymes in the body. An example is the drug codeine, which is converted to the analgesic form (morphine) by CYP2D6. Some people (1-6% of the population depending on ethnic origin) inherit mutations in this gene that inactivate the enzyme it codes for; such people are incapable of converting codeine to morphine and thus derive no analgesic effect from this drug.

Adverse reactions / toxicity – the rate at which a drug is metabolised is also a factor in determining whether patients suffer harmful side-effects. The enzyme produced by the CYP2D6 gene is known to metabolise more than 100 drugs, including many used to treat psychiatric and neurological disorders. Research has shown that adverse reactions to psychiatric drugs are often associated with mutations in the CYP2D6 gene that inactivate the enzyme it produces. Another example is the metabolism of the drug 6-mercaptopurine (used to treat childhood leukaemia) by the enzyme thiopurine methyltransferase (TPMT). Children who have inherited TPMT deficiency show toxic responses when treated with normal doses of the drug.

Drug-drug interactions – each cytochrome P450 enzyme usually metabolises a range of different drugs. This could cause problems if two drugs are co-administered that interact with the same enzyme. For instance, if one of the drugs binds the enzyme so tightly that it temporarily inactivates it, then the other drug may only be metabolised very slowly.

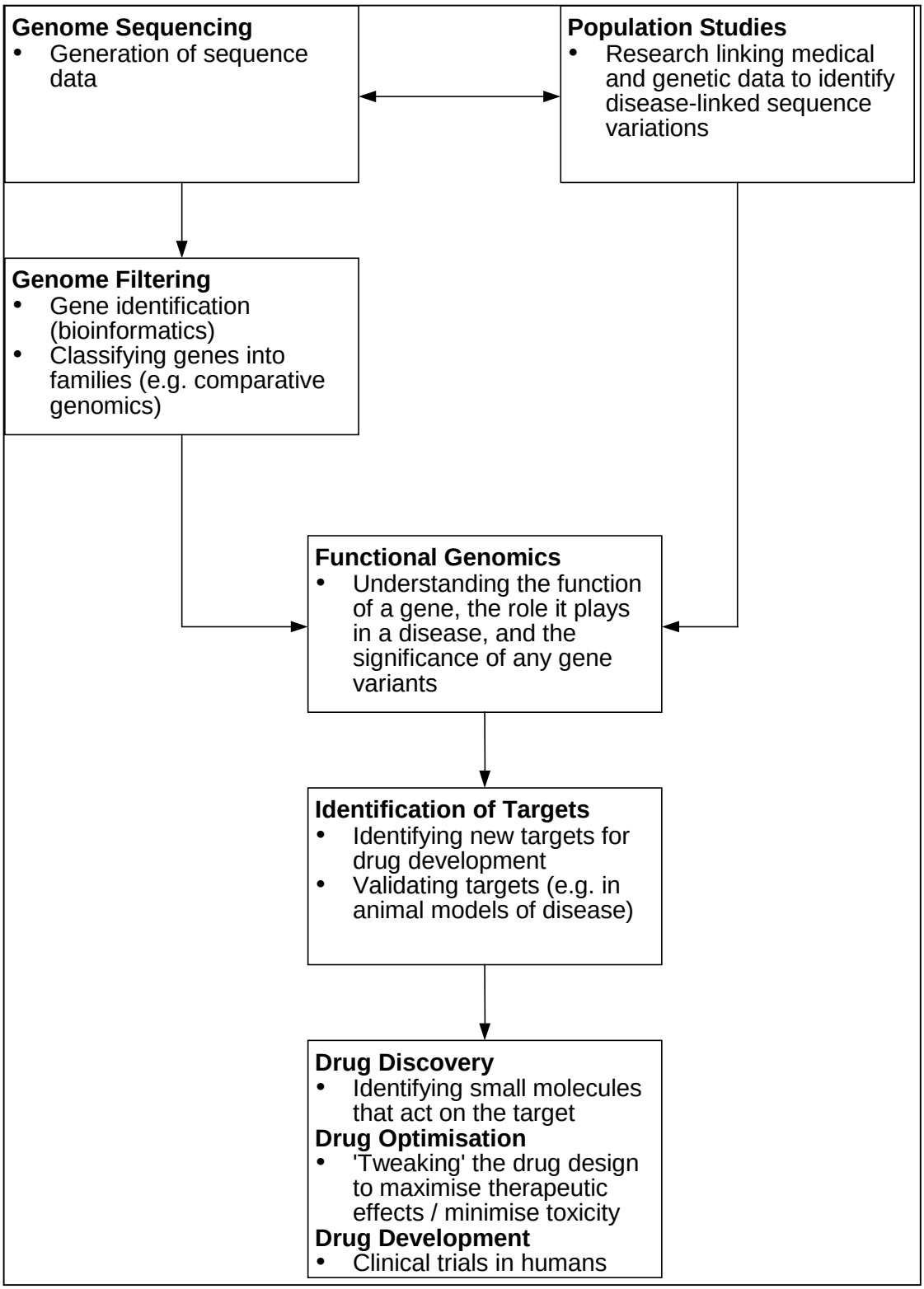
*Source: Wolf CR et al, 2000. 'Pharmacogenetics', BMJ, **320**, 987-90*

Bioinformatics is the key to turning the output from the human genome project – finished sequence data – into potentially useful information. Computers are used to search for the tell-tale nucleotide sequences that mark the beginnings or ends of genes. Once genes have been identified, other computer programmes compare their sequences with other genes of known function (e.g. from other species), and classify related genes into families. For instance, some 12,000 genes that code for proteins that are secreted outside the cell or are closely associated with cell membranes have already been identified. These are of potential interest as targets as they may be involved in cell signalling, act as cell surface receptors, etc.

The other main approach to identifying genes of potential interest is via epidemiological research on populations of people with and without disease (Figure 4.1). By comparing patterns of variations in genetic markers such as SNPs in people with a particular disease with those without that disease, researchers can identify regions of the genome that may carry genes of interest. The number of potential new targets revealed by such approaches is small, especially when compared to the tens of thousands 'churned out' by the genome

sequencing approach. But genes identified by this route have been directly linked with a specific disease and are thus more likely to help identify new targets for drug development.

FIGURE 4.1 GENETICS/GENOMIC RESEARCH AND DRUG DISCOVERY/DEVELOPMENT



Overall, a survey of pharmaceutical companies cited at a recent conference[13] suggested that 44% of targets researched within the industry will be genome-derived this year (2000) compared to only 5% in 1996. But identifying genes as being of potential pharmaceutical interest by either of the main routes above is merely the first step in the drug discovery and development process. The next step is to use functional genomics (Figure 4.1) to assess which genes are most closely related to the disease in question, and to understand the exact role of the gene product(s) in the disease process. This encompasses a variety of different approaches, including:

- Differential gene expression. Thousands of candidate genes (e.g. identified from genome sequencing) may be immobilised on microarrays and used to screen mRNAs isolated from human cells. For instance, by comparing gene expression in disease cells with that in normal cells scientists can identify the genes most closely implicated in that disease.
- Proteomics can also be used in a similar way for screening candidate genes. Comparing the protein profiles in disease and normal cells allows researchers to isolate those proteins most likely to be involved in the disease process. The amino acid sequences of these can be used to screen candidate genes for the corresponding base sequences.
- Transgenic animal models of a particular disease can be used to investigate the exact role a gene plays in the disease process. Such models are also valuable in assessing the effectiveness of potential new treatments.

Once suitable targets have been selected and validated, the aim is to find a small molecule that interacts with the target in a way that is therapeutic. For instance, if the target is an enzyme or a receptor protein the aim may be to find a small molecule that binds to it and inhibits its action. Candidate drugs may be screened for effectiveness using a range of techniques including microarrays (to check their action on gene expression) and proteomics. More often than not, researchers will try to design the new drug to mimic the shape, chemistry, etc. of the molecule (e.g. enzyme co-factor) that the target normally binds to in the cell. However, other considerations such as the rate at which potential new drugs are likely to be broken down in the body, their likely toxicity, etc., also have to be taken into account.

As noted previously, individual genetic variations mean that drug activity, metabolism and toxicity may vary from one person to another; knowledge of such variations may increasingly inform the processes of target selection, drug design and optimisation. It may also assist the evaluation of new drugs in clinical trials, by allowing the exclusion of patients whose genetic variations suggest they would not benefit from the drug. As discussed in Section 5, this has implications for the way in which clinical trials are regulated. Overall, while the advances outlined above may shorten drug discovery and development times, it will still be several years before current research yields new medicines.

13 Biotechnology: The Science and the Impact, the Hague, organised by the US Embassy in January 2000. See http://www.usemb.nl/bioconf.htm for more details.

5 ISSUES

The recent advances in human genetics in general and genome research in particular raise a large number of issues of concern to policy makers. In a recent public consultation exercise[14], the HGC identified five main areas as possible priorities:

- gene patenting;
- developments in genetic testing;
- consequences of genetic reproductive choices;
- storage and use of genetic information;
- provision of genetic services.

These and other issues are discussed in more detail in the following sections.

5.1 INTELLECTUAL PROPERTY RIGHTS (IPR) ISSUES

Disputes over IPR have been an on-going feature of the HGP since its inception. As detailed in **Box 5.1**, the US National Institutes of Health (NIH) attempted to obtain patents on several thousand partial gene sequences in the early 1990s, a move that caused considerable tension between collaborators in the publicly funded HGP. One of the main objections to these patent applications was that the sequences were derived from genes of unknown function. These tensions were eventually resolved when the NIH (and MRC, see Box 5.1) decided not to pursue the patent applications. Full and free exchange of all sequence data is now a fundamental principal of the publicly funded HGP and HUGO requires all collaborators to deposit finished sequence in publicly accessible databases within 24 hours of obtaining it.

This episode helped to forge an international consensus among genome researchers that patents were not appropriate where the only intellectual property disclosed by claimants was the DNA sequence itself. However, the emergence of large-scale, privately funded genome companies, several of which are filing large numbers of patent applications on whole or partial gene sequences (see Box 5.1) has re-awakened the debate and raised a number of issues:

- Should gene sequences be patentable at all?
- If so, under what circumstances (e.g. what information should the applicant be required to disclose, how broad should the scope of the patents be, should so-called prophetic claims be allowed, etc.)?
- Harmonisation of the different national patent systems.

5.1.1 Should Patents be Awarded on Gene Sequences?

As outlined in **Box 5.2** this has long been a bone of contention between environmental and similar groups on the one hand and the biotechnology and pharmaceutical industries on the other. However, the new European Directive on the Legal Protection of Biotechnological Inventions – which will be implemented into UK law later this year - leaves little room for doubt. It stipulates that genes or other body parts in their natural state **cannot** be patented, but inventions concerning isolated genes identical to those found in nature **can**, provided they satisfy the three general conditions laid down in patent law:

14 For details see www.hgc.gov.uk

- **novelty** – an invention must be new;
- it must also be **non-obvious** to skilled practitioners working in the area at the time;
- and it must have an **industrial application**.

In practice, USPTO and patent agencies throughout Europe have been granting patents on inventions involving human gene sequences for more than a decade. The debate has thus shifted away from the question of whether patents should be awarded on human gene sequences, towards a more detailed examination of the patenting and licensing processes.

BOX 5.1 LARGE SCALE APPLICATIONS FOR PATENTS ON GENE SEQUENCES

The first attempt to claim ownership of gene sequences on a large scale came in the early 1990s, when the NIH filed patent applications for nearly 7,000 partial gene sequences with the US Patent and Trademarks Office (USPTO)[15]. All the other collaborators within the HGP opposed these applications, although the MRC also applied for patents on some 1,100 partial gene sequences in a defensive measure designed to protect UK interests in the event of the US applications being granted. Objectors questioned whether the applications met any of the main criteria normally required for a patent to be granted.

- **Inventiveness** - they argued that the process of obtaining a partial gene sequence was not sufficiently **inventive** to reward with a patent (since it involved routine and largely automated procedures).
- **Utility** (usefulness) - here the argument centred on whether it was appropriate to patent sequences from genes of unknown function. The NIH claimed that a sequence could be used to find the gene from which it was derived. But objectors saw this as an inherent property of all DNA sequences, and suggested that the granting of a patent would require (at the very least) knowledge of the function of the gene in question.
- **Novelty** - those opposed to the NIH applications also argued that some of them lacked novelty, since they originated from DNA libraries that were in the public domain.

NIH withdrew the applications in August 1992. Following decisions in the US and UK not to pursue the applications further the fuss subsided, and a spirit of international co-operation resumed. However, the issue of patents has re-emerged in more recent years as several US companies have filed applications for patents covering large numbers of gene sequences. Such companies share their information with pharmaceutical partners or subscribers to their databases. Among the biggest players are:

- Celera –intends to publish all of its human genome sequence on the Internet, but will first seek patents on any sequences identified by its pharmaceutical partners as being medically interesting. By October 1999, Celera had made provisional applications for patents on some 6,500 gene sequences (the company had previously stated to the US congress that it expected to obtain patents on 100 to 300 gene sequences).
- Human Genome Sciences Inc. (HGS) – as of January 2000, HGS had filed patent applications describing the medical use of more than 7,400 human genes. The USPTO has so far allowed patents on 153 of these; 112 of these patents have already been issued.
- Incyte – claims that its IPR portfolio currently consists of patent applications filed on more than 1.3 million partial gene sequences (ESTs) and over 5,300 full length genes. Of these, around 250 patents on pharmaceutically important genes have already been issued. Under the terms of its agreements with its subscribers, Incyte could receive future payments and royalties on sales of products developed with Incyte technology and database information.

5.1.2 Requirements for Patents on DNA Sequences

Now that the principle of patenting human gene sequences has become widely accepted, attention has focused on the detail of the patenting process. The issues here are more technical, and hinge on nuances of the interpretation of patent and case law, particularly where the claims refer to partial gene sequences such as ESTs. Among the main questions that have still to be resolved are:

15 See POSTnote 37 (November 1992) and POST report 'Patents, Research and Technology' (March 1996) for more details.

- How much information an applicant needs to disclose in order to demonstrate that an invention is useful (has an industrial application under EU patent law, or has utility under US law);
- How broad should the scope of a patent be? Should patents be awarded that effectively grant the applicant a monopoly on all future therapeutic and diagnostic uses of a gene? To what extent should 'prophetic' claims based on predictions (e.g. where an applicant claims that a sequence isolated from one species can be used to isolate the same gene from other species) be allowed?
- How will the issue of multiple patents covering different portions of the same gene be resolved? While it is possible for different patent holders to negotiate licenses to exploit overlapping sequences, the more licenses that have to be agreed, the greater the risk that negotiations will fail.

BOX 5.2 PROS AND CONS OF ALLOWING PATENTS ON GENE SEQUENCES

Environmental and other interest groups argue against allowing patents on gene sequences on a number of grounds. These include:

- it is morally wrong to patent the components of living things;
- gene sequences are discoveries (which cannot be patented) not inventions (which can);
- the rush to patent such sequences threatens the free exchange of information and thus hinders research;
- patenting restricts the research agenda and awards an unfair monopoly to the patent holder (particularly where the patent is broad in its scope);
- patents may restrict access to new diagnostics and therapies.

Such claims are not accepted by the pharmaceutical and biotechnology industries. The main thrust of their argument is that without the protection that patents afford, companies would not be willing to invest the large sums of money required to turn genome research into potentially life-saving new diagnostics and therapies. They also suggest that the requirements for inventiveness and non-obviousness limit the scope for patenting gene sequences anyway. In other words, patent law will not allow researchers patent gene sequences found or isolated by routine means; patenting will instead be restricted to novel sequences that were isolated or cloned by means that were not obvious to skilled researchers in the area at the time.

5.1.2.1 Usefulness

Applicants for patents need to demonstrate that a gene-based invention is useful, although the exact requirements vary from one country to another. As noted previously, European patent law requires applicants to supply evidence that their invention has an 'industrial application'. Simply disclosing the sequence of a gene and knowing its function is not enough - researchers must also submit evidence demonstrating an (e.g. therapeutic or diagnostic) application for this knowledge.

US patent law is slightly different: applicants must demonstrate that an invention has utility. In the past some applicants have attempted to claim utility on the basis that a partial gene sequence can be used as a ‘probe’ to find the gene it came from. The fact that this is an inherent property of DNA means that researchers have been able to attempt to claim utility for sequences from genes of unknown function. Some private companies have applied to USPTO for patents covering large numbers of partial sequences from genes of unknown function (as detailed in Box 5.1, Incyte has applications pending on some 1.3 million ESTs). To date, USPTO has only granted patents on nucleotide sequences derived from genes of known function. For instance, it has awarded patents to Incyte covering ESTs derived from genes of known function and to HGS for applications describing medical uses of whole gene sequences (Box 5.1).

Such developments recently prompted the USPTO to release[16] revised interim utility guidelines, to assist patent examiners in determining whether an invention is useful. These revised guidelines effectively represent a tightening up of the utility requirements. Applicants must show that their invention has:

- specific utility (that is particular to the subject matter claimed) and
- substantial utility (that defines a 'real world' use) and
- credible utility (that ensures that the facts upon which an assertion is based are consistent with the logic of the underlying assertion).

5.1.2.2 Patent Scope

A related issue is that of the scope of claims allowed. Applicants for patents may seek to maximise their patent portfolio by claiming the widest possible rights for their invention. This means that claims are often framed in very broad terms – for instance claiming that the gene sequence can be used for therapeutic and / or diagnostic purposes in humans and other species. If granted, such claims effectively award the patent holder a monopoly on all possible future uses of the gene sequence in question.

An illustration of some of the issues that can arise is provided by the example of the CCR5 receptor gene, isolated by HGS in the mid 1990s. The company's research indicated that the gene product was a chemokine receptor, and thus of potential interest in inflammatory diseases such as arthritis. HGS sought a patent on the gene; this was granted in January 1999. However, in the intervening period, it became apparent that the CCR5 receptor was more significant than the company had first thought. By 1997, publicly-funded research had discovered that the CCR5 receptor was one of the co-factors that enabled HIV to infect cells of the immune system. HGS had no inkling of the gene's role in HIV / AIDS when it applied for the patent. But the patent contains a broad claim to 'medical uses of CCR5 such as therapies to block or enhance the receptor function'; HGS thus claims that its patent covers such applications of the gene. This is contested by the publicly-funded scientists who uncovered the role of CCR5 in HIV / AIDS, some of whom are seeking patents of their own. They claim that it is unfair to award ownership rights to a gene to a company that were completely unaware of its role in a disease[17].

The extent to which broad-ranging patents encourage monopolies will depend on whether the patent holder grants licenses on an exclusive or non-exclusive basis. Some have expressed fears that exclusive agreements could lead to a situation where a single organisation was granted a monopoly on "*an entire gene and its mutations for all diagnostic and therapeutic purposes*"[18]. A recent survey[19] of US patents issued for the diagnosis of human genetic disorders looked at the licensing arrangements for 27 patents between 1991-97. Of these, 14 were licensed on an exclusive basis. The authors concluded that this was largely because of practical considerations: the academic institutions that held the majority of the patents in the survey simply lacked the resources to manage more widespread (non-exclusive) licensing.

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16 USPTO Press Release #00-15, March 1, 2000 (www.uspto.gov)

17 The situation is further complicated by the fact that the original sequence patented by HGS contained a number of errors, which some claim may invalidate the patent.

18 Thomas SM *et al* , Nature **380**, 387-388 (1996)

19 Schissel A et al, Nature 402, **118** (1999)

There are also concerns that broad scope patents might inhibit research. In the case of the BRCA genes, Myriad Genetics' attitude is not to require licenses for research purposes; rather it is only concerned with commercial infringements of the patents. The survey mentioned previously also looked at whether the patent holders required a license for research activities. Of the 27 patent holders, only 6 required research licences under all circumstances. Another 6 exempted academic researchers from the requirement for licensing, 3 required research licences but demanded no royalty and 12 had no licensing requirements for research purposes at all.

5.1.2.3 At What Stage is Patenting Most Appropriate?

The issues of scope and usefulness discussed above raise the question of at what stage in the development process is it most appropriate to patent. There is near universal agreement that raw sequence data should not be patentable *per se.* This position was reiterated by the recent joint statement[20] by President Clinton and Prime Minister Blair, which stated that:
"We applaud the decision by scientists working on the Human Genome Project to release raw fundamental information about the human DNA sequence and its variants rapidly into the public domain, and we commend other scientists around the world to adopt this policy".

On the other hand, there is also a consensus that patents have a role to play at some stage in the development of gene based inventions. For instance, the joint statement also noted that:
"Intellectual property protection for gene-based inventions will also play an important role in stimulating the development of important new healthcare products".

From a commercial point of view, the 'one-off' nature of the genome project provides a powerful incentive to patent at the earliest possible stage. Companies that spend too long researching a gene's function, how the gene product fits into metabolic pathways, its role in disease processes, etc., run the risk of 'missing the boat' if another organisation applies for patents ahead of them. Companies may also be under other pressures to seek patents: an impressive intellectual property portfolio is useful for attracting investment. However, many in the public research sector feel that patents should only be granted at a much later stage in the development process, and only for highly specific applications of the gene (rather than patenting the gene *per se*). This would allow different researchers to patent different applications for the same gene. For instance, two different groups could hold different patents on applications of the CCR5 receptor gene, one covering its role in inflammatory disease, the other its role in HIV / AIDS.

In practice however, many of these issues will only be resolved in time, as a jurisprudence emerges from the application of patent law and challenges to it through the courts.

5.1.3 Harmonisation

Another patent issue affecting the EU has been the variability in patent practice between individual member states. In an attempt to harmonise practice throughout the EU the European Parliament agreed a Directive on the Legal Protection of Biotechnological Inventions in May 1998. As noted previously, this clarified what can (and cannot) be patented in biotechnology.

20 White House Press Release, March 14th 2000

However, differences between the US and EU patent systems remain. Discussions on harmonisation of international patent systems - conducted for many years under the auspices of the World Intellectual Property Organisation - have focused on two main areas:

- first to file (EU) relative to first to invent (US);
- and the length of any period of grace allowed (between publishing an invention and being able to file for a patent).

There are many other differences between the two systems, and there appears to be little prospect of significant progress being made on harmonisation in the near future. Some observers feel that the overall effect of these differences add up to it being easier for applicants to obtain patents on gene sequences in the US than in Europe.

5.1.4 The Relationship Between Publicly and Privately Funded Research

The recent emergence of privately funded companies seeking to exploit genome related data raises a number of issues relating to the relationship between such ventures and the publicly funded HGP. Some of these have their basis in the different attitudes to IPR adopted by the different approaches. On the one hand, the publicly funded HGP is intent on lodging finished sequence, SNPs, etc. in public databases to ensure its availability to researchers in the future. On the other hand, private companies are keen to stake intellectual property claims on as much genome data as possible for commercial purposes.

This difference in attitude has led to concerns that private ventures might end up claiming a disproportionately high share of intellectual property rewards for what amounts to little more than a routine activity (sequencing). Some have suggested that this could have very wide-ranging implications for future genome related research. In theory at least, a patent holder could claim intellectual property rights to any product developed using the gene sequence in question. There are also concerns that large-scale genome patenting by the private sector could inhibit academic research, particularly outside the US. The extent to which such concerns prove to be valid will only become apparent in the next few years. It will depend on a number of factors, among the most important of which are:

- the outcome of the sequencing 'race' between the public project and private ventures;
- the number and nature of patents granted by USPTO and other patent agencies;
- the attitude of patent holders (e.g. are keen to collaborate with researchers elsewhere?).

Finally, some concerns have centred on the duplication of effort involved in large-scale sequencing in both the public and private sectors. This is particularly true of Celera's attempt to obtain the entire human sequence by whole genome shotgun sequencing. However (assuming that Celera's supercomputers are able to piece the whole genome fragments back together in the correct order) one advantage is that the availability of sequences from two different approaches should aid verification.

5.2 Impact of Genome Research on the NHS

As outlined in Sections 3 and 4, there are a number of reasons for assuming that genome research will have an increasing impact on the NHS in the next few years. Key factors driving trends will be:

- The development of new genetic tests. In the first instance these will largely be new tests for SGDs. But as genome research informs a shift towards the use of genetic information in classifying and staging disease, so the demand for diagnostic, susceptibility, etc. tests (see Box 3.1) for a range of common complex disorders will rise.
- New technology - the development of 'gene chip' technology and other high throughput approaches (see Box 3.5) promises to deliver faster, cheaper, more comprehensive and accurate genetic tests.
- New treatments – although these will take longer to materialise, the identification of new drug targets will lead to the development of more effective drugs.
- Personalisation of medicine – using gene tests to target drugs at those who will benefit from them.
- Public demand – media influence could fuel (unrealistic) expectations among the general public over what the new genetics can deliver.

Such factors are likely to lead to new genetic tests and treatments for a wide range of conditions, with implications for the NHS, medical profession and policy makers alike. These implications and the issues that they raise are discussed in more detail in the following Sections.

5.2.1 Organisation of Genetic Services

5.2.1.1 Testing for Rare Disorders

One result of human genome and related research is likely to be the development of an increasing number of tests for rare SGDs. As outlined in Section 3, testing for SGDs makes up the bulk of the workload of the current NHS Regional Genetics Centres. Tests for rare disorders already pose problems for this regionally-based service (see below); any increase in the number of rare disorders which can be tested for could thus exacerbate these problems. The main problems posed by genetic testing for rare disorders within the current NHS framework have been laid out in a recent BSHG discussion paper[21]. They include:

- Discontinuity between the ending of research-funding for studies on an individual disease and the establishment of a service. The Commons Science and Technology Committee[22] noted that "*diagnosis for a rare inherited condition can be offered on one occasion since it is part of a research project, and withheld on another*".
- The total clinical demand across the UK for any individual rare disorder is less than 100 tests per year; for many such disorders, each health district might expect to encounter (on average) less than one case per year. According to the BSHG, this means "*purchasers see too little demand from their population to justify establishing a service for any one disease*".
- "*Inefficiencies and inconsistencies*" in the mechanism by which testing for rare disorders is funded.

21 'Co-ordinated Arrangements for Genetic Testing for Rare Disorders', BSHG, 1999.

22 'Human Genetics: The Science and its Consequences', House of Commons Science and Technology Committee, 1994/95.

Such problems mean that the BSHG see a "*substantial current unmet need for genetic testing for rare disorders*" within the UK. It has proposed that a comprehensive audit of current research and funding in this area be carried out and that the need for testing services be assessed. The Joint Committee on Medical Genetics is one mechanism for achieving such aims. BSHG has also proposed the establishment of a specialist UK Genetic Testing Network (UKGTN) with the aim of "*promoting efficient and comprehensive services of high quality for molecular diagnosis of rare genetic disorders*". One of the guiding principles behind the formation of such a network is that two Regional Genetics Centres should offer tests for any single rare disorder. Two is seen as the ideal number as it will maximise reliability, quality assurance and patient access on the one hand, while minimising inefficiency on the other. BSHG envisage centres submitting bids to offer testing for specific rare disorders, and sees the setting up of a mechanism to peer review these bids as a priority.

One issue to be resolved concerns the funding of any such UK network. Individual Regional Offices are responsible for commissioning specialist services (including genetic services) under new arrangements[23] published by the NHS Executive in 1998. BSHG see co-operation between regional genetics centres – possibly including some element of centralised funding to cover set-up and evaluation costs for new tests – as key features of the proposed UKGTN, and has identified a number of funding options:

- Making central funding available equivalent to the amount spent on genetic testing for rare disorders through the old funding system in its last year of operation (1998/99). This would have to be determined by audit: the estimated figure for 1996/97 was £615,000.
- Making funding available through the NHS central research and development programme for an initial period or development and evaluation.
- Supra-regional funding via top-slicing of regional budgets.
- Central funding of start-up costs followed by payment on a cost-per-case basis.

The issue of testing for rare disorders has been considered by the ACGT as part of its Consultation on Pre-Natal Genetic Testing. This Committee endorsed the overall approach of organising testing services for such conditions on a supra-regional or national level, and recommended that "*appropriate funding for such testing should be identified*"[24].

5.2.1.2 Testing for Common Disorders

Testing for genetic pre-disposition factors for common conditions such as breast and ovarian cancer, diabetes, etc. currently constitutes only a relatively small proportion of the UK clinical genetics caseload. But this is likely to change as genome research identifies increasing numbers of genetic factors involved in such diseases. This raises a number of questions over who should deliver the new tests, how best to organise testing services and the likely impact on current services.

As far as the delivery services is concerned, one question is whether the new tests should be offered within the NHS, or whether all or some could be purchased from commercial testing centres. This question has been the focus of recent debate because of the situation regarding Myriad Genetics, a US company which owns intellectual property rights on a highly specific and sensitive test for BRCA1 and 2 mutations and their use in the predisposition testing for

23 'Commissioning in the new NHS. Commissioning Services 1999-2000', NHS Circular 1998/198.
24 ACGT Report for Consultation on Prenatal Genetic Testing, ACGT/DH 2000.

breast and ovarian cancer. Its licensing agreements with US healthcare providers require all BRCA tests to be conducted in Myriad's own laboratory in Salt Lake City. The company has announced its intention to market its testing services in Europe and has recently signed an agreement with a UK company (Rosgen).

Professional bodies and patient interest groups have expressed concerns that a "US-style" licensing agreement on the provision of BRCA-testing services in the UK would effectively create a service monopoly excluding NHS laboratories. Such groups see significant advantages to developing molecular genetic testing within the existing NHS framework, to allow competition between NHS laboratories and the private sector. They argue that this is the best way of ensuring comprehensive cover and equitable access to testing services, of maintaining the UK's research strengths in this area, and of guaranteeing quality within an ethical service framework. However, this approach requires the development of a national strategy to address such issues as:

- Funding – to what extent can more comprehensive services be offered through increased public sector investment? Will the new services offer scope for greater investment through re-deployment of funds within the NHS? What mechanisms are available for encouraging investment from the private sector to the overall benefit of the public?
- Size – an assessment of what services are likely to become available and when is required to inform estimates of the likely extent of expansion in genetic testing services.
- Organisation – current services are set up on a regional basis, geared towards testing for rare disorders. While bodies such as the CMGS are keen to maintain this overall structure, an increase in testing for common disorders may eventually require the delivery of services at the primary care level[25]. A three tier approach (district, regional and national) for providing cancer services has been proposed by the DH[26]: the RCP[27] has suggested that this may form a suitable model for the provision of genetic services for other common disorders.

Such issues are being assessed by an expert working group on laboratory services for genetics, set up by the NHS Executive Board. This non-statutory body will report to the Board and the HGC by summer 2000, and has terms of reference which include:

- assessing the current extent of genetic testing within the NHS;
- identifying those tests / technologies likely to become available in the next 5-20 years and considering the potential organisational and financial implications for the NHS;
- identifying potential barriers to testing (e.g. technical, organisational, or resource constraints, education / training needs);
- developing models of service delivery for genetic tests.

5.2.2 Laboratory Quality Assurance

As with other clinical laboratories, genetic testing centres have to ensure that the services they offer conform to accepted quality standards. Such measures cover all aspects of testing – from sample handling (e.g. to ensure that no mix up of samples occurs), through the test

25 Louise A et al, 1998. "The New Genetics. Implications for Clinical Services in Britain and the US", BMJ, **316**, 767-770.

26 'Genetics and cancer services', Report of a working group for the Chief Medical Officer, DH, 1998.

27 'Commissioning clinical genetic services', Report from the Clinical Genetics Committee of the Royal College of Physicians of London, December 1998.

protocols themselves, to the interpretation (and delivery) of results. Current QA arrangements for genetic testing services in the UK have three main components:

- **Accreditation of laboratories** by Clinical Pathology Accreditation (UK) Ltd.(CPA), an independent company. This involves an initial inspection of the management structure, laboratory equipment and facilities, safety and maintenance standards, quality / consistency of documents tracking samples through the system, staff facilities and training. Continued registration depends on satisfactory audit results from an external quality assessment (see below).
- **External quality assessment** (EQA) - accredited laboratories undergo an external audit by the CPA every 12 months to ensure that they reach standards reflecting best professional practice for the tests they offer. Because of the rarity of some of the conditions tested for, such external audits may involve international co-operation.
- **Internal quality control**, - the procedures instituted by individual laboratories to prevent sample mix up, to ensure the quality of the reagents they use, the validity of test protocols, etc (laboratories are increasingly being encouraged to comply with standards such as BS EN ISO 9002). Such measures are informed by guidance on best practice published by professional bodies such as the RCP, RCPath and CMGS.

Such measures are currently voluntary, although NHS Trusts are increasingly requiring accreditation, EQA, etc. as a pre-requisite to commissioning genetic services from laboratories. A recent ACGT Report[28] endorsed this approach, stating that "*all laboratories offering genetic testing services should…be appropriately accredited…join an appropriate external quality assessment scheme…and perform adequate internal quality control*".

These arrangements should ensure that existing tests are delivered to appropriate quality standards. However, any increase in the number of new tests on the market is likely to put pressure on this system, since the tests will need to be clinically validated. Harmonisation of the different national validation and quality assurance schemes would assist the introduction of new tests: a test validated in one country could be introduced into laboratories in other countries participating in such a scheme. The proposed *In Vitro* Diagnostics Directive should bring about progress towards harmonisation within the EU (international harmonisation is being considered as a subject for an OECD workshop).

5.2.3 Counselling

One feature of the current UK genetics service is that it encourages extremely close links between the laboratories that conduct the tests, clinical genetics specialists and the clinicians that refer patients. Such links mean that genetic counselling (**Box 5.3**) from clinical geneticists and / or genetic nurse specialists is an integral part of the service. It is offered to individuals / families affected by or identified as being at increased risk of a genetic disorder, with the aim of allowing them to make fully informed choices about their future. How will the implementation of new genetic tests affect counselling in the future?

At a simplistic level, any increase in genetic testing is likely to increase the demand for genetic counselling. The development of diagnostic or predisposition tests for a range of common disorders could also lead to counselling increasingly being offered by medical practitioners who have received no specialised training, either in medical genetics or in

28 'Report on Genetic Testing for Late Onset Disorders', ACGT, July 1998.

counselling skills. This raises potential concerns over the quality of the advice offered, and over the way in which that advice may be given.

The quality of counselling offered by clinicians in general has been examined in a National Confidential Enquiry into Genetic Counselling by Non-Geneticists (CEGEN). This Enquiry was funded by the Department of Health (DH) and backed by the RCP; it audited documented evidence (from case-notes) of the information and services offered to patients and their families for five genetic disorders. CEGEN[29] found that details of the counselling and services offered by non-geneticist clinicians (mainly obstetricians) were often poorly documented, that there was confusion over responsibilities and accountability between specialities and that geneticists were sometimes not consulted even in high-risk situations. Among the main recommendations were:

- Commissioners of clinical services should require that genetic management is at least as well documented as surgical operations, drug records, etc; national standards should be set for antenatal records to include such details in future.
- Improvements in undergraduate medical and nursing education. These should include basic genetics management, awareness of the importance of family history, and details of a range of common genetic disorders and disease prevention measures. Training issues are discussed in more detail in Section 5.2.4.
- Regular audit of counselling provided by non-geneticists to monitor clinical improvements and ensure that standards are met.

BOX 5.3 GENETIC COUNSELLING

Genetic Counselling –"*A process of consultation by which information is imparted to individuals or families affected by, or at risk of a genetic disorder. It includes information on the nature of the disorder; the size and extent of genetic risks; the options, including genetic testing, that may help clarify the risks; the available preventive and therapeutic measures, and the provision of psychological, social and practical support. In the context of genetic testing it may include responding to the concern of individuals referred and their families, discussing the consequences of a test, and enabling them to choose the optimal decision for themselves, but not determining a particular course of action.*"

Because of the historical focus on rare inherited disorders, genetic counselling in the UK has mostly been offered to pregnant women or couples planning a family. It may be required both before (to allow an informed choice of whether to proceed with testing) and after (to discuss the implications of the results and how best to proceed) a genetic test. In practice, pre-test counselling may be provided by non-genetic specialists, particularly by obstetricians in antenatal clinics. Specially trained genetic counsellors (e.g. clinical geneticists, 'genetic nurses' or genetic associates) are more likely to become involved at the post-test stage, after the diagnosis of a rare genetic condition.

Sources: Definition of genetic counselling from 'Genetic Testing for Late Onset Disorders', ACGT, July 1998; 'The Future of Genetic Counselling: An International Perspective', Biesecker, BB and Marteau, TM, Nature Genetics, 22, 133-137.

Patients' decisions are not only influenced by the quality of the advice given - the manner in which it is offered is also important. A key goal of trained genetic counsellors is to deliver 'non-directive' advice: i.e. they attempt to encourage informed, autonomous decision making. Concerns have been expressed that clinicians with no training in counselling may

29 See http://www.medicine.man.ac.uk/geneticenquiry/counsell.htm

advise patients in a way that is more 'directive'[30] – for instance in a manner that encourages them to undergo testing. While there is little direct evidence from studies in the UK one way or another on this matter, research in the US suggests that advice from obstetricians is more 'directive' than that from genetic counsellors.

Another issue concerns the changing nature of the tests themselves: to what extent will counselling need to adapt to the type of tests likely to be developed in the future? Historically, genetic testing has largely been offered to women in the early stages of pregnancy or to couples planning a family; counselling has thus mainly been associated with informing difficult reproductive decisions. This is likely to change in the next few years, as tests are developed for genes that contribute to – but will not necessarily cause - common diseases. Counsellors will need to develop new areas of expertise (e.g. in risk assessment) to interpret such tests. Where people are identified as being at increased risk, counselling will also need to include specific medical or lifestyle recommendations to minimise the likelihood of a condition developing. The way in which this is done will influence the outcome: new methods of risk communication / health education may need to be developed.

The future extent and nature of counselling services is also likely to be shaped by resource considerations. For instance, a report[31] to the NHS Health and Technology Assessment Programme (HTAP) put the cost of screening for CF at ~£46,000-53,000 per CF pregnancy detected for ante-natal tests, and ~£4,400-6,400 per CF individual detected for neo-natal tests. The difference in costs is largely due to the reduced need for counselling in the case of neo-natal tests. This expense was acknowledged in the report to HTAP, which noted that "*counselling is an important component of screening but unless an appropriate level is adopted the cost will be insupportable*". One priority identified by the report was research into "*innovative methods for giving information on genetic screening*".

Such considerations are likely to lead to pressures on existing counselling services, and this could affect the quality of the services offered. The CEGEN enquiry has considered[32] the whole area of improving quality in genetic counselling services. It sees an urgent need to establish minimum national standards for each disease for which genetic tests are available, and to implement a programme of clinical audit linked to training and education programmes to ensure that such standards are met.

5.2.4 Education and Training

The recent rapid advances in medical genetics also raise a number of questions regarding training and education. With genetic testing predicted to become widely integrated into medical practice[33], such issues potentially affect a wide range of practitioners. As the CEGEN enquiry noted, "*newly qualified doctors are not well prepared to cope with medical advances*" in genetics. Among the most pressing priorities identified by patient groups such as GIG (Genetics Interest Group) and professional bodies (e.g. the Royal Colleges) are:

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30 The Future of Genetic Counselling: An International Perspective', Biesecker, BB and Marteau, TM, Nature Genetics, **22**, 133-137

31 'Screening for CF', Murray J, Cuckle H, Littlewood J, Taylor G and Hewison J, Health Technology Assessment, **3** (8), 1999.

32 'Clinical Governance and Genetic Medicine', CEGEN, Manchester.

33 Bell J, 1998. "The New Genetics in Clinical Practice", BMJ, **316**, 618-620.

- Education - initiatives to improve the teaching of medical genetics at undergraduate level and during nurses' training. Such changes should help ensure newly qualified nurses and doctors have sufficient expertise in molecular genetics to assess genetic risks and refer patients on for more specialised advice as appropriate.
- Continued training – initiatives to improve currently qualified doctors' and nurses' knowledge of medical genetics. Such initiatives may have to encompass a wide spectrum of practitioners including GPs as well as appropriate medical specialities such as obstetricians. Various approaches may be used[34], including continued education courses run by the Royal Colleges, contacts with specialist centres, special interest groups, development and use of guidelines, collaboration in research projects, etc.
- Manpower issues – a national strategy to assess future need for specialised medical geneticists, genetic counsellors and laboratory service staff, and to ensure that sufficient numbers of suitably qualified people are trained.

Assessing who to train to what level is difficult; it will be influenced by factors such as the type of tests developed, public demand for them, the extent to which companies attempt to market tests direct to the public, etc. It is likely that there will be an increase in demand for the services currently supplied by clinical geneticists, genetic counsellors and 'genetic nurses' based in regional centres. Such an increase could arise from the development of new tests for rare inherited disorders, or tests with life-altering implications, etc, and may have significant manpower and resource implications for the NHS. The Joint Committee on Medical Genetics is currently considering how manpower planning for medical genetics could be co-ordinated on a national basis.

However, not all the new tests likely to be developed will necessarily raise the 'life and death' issues commonly associated with current genetic tests. For instance, a genetic test assessing the risk of heart disease would raise issues of lifestyle changes rather than agonising decisions on reproductive matters. Such tests are more akin to 'conventional' procedures currently offered through the primary health care system such as measurement of cholesterol levels. It may thus be more appropriate to offer them through GPs or nurses, rather than calling upon the more specialised services available at regional level.

Of course, this would involve training/educating GPs and nurses in assessing genetic risk and advising patients on the implications. Guidelines for the training of genetic nurses and counsellors in the UK have been published[35] by the Association of Genetic Nurses and Counsellors; some see a need for similar training to be extended to all nurses and social work practitioners[36]. Clinical geneticists[37], the Institute for Public Policy Research (IPPR)[38] and the RCGP[39] have all called for GPs to play an increasing role in providing genetic services in the future. However, not all agree with the idea of training GPs to deliver

34 Kinmouth, AL *et al*, 1998. "The New Genetics: Implications for Clinical Services in Britain and the US" BMJ, **316**, 767-770, 1998.
35 Skirton H et al, 1998. "Recommendations for Education and Training of Genetic Nurses and Counsellors in the UK", Journal of Medical Genetics, **35**, 410-412.
36 Fears R et al, 2000. "Rational or Rationed Medicine? The Promise of Genetics for Improved Clinical Practice", BMJ, **320**, 933-935.
37 Bell J, 1998. . "The New Genetic sin Clinical Practice", BMJ, **316**, 618-620.
38 Lenaghan J, 1998. "Brave New NHS? The Impact of the New Genetics on the Health Service", IPPR.
39 RCGP, 1998. "Genetics in Primary Care. A Report from the Faculty Genetics Group", RCGP.

specialist genetic services such as counselling; a recent survey[40] identified some resistance among GPs themselves towards any such move. One of the problems identified was that of the 'therapeutic gap' – some GPs felt there was little point in raising the issue of genetic risk for common diseases with patients until therapies for these conditions had been developed. Another concern was that increased specialisation might threaten the traditional skills (e.g. a commitment towards a holistic view of medicine) associated with general practice.

5.2.5 Uptake of Products by the NHS

The impact on UK healthcare of new treatments / tests arising from genome research will ultimately depend on the extent to which they are taken up by the NHS. Recent years have seen considerable progress in establishing an evidence-based approach to interventions offered by the NHS, with the establishment of mechanisms for:

- assessing the clinical effectiveness and evaluating the cost-effectiveness of new treatments;
- formulation and dissemination of advice / guidelines on best clinical practice;
- regular audit / monitoring of clinical practice / outcomes to encourage uptake of advice by clinicians and to allow review of guidelines where appropriate.

Such activities fall within the remit of the National Institute for Clinical Excellence (NICE)[41], set up as a Special Health Authority in April 1999 to provide the NHS with guidance on current best practice. This guidance covers individual health technologies (drugs, medical devices, surgical procedures, etc.) as well as the clinical management of specific conditions. Technologies for assessment are selected by the Department of Health (DH) and the National Assembly for Wales (NAW) according to a number of criteria:

- whether it will result in significant health benefit, taken across the NHS as a whole;
- the extent to which a technology is likely to result in a significant impact on other health-related government policies (e.g. reduction in health inequalities);
- the technology's likely impact on other NHS resources (financial or other);
- an assessment of the extent to which national guidance is needed (e.g. in the absence of guidance, is there likely to be controversy over interpretation / significance of the available evidence on clinical and cost effectiveness?).

Including an assessment of cost-effectiveness in NICE's remit has proved controversial. Some within the pharmaceutical industry see this as the introduction of a fourth regulatory hurdle: in addition to demonstrating the safety, efficacy and quality of a product for marketing approval, companies may now also have to show it is cost-effective. Of course, this only applies to those products selected (according to the criteria above) for evaluation by NICE; it remains to be seen how many of the products arising from genome research will be evaluated in this way.

Others have pointed to the difficulties inherent in the economic evaluation of a health technology. Strictly speaking, a **cost-effectiveness** analysis merely expresses a technology's effectiveness in terms of amount of effect per £ of technology. Such an approach is best suited to simple like with like comparisons: for instance comparing a new drug with a drug currently in use. But the economic evaluation of new health technologies (such as those

40 Kumar S and Gantley M, 1999. "Tensions Between Policy Makers and GPs in Implementing New Genetics: Grounded Theory Interview Study", BMJ, **319**, 1410-1413.

41 www.nice.org.uk/index.htm

likely to stem from genome research), where there is no existing basis for comparison, is more difficult; it requires a wider assessment of benefits. One approach is **cost-utility** studies, where benefits are evaluated in terms of their impact on the quality and length of a patient's life. Another is a full **cost-benefit** analysis, which can include indirect benefits such as productivity gains (or the avoidance of losses) arising from a health technology. Both of these last two approaches are complex, requiring assumptions about the monetary value of life, quality of life, indirect benefits, etc.

Overall, there is no clear consensus among health economists over the most appropriate method of evaluating the 'economic performance' of a new health technology. The pharmaceutical industry is keen to ensure that such evaluations are not just confined to a narrow assessment of immediate (short-term) costs to the NHS, but also allow any broader benefits to be taken into account. These benefits may not accrue directly to the NHS, but may occur elsewhere in the system (e.g. savings in social services). Some[42] thus see a need for more research on the best way to evaluate new drugs and other interventions. Such research could inform more explicit guidance on the evidence required by NICE to conduct its evaluations.

5.3 Uses of Genetic Tests

5.3.1 Tests Supplied Direct to the Public

While the development of national standards and implementation of clinical audit should ensure the quality of tests offered through the NHS, they will not apply to tests marketed directly to the public. The Advisory Committee on Genetic Testing (ACGT – now subsumed within the HGC) drew up a Code of Practice / Guidance[43] for such tests (**Box 5.4**). It requires testing laboratories to be registered, accredited, and perform internal quality control), and companies to ensure confidentiality, provide accurate and appropriate information, allow access to counselling and encourage customers to inform their GPs of test results. It also recommends that tests should only be permitted for determining carrier status in adults (over 16) for disorders such as CF where an abnormal test result carries no direct health implications for the individual tested.

ACGT envisage a situation where companies wishing to market such tests should seek approval from the Committee prior to introducing their service. While the Code has no statutory basis, ACGT are hoping to maximise compliance by adopting a 'naming and shaming' policy. Each year it will publish a list of those testing proposals it has considered that do not comply with the Code / Guidance along with those services the Committee is aware of that have not been submitted for consideration at all. ACGT will also publish a list of those services submitted that do comply with the Code / Guidance.

42 Fears et al, "Rational or Rationed Medicine? The Promise of Genetics for Improved Clinical Practice", BMJ, **320**, 933-935

43 'Code of Practice and Guidance on Human Genetic Services Supplied Direct to the Public', DH 1997.

BOX 5.4 ACGT CODE OF PRACTICE/GUIDANCE ON TESTS DIRECT TO THE PUBLIC

The ACTG Code of Practice/Guidance has no statutory basis, although ACGT aim to encourage compliance by publishing a list of companies conforming to the requirements. It covers:

- Testing laboratories, equipment and reagents (all laboratories should register with a National Accreditation Body, accredited by the CPA, and perform adequate internal quality control).
- Confidentiality and storage of samples and records (companies should ensure confidentiality, should inform the customer of their security procedures and retain samples/data only for sufficient time to allow rechecking in cases where a test result is challenged).
- Tests that may be supplied (only appropriate to supply tests determining carrier status for inherited recessive disorders where an abnormal result carries no direct health implications for the customer).
- Who may be supplied tests (only appropriate to supply tests to people aged 16 or more).
- Customer information (information on the nature of the test, its scope, limitations and accuracy, the significance of the result, any insurance implications, and details of professional or voluntary groups that may offer support to those with abnormal test results).
- Genetic consultation (suppliers should give the customer their medical practitioner opportunities for appropriate pre- and post-test counselling).
- Involvement of GPs (test suppliers should encourage customers to provide their GP with a copy of the test result).

Source: 'Code of Practice and Guidance on Human Genetic Services Supplied Direct to the Public', ACGT, DH, 1997.

5.3.2 Screening

Advances in technology (e.g. bio-chips) coupled with developments in human genome research mean that it may soon be technically feasible to apply genetic testing to very large numbers of people. Expanding genetic testing from its current family-based context into the screening of populations raises a number of additional issues, first examined by the Nuffield Council on Bioethics in 1993[44]. In its 1998 report[45], the ACGT identified the following:

- A test may give a higher error rate when used in a screening programme than when used for individual referrals.
- Those being screened are likely to know less about the disorder, the test and its implication than individuals testing because of a family history. This increases the need for pre-test counselling and support, but the numbers involved make it less likely that these will be adequately provided.
- Those receiving an abnormal test result may have been unaware that their condition had a genetic basis. This has consequences for their relatives.
- As a general principle, screening should only be introduced where there is a potential benefit to those being screened. For instance, if there is an appropriate and effective treatment or other intervention available, or where treatment of the disorder at the earliest possible stage is beneficial.
- Screening programmes may raise a conflict between individual choice and 'public health goals' (e.g. reducing the frequency of a disorder). The aims of a screening programme should thus be made explicit from the start.

Health Ministers (and NHS Executive boards) receive advice on screening programmes from the National Screening Committee (NSC). Where potential programmes involve genetic tests, this Committee liaises closely with the ACGT. It has published a National Handbook that (*inter alia*) lays down detailed criteria for introducing and managing screening

44 'Genetic Screening: Ethical Issues', Nuffield Council on Bioethics, December 1993.
45 'Genetic Testing for Late Onset Disorders', ACGT, July 1998.

programmes. As detailed in **Box 5.5**, these cover the disorder itself, the screening test, the availability of an effective treatment or other intervention and various aspects of programme management.

BOX 5.5 THE NSC's CRITERIA FOR SCREENING PROGRAMMES

The condition

- should be an important health problem;
- its epidemiology and natural history (including development from latent to declared disease) should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage;
- all the cost-effective primary prevention interventions should have been implemented as far as practicable.

The test

- there should be a simple, safe, precise and validated screening test;
- the distribution of test values in the target population should be known and a suitable cut-off level defined and agreed;
- the test should be acceptable to the population;
- there should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

The treatment

- there should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment;
- there should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered;
- clinical management of the condition and patient outcomes should be optimised by all health care providers prior to participation in a screening programme.

The screening programme

- there should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity;
- there should be evidence that the complete programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public;
- the benefit from the programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment);
- the opportunity cost of the programme (including testing, diagnosis and treatment) should be economically balanced in relation to expenditure on medical care as a whole;
- there should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards;
- adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the programme;
- all other options for managing the condition should have been considered (e.g. improving treatment, providing other services).

Source: 'The NSC Handbook of Population Screening Programmes', DH, 1998.

It remains to be seen how many of the new genetic tests will satisfy the NSC's criteria. For instance, reliable genetic tests are available for serious (but well understood) conditions such as CF, but their use in screening programmes raises a number of more detailed considerations (see **Box 5.6**). These include the question of who to test (e.g. parents or new-borns) and when (e.g. pre-conceptual or pre-natal testing), the aims of screening, the extent to which early detection leads to long-term clinical benefits, costs, and the availability of counselling and support. The various pros and cons of CF screening outlined in Box 5.6 were considered in a report to the NHS HTAP, which recommended:

- Some form of CF carrier screening should be offered nationally in a reproductive context (i.e. in family planning and antenatal clinics).

- Neonatal screening for CF should be conducted on a routine basis, although more research is required on the psychological and medical consequences for carriers detected by this method.
- CF carrier screening for sperm donors and infertile men.

BOX 5.6 PROS AND CONS OF CF SCREENING PROGRAMMES

Who to test and when? - in general, there are two main approaches to CF screening - testing prospective parents, or testing newborn babies. Prospective parents may be tested:

- **Pre-conceptually**, so that couples who both test positive for mutations have the widest possible range of options open to them. These include 'letting nature take its course', pre-natal diagnosis (e.g. via amniocentesis or chorionic villus sampling) with the option of terminating the pregnancy, avoiding pregnancy, changing partners, artificial insemination using a donor sperm or egg, and genetic testing of (*in vitro*) fertilised eggs to select those unaffected for implantation.
- **Ante-natally**, when parents seek medical advice about a pregnancy. Carrier couples identified at this stage have fewer options open to them, but still face decisions over whether to consider pre-natal diagnosis and termination. Counselling is given to all couples in this position **before** they opt for pre-natal diagnosis since such procedures carry a risk (~1%) of foetal loss.

The main alternative to testing parents is to screen newborn babies (**neo-natal** screening). This can be achieved using genetic tests, or by other methods such as IRT tests (see Box 3.4). Some regional health authorities routinely do this at present, in order to identify babies with CF at the earliest possible stage, and thus allow treatment to start as soon as possible, although the long-term clinical benefits of early treatment have yet to be unequivocally demonstrated.

Aim of screening - pre-conceptual or ante-natal tests are aimed at increasing choice in reproductive life. However, they also have the potential to reduce the overall number of babies born with CF. They are thus opposed by 'Pro-Life' groups, which argue such tests will lead to a rise in the number of terminations (research suggests that many carrier couples who know their child will be born with CF opt for termination). Neo-natal screening avoids the issue of termination.

Cost - tests that reduce the number of babies born with CF may lower the overall costs of caring for CF sufferers (~£164,000 - £500,000 for lifetime treatment). But genetic tests are expensive, with ante-natal screening costing ~£46-53,000 per CF pregnancy detected. Neo-natal screening is cheaper (~£4,400-£6,400 per CF individual detected) largely because of the reduced need for counselling. This approach may offer benefits in terms of earlier treatment, but has little effect in reducing NHS costs for caring for CF sufferers.

These recommendations are currently being considered by the NSC, which will have to decide whether CF screening meets the criteria laid out in Box 5.5. Despite the fact that a wide range of pilot studies on CF screening have been published, there is scope for debate over the extent to which early detection and treatment of CF leads to long-term clinical benefits, and thus also over whether CF screening will reduce mortality or morbidity.

5.3.3 Genetic 'Risk Factors'

The development of new genetic tests for common diseases will pose new challenges for the interpretation of test results. For many of the diseases of most significance to the NHS (e.g. see Box 3.6), genetics is just one of the factors involved: lifestyle / environmental factors play at least as important a role in determining whether a disease develops. In such cases, an abnormal test result does not automatically mean that a person will develop the disorder in question; it merely indicates that they are at increased risk of doing so. Interpreting the results of genetic tests for such diseases will require an assessment of the extent of this increased risk. This will have to be based on extensive epidemiological and molecular research. Medical practitioners will need to know how widely a particular genetic 'risk

factor' is distributed through the population, how it interacts with the relevant environmental / lifestyle factors, how often this leads to the development of disease, etc.

It is very much in the nature of genome research that the technical developments leading to the marketing of new genetic tests outpace the research needed to interpret the results of these tests. For instance, tests for mutations in the BRCA1 and 2 genes (Box 3.6) were widely available in the US *before* the results they yielded could be accurately interpreted. Extensive further research was needed to collect the epidemiological and molecular data necessary to allow interpretation of BRCA test results and to inform treatment / prevention strategies. Such research suggests that the tests are inappropriate for use as a general screening tool, but are of value to those (minority of) cases in women with a family history of the disease.

Interpreting test results for other diseases with a genetic component is likely to be equally as complex. For instance, the apolipoprotein E (ApoE) gene is implicated in late-onset Alzheimer's disease (AD). Two forms of the gene have been identified: ApoE 4, which is linked to increased likelihood of developing AD, and ApoE 2, which is thought to protect against the onset of AD (see Box 3.6). But other genes are also thought to be involved, along with (as yet unidentified) environmental / lifestyle factors. Thus, while genetic tests for the ApoE variants have been developed, the lack of information on the role of other genetic and environmental factors means that they are currently of low predictive value. This, coupled with the fact that no positive intervention is available to those identified as being at increased risk, means that ApoE tests are generally not conducted in the UK.

Such examples illustrate the need for new tests to be scrutinised by bodies such as the NSC to ensure that they are not introduced before the data needed to interpret them is available. Patient interest groups such as GIG and the Continuing Care Conference see research into the interactions between genetic and lifestyle risk factors for common diseases as a major priority.

5.3.4 Pre-natal Diagnosis (PND)

One of the more controversial applications for genetic tests is for pre-natal diagnosis (PND), since women opting for tests at this stage potentially face difficult decisions about terminating their pregnancy. Any increase in the range of genetic tests available in the future could increase the number of PND tests offered; this might lead to an overall rise in the number of terminations performed. Such a rise is not inevitable. The overwhelming majority of terminations are not connected with PND; they are elective terminations of healthy pregnancies. The overall effect of PND on termination rates will depend both on the proportion of women accepting the offer of PND, and on the proportion of those with abnormal test results opting for termination.

Evidence from CEGEN suggests that uptake in both cases is high. For instance, 80% of women with a previously affected child offered PND for CF accepted the offer: 96% of those with abnormal test results opted for termination. Fewer (76%) of the cohort at higher risk of giving birth to a Down's baby accepted the offer of PND, but the proportion of those with abnormal test results opting for termination was still high (91%). Such figures emphasise the importance of ensuring that testing in the context of PND is offered in an appropriate manner.

BOX 5.7 ACGT RECOMMENDATIONS ON PND

Undertaking testing

- At each pregnancy, bearing in mind advances in technology and knowledge, women should be offered information on prenatal genetic tests appropriate to their individual risk factors.
- All women capable of giving consent can accept or refuse any or all of the tests offered.
- In all cases of prenatal genetic testing of a woman capable of giving consent, specific consent - verbal and recorded or written - should always be obtained. Consent should be obtained for each procedure and each test.
- Consent should be freely given, without pressure from third parties.
- Where a woman is permanently incapable of giving consent (e.g. because of a learning disability) the testing decision will be made by the doctor responsible for her clinical care. Doctors will be guided by the best interests of the woman and where appropriate take into account the views of the family or other close carers. If the incapacity is temporary, genetic testing should be delayed until consent is possible unless it is essential in the individual's therapy and/or in their best interests.
- Appropriate support in preparation for and subsequent to genetic testing should be part of the prenatal genetic testing process.
- Full information should be supplied to the woman in an appropriate form giving details of the tests. The information should enable the woman to understand the nature of the test, its scope and limitations, and the accuracy, significance and use of the result, and, where appropriate, its possible implications for family members. Information should also be provided on appropriate professional and voluntary bodies able to offer support, as they may be able to provide advice about information materials.

Outcome of testing

- Pre-test genetic counselling and post-test consultation opportunities should be provided to women, and if appropriate to their partners, by suitably qualified and experienced professionals.
- The general medical practitioner or other professionals who continue the care of the woman and, where appropriate, her family should be provided with appropriate information pre and post test.
- Where diagnosis is unknown or uncertain, facilities should be available for further assessment by a paediatric/foetal pathologist and/or clinical geneticist to allow parents access to accurate information.
- There should be good communication between referring units and more specialised Foetal Medicine centres about the ongoing pregnancy of women who have prenatal genetic testing as appropriate.
- If a termination of pregnancy is to be considered in the light of test results, access to a unit with appropriate medical and counselling services should be arranged. There should be close liaison between the diagnostic team and staff at the unit where the termination is carried out. Adequate support and care during and after termination should be available for the parents.

Service standards

- All laboratories undertaking prenatal genetic testing should be appropriately staffed and equipped, and be registered with a National Accreditation Body and conform to the requirements of BS 5750 (IS09002). Continued registration is dependent on satisfactory audits performed every six months by the Accreditation Body. All laboratories should also be accredited by the Clinical Pathology Accreditation (UK) Ltd (CPA), perform adequate internal quality control, undertake regular audit to identify areas where improvements in practice are possible and participate in relevant external quality assessment schemes.
- All equipment, reagents and procedures used in testing laboratories should reflect current best practice and provide assured levels of accuracy and reliability as a prerequisite of good practice.
- Staff involved in PND in regional genetic and foetal medicine centres should ensure their continued professional development. Clinicians should be able to demonstrate regular audit of their services.

Research

- Research should only be performed when approved by an appropriate Research Ethics Committee.
- Prenatal genetic tests undertaken for research purposes should only take place after the individuals participating have given their consent. Such consent should be recorded.
- All test results obtained through research are confidential and should not be given to anyone without the consent of the participant.
- Women taking part in genetic research should be fully aware of the use of their sample. No further tests should be undertaken on identifiable samples without explicit explanation to, and consent from, the woman.
- It should be made clear to women that in some cases a test that is available on a research basis to individuals is not suitable or available for prenatal testing.

Source: 'Report for Consultation on Prenatal Genetic Testing', ACGT/DH, February 2000.

The issues surrounding PND have been examined in a recent consultation report from the ACGT. This considered all aspects of PND including issues such as service organisation, consent, access to testing services, counselling and service standards. The main recommendations (outlined in **Box 5.7**) emphasise the importance of obtaining fully informed consent and providing access to pre-test counselling and post-test consultation.

As far as access to tests are concerned, the ACGT consultation report[46] noted that most women access PND services through one of three routes: via initial referral from their GP or primary care team; through a genetics or foetal medicine department that are already familiar with the woman or her family history; or through a referral from the obstetrician in the ante-natal clinic. The report recommended that:

- genetic and foetal medicine services should be available to enable local access to those who need them;
- sufficient resources should be made available in primary care and hospitals for referrals, testing and counselling;
- there is need for good communication between referring units and specialised foetal medicine centres;
- where a woman elects for termination on the basis of test results, there is a need for close liaison between the diagnostic team and the unit where the termination is conducted.

Another closely related concern is that new genetic tests offered in the context of PND might have 'eugenic overtones'. This would certainly be the case if such tests were offered in national screening programmes as part of a public health strategy. But there is a general consensus against any such use; it is a fundamental principle of PND that it is only offered to selected individuals identified as being at higher risk of passing on an inherited disorder to their offspring. Of course, the more widespread use of genetic counselling and PND among targeted individuals can lead to effects that are detectable at the population level, although few would consider this to be 'eugenic' in nature.

5.3.5 Pre-implantation Genetic Diagnosis (PGD)

Concerns have also been expressed over the use of genetic tests to select embryos prior to implantation during *in-vitro* fertilisation (IVF). As outlined in **Box 5.8**, such tests are currently licensed by the Human Fertilisation and Embryology Authority (HFEA) to detect severe or life-threatening disorders in a limited number of UK clinics. To date, these have included detection of sex-linked disorders such as Duchenne Muscular Dystrophy (where the risk can be avoided by selecting female embryos), single gene disorders such as CF and age-related chromosome disorders.

PGD is regulated by the HFEA under the Human Fertilisation and Embryology Act 1990. This Act allows certain types of embryo research and prohibits others, charging the HFEA with responsibility for formulating guidance in this area. HFEA recently engaged in a joint consultation exercise with the ACGT to review PGD and its regulation. This was deemed necessary for a number of reasons:

- the growth in the number of genetic tests available;
- increasing public awareness of human genetics and genetic testing;
- the potential for the demand for PGD to increase.

46 ACGT Report for Consulation on Prenatal Genetic Testing, ACGT/DH 2000

A joint HFEA/ACGT consultation document[47] poses a number of questions for consideration. In addition to questions about the general regulatory approach, quality assurance of the tests, etc., these cover the following issues:

- **Access to PGD**. PGD is currently limited to people at risk of having a child with a serious genetic/chromosomal disorder. In future, other groups may want access to PGD. For instance, IVF patients with no known genetic risk may ask for PGD to check that the embryos chosen are normal/viable. Or the wider public might even seek PGD/IVF (despite the fact that IVF itself is a physically and mentally demanding process with no guarantee of success) in an attempt to ensure a healthy child is born. The consultation document thus seeks views on who should have access to PGD in the future.
- **Seriousness of disorder**. PGD is currently confined to testing for severe or life-threatening conditions. In practice, individual clinics follow guidance on termination of pregnancy for foetal abnormality from the RCOG. This limits such procedures to cases where there is a precise diagnosis and a '*substantial risk*' of '*serious handicap*'. For regulating future uses of PGD, HFEA has to choose between producing (and continually updating) a list of conditions for which PGD is permitted. Or providing more general guidance for clinicians to use when discussing whether PGD is appropriate with individual patients. The provision of general guidance (rather than compiling a list) is HFEA/ACGT's preferred option; the consultation invites views on the appropriateness of this approach and the scope of the aspects it should cover.

BOX 5.8 PREIMPLANTATION GENETIC DIAGNOSIS (PGD)

PGD is a two stage technique. First, *in vitro* fertilisation (IVF) is used to create embryos outside the human body. Second, these are tested for a particular genetic disorder, or to establish the embryo's gender (if the disorder is sex-linked). This second stage involves taking one or two cells from the embryo (biopsy) 2-3 days after fertilisation (when the embryo itself consists of only 6-10 cells in total); removal of cells at this stage does not appear to affect embryo development but long-term monitoring continues. Genetic diagnosis of the biopsy cells may involve techniques such as hybridisation with fluorescent probes (to detect chromosomal disorders) or PCR (to amplify the DNA for tests for specific mutations, repeats, etc.). Embryos with the desired genetic characteristics may be selected and placed into the uterus. The overall live birth rate per treatment cycle of IVF in the UK is around 17%; HFEA consider that the live birth rate for PGD is likely to be a little lower than this.

To date, PGD has been used to test for a number of genetic disorders including:

- sex-linked disorders such as Duchenne's muscular dystrophy and Lesch Nyhan syndrome;
- single gene (recessive) disorders such as cystic fibrosis, Tay Sachs disease and Rhesus D blood typing;
- other (dominant) genetic disorders such as polypsis coli (an inherited form of colon cancer) and Marfans syndrome.
- chromosomal disorders such as Down's syndrome.

PGD is licensed by the HFEA under the Human Fertilisation and Embryology Act 1990. Four centres in the UK are currently licensed to carry out PGD; one centre is licensed for the biopsy part of the procedure alone. HFEA has drawn up training and assessment criteria for individuals carrying out embryo biopsy; each must be individually licensed and assessed. PGD clinics are inspected annually by the HFEA, and the licence stipulated which tests for which disorders the clinic is approved to conduct. Clinics wishing to conduct new tests must first seek approval from the HFEA.

Source: 'Consultation Document on Preimplantation Genetic Diagnosis', HFEA/ACGT, 2000.

- **Replacing carrier or affected embryos**. PGD can identify embryos that are carriers of (recessive) genetic disorders such as CF. Use of such embryos in IVF can only give rise

47 'Consultation Document on Preimplantation Genetic Diagnosis', HFEA/ACGT, 2000.

to healthy children who are unaffected by the disease despite their carrier status. However, there is a risk that future generations produced by these individuals may be affected by the disorder. The consultation paper canvasses views on the general issue of replacing carrier errors. There are also some exceptional circumstances where couples might request that embryos that have been identified as being affected by a genetic disorder through PGD be used in IVF. The consultation paper cites as an example a congenitally deaf couple wanting a deaf child (because they feel that a child with normal hearing would be alienated from their environment). It seeks views on the ethics of deliberately initiating a pregnancy knowing that any child born will have a genetic disorder, and how this meshes with the clinician's legal responsibility to consider the welfare of a child prior to PGD.

- **Late onset disorders**. Such disorders vary considerably over the age of onset (e.g. Lesch-Nyhan syndrome manifests itself in infancy, Huntington's disease usually not until after 30 years) and the seriousness of the condition. Because of this variation, HFEA / ACGT suggest that the fact that a disorder is late onset should not be an '*overriding*' factor in deciding whether PGD tests (where available) should be offered, merely one of a number of considerations. The consultation paper canvasses opinions on the appropriateness of this approach.
- **Predisposition testing**. In predisposition testing, detecting a gene merely indicates that there is a chance of a condition developing; certain genes are likely to be more predictive of a serious disorder than others. The consultation thus seeks views on whether guidance should distinguish between "*PGD for genes that are highly predictive for a serious disorder and those where the genetic component is more complex*".
- **Testing for more than one disorder**. As discussed previously, technology may soon allow simultaneous testing for many different genetic disorders. HFEA / ACGT noted that it would be of '*doubtful value*' to test embryos for conditions where there was no evidence of increased risk. Multiple testing might also be seen as being contrary to the spirit of the Human Fertilisation and Embryology Act, which was designed to ensure that "*human embryos are not used frivolously or unnecessarily*". In view of these considerations, the consultation asks whether there "*should be any restrictions on the number and range of tests to be carried out*" in PGD where there is no clear indication of increased genetic risk.
- **Regulation**. HFEA licences clinics to perform PGD, and is introducing a licensing scheme (covering training and assessment criteria) for individuals who carry out the embryo biopsy part of the procedure. At present, clinics must seek approval from the HFEA for each new test they plan to introduce, although this may not prove to be feasible if the number of tests available increases significantly in the future. HFEA / ACGT are thus seeking views on whether clinics should be licensed "*for PGD in general or in relation to each specific test and condition*".

Advances in genome research may lead to an increasing number of 'desirable' genetic traits being identified. This has led to concerns over the possibility of producing 'designer babies' where embryos are selected on the basis of traits linked to (say) intellectual or musical ability, athletic prowess, etc. In practice however, such considerations are unlikely to be a major concern for public policy in the immediate future. For a start, the 'desirable' characteristics supposedly sought after by parents are highly complex in nature, most likely involving multiple genes and significant contributions from environmental factors. They will thus be difficult to test for, and the tests may not be highly predictive. In addition, the

HFEA has already made it clear that it will only licence PGD for testing for serious inherited disorders. In this context, following a public consultation in 1993[48], HFEA rejected the use of PGD for sex selection for 'social reasons'.

5.3.6 Genetic Information - Ethical/Legal/Social Issues

Although nobody can predict the rate at which it will happen, it is widely agreed that the future will see more people taking more genetic tests for a wider range of diseases. Such developments will raise a number of ethical, legal and social issues. Some of these relate to whether or not third parties such as insurers or employers should have access to the results of genetic tests. And if so, under what circumstances and for what purposes? As summarised in Box **5.9**, genetic testing is not directly regulated under UK law, although related aspects such as the confidentiality of medical information, protection against discrimination, health and safety at work, etc., are subject to legislation. Other general ethical and social questions raised by genetic testing are dealt with in Section 5.3.6.4.

BOX 5.9 LEGISLATION RELEVANT TO GENETIC INFORMATION

Regulation of genetic testing in the UK is largely via non-statutory bodies that advise Ministers on policy (see Box 3.3). However, various aspects of testing – confidentiality, discrimination, and health and safety – are covered by relevant UK legislation; these are outlined below.

Confidentiality of personal information (including genetic information) is protected under common law. Two additional laws give individuals rights of access and control of medical information. They are:

- Access to Medical Reports Act 1988 – covers reports made for employment or insurance purposes by a subject's own doctor. It requires a subject to give permission for the report to be made, and grants him or her the right to see the report before it is forwarded.
- Data Protection Act 1998 – lays down conditions which must be met before personal data can be processed (a term that covers collection, analysis, storage and destruction). Individuals must consent to the data being collected, be made aware of the purposes for which it will be used and of any disclosure to third parties. The Act also requires that the data is adequate (but not excessive), relevant, and accurate; it may not be kept longer than necessary and must be regularly updated.

Discrimination – a number of UK laws protecting individuals against discrimination might be relevant to genetic testing under certain circumstances. For instance:

- Employers requiring people to take tests for conditions that are found predominantly in one gender (e.g. haemophilia) or ethnic group (e.g. thalassaemia) may find themselves in breach of the Sex Discrimination Act 1975 or the Race Relations Act 1976 respectively.
- Employment Rights Act 1996 – protects those with 12 months continuous service with an employer against being unfairly dismissed through their refusal to take a genetic test (unless an issue of public safety is involved).
- Disability Discrimination Act 1995 – offers some protection against discrimination (in the workplace, for provision of services, etc.) to people with genetic disorders. The definition of 'disability' in the Act only covers those with a current disability who take a genetic test for reasons connected to that disability: it does not cover predisposition to a future disability.

Health and Safety – the Health and Safety at Work Act 1974 obliges employers to ensure (as far as reasonably practicable) the health of employees in the workplace. Health surveillance – including genetic testing – may be used to detect early ill health effects; where detected the ethos of the Act is to remove the risk from the worker rather than *vice versa*.

Source: *Compiled from 'The Implications of Genetic Testing for Employment'*, HGAC, June 1999.

5.3.6.1 Genetic Testing and Insurance

A 1995 report from the Hose of Commons Science and Technology Committee was among the first to highlight issues concerning genetic testing and (particularly life) insurance. Since

48 'HFEA Public Consultation on Sex Selection' HFEA, January 1993.

then, the area has been scrutinised by the Human Genetics Advisory Commission (HGAC), the Continuing Care Conference (CCC), Genetics Interest Group (GIG), the Association of British Insurers (ABI) as well as by a number of other bodies. Such groups have identified a number of insurance-related issues relevant to any increase in genetic testing among the population. These include:

- The pace of change. How soon might we see widespread genetic testing?
- Disclosure. Under what circumstances should insurers be able to require applicants to disclose genetic test results?
- What are the likely implications of genetic testing for the insurance industry?
- What are the likely implications for those seeking various different types of insurance?
- What safeguards are needed to arbitrate in disputes, to ensure that tests are validated, to maintain confidentiality, etc.?

As far as the pace of change is concerned, there is a consensus that the widespread application of powerful predictive tests for common diseases is unlikely to happen in the immediate short-term. As HGAC has noted, very little is known about the interactions between different genes, or between genes and environmental/lifestyle factors for the majority of common diseases. The Commission felt that a considerable amount of detailed research would be needed to provide the information necessary to interpret genetic tests. It thus concluded "*it is unlikely that actuarially important genetic predictions of common causes of adult death will be available and validated, for some time to come*"[49].

Recent years have seen considerable progress made on the issue of disclosure, with the publication of the ABI Code of Practice and Guidelines on Genetic Testing in December 1997 (see **Box 5.10**). This established two basic principles:

- insurers cannot require applicants to undergo a genetic test to obtain insurance;
- but may require disclosure of existing test results under certain circumstances.

Specifically, insurers can only require disclosure where a genetic test shows an increase risk, and where the test has been 'validated'. This process requires (see Box 5.10) showing a test to be reliable and relevant to the insurance product in question; the Genetics and Insurance Committee (GAIC) are responsible for test validation. It has already made it clear that the same test can have different relevance for different types of insurance. Thus a test that reliably predicts a long period of illness with normal life expectancy would be more relevant to long-term care insurance than to life insurance. The CCC thus recommended GAIC to "*make multiple assessments of each test, classifying them…for each class of insurance product*".

GAIC has published[50] an application form with accompanying notes for use by the insurance industry to seek approval to use genetic test results for insurance risk assessment. These set out the criteria GAIC will use to evaluate specific genetic tests; the Committee is currently reviewing consultation comments from relevant stakeholders (affected individuals, patients' associations, medical practitioners, geneticists, genetic counsellors, academics, insurers, actuaries, and the general public).

49 'The Implications of Genetic Testing for Employment', HGAC, June 1999.
50 http://www.doh.gov.uk/genetics/gaiccons.htm

BOX 5.10 THE ABI's GENETIC TESTING CODE OF PRACTICE

The Association of British Insurers' (ABI) Genetic Testing Code of Practice was published in December 1997, and took effect from 1st January 1998. It is followed by all ABI members (the ABI represents ~95% of UK insurance business) and applies to all relevant types of insurance (including life, permanent health, critical illness, long term care, and private medical insurance). In essence, the Code:

- Prohibits insurers from requiring applicants to undergo a genetic test to obtain insurance;
- Reserves the right to require applicants to disclose results of genetic tests they have already taken, but only under certain circumstances (see below).

Disclosure of existing genetic test results does not apply to applications for life assurance up to £100,000 which are directly linked to a new mortgage for a house to be occupied by the applicant. Where applicants do disclose existing genetic test results, the Code specifies that:

- underwriters must consult a medical practitioner (normally the insurance company's Chief Medical Officer) before reaching a decision;
- insurers may only take account of the result where the reliability and relevance of the test to the insurance product has been established;
- insurers may only increase premiums where validated and relevant test results indicate an increased risk (an increase in risk will not necessarily justify an increase in premium);
- insurers must not offer individuals lower than standard premiums on the basis of their test results.
- insurers must provide written reasons (on request) for any increase in premium or rejection of an application (this is normally given direct to the applicant's medical adviser, as agreed with the British Medical Association in order to maintain the doctor/patient relationship).

The Code also requires insurance companies to monitor their staff's compliance with the Code and to report in detail to the ABI on annual basis (this compliance report is a condition for continued certification). Each company must also have a confidentiality policy in place governing the security, handling and storage of medical and other sensitive information (based on detailed ABI guidelines). ABI will conduct a full review of the Code each year to ensure that it keeps abreast of developments in this fast-moving area.

Source: 'Genetic Testing Code of Practice', December 1997, ABI, London.

GAIC endorses the ABI Code of Practice, which states that "*applicants must not be asked to undergo a genetic test in order to obtain insurance*". The Committee thus anticipates that "*applications for its consideration will relate only to predictive genetic tests, which have been initiated before the proposal for insurance is made*". In order to assess a genetic test for such purposes, the draft GAIC application form requires insurance companies to submit details of the specified medical condition(s) for which the results of tests may indicate a change in susceptibility. It also seeks details of the genetic test(s) for which approval is sought and the type of insurance (e.g. life insurance, critical illness cover, income protection, long term care, medical expenses, etc.). The application form requires companies to:

- Provide peer-reviewed evidence of the clinical impact of the medical condition(s) to which the application relates.
- Submit details of other conditions that the test may also be relevant to.
- Describe the natural history of the condition, including factors which influence its expected clinical course, associated illness and life expectancy.
- Describe the genetic basis of the condition, including details on the strength of the relationship between a gene and a disorder, and the significance of any genetic variants.
- Provide details of the testing method(s) available for detection, and how the interpretation of the result of the test are influenced by the genetic findings in affected family members.
- Provide details of any inherent weakness or technical imperfections in the genetic test or in its interpretation.
- Provide evidence to justify the actuarial relevance of the test and/or in it's interpretation to the type of insurance covered by the application.

- Describe any factors that influence the extent of the additional mortality / morbidity risk conferred by particular results of the genetic test(s) to which the application relates.
- Describe the provisions that will be made to ensure that underwriters and other insurance practitioners who will interpret results of the genetic test(s) covered by this application are sufficiently knowledgeable to do so.

HGAC[51] has already noted that the "*industry generally does not have the information…needed to make actuarially sound use of genetic test results*"; gathering this will require epidemiological / medical research to establish "*what health and life-span estimates can be inferred from a given genetic test result*". It concluded that companies would need to show a "*quantifiable association between a given pattern of test results and events actuarially relevant for a specific insurance product*" before they could require disclosure of test results.

One of the reasons given by the insurance industry for reserving the right to require disclosure of genetic test results is the danger of 'adverse selection'. This can occur if more 'high risk' people buy insurance, thus upsetting the distribution of risk among the pool of all those insured. It can lead to a 'vicious circle' of rising insurance costs which in turn deters 'low risk' people from seeking insurance. The industry draws a parallel between non-disclosure of genetic tests and the situation concerning HIV / AIDS testing in the 1980s. It claims that it suffered adverse selection at this time because people who knew they were HIV positive bought insurance they would not normally have taken out, without disclosing their HIV status or paying higher premiums.

Assessing the extent to which non-disclosure of genetic test results might lead to adverse selection is difficult. HGAC cited estimates[52] suggesting life insurance companies would face additional costs of around 10% if they refrained from using such results in underwriting. The recent CCC Report[53] cites a similar figure (slightly higher than 10% for males, slightly lower for females) for increases in long-term care costs relating to genetic predisposition to Alzheimer's disease. It suggests that 10% additional risk represents the boundary at which extra underwriting terms are considered for long-term care insurance; insurers thus "*now need to consider whether this degree of 'extra risk' can be absorbed into the standard underwriting pool*".

Not all agree with this 10% figure. For instance, HGAC noted that some actuarial models used by insurance medical officers produced much higher additional costs. However, it concluded "*the life insurance industry could currently withstand limited adverse selection that might occur as a result of non-disclosure of genetic test results for life insurance*". Of course, this could change if (genetic) predisposition tests for common diseases became more widely available. This was acknowledged by the CCC, which recommended that (in addition to GAIC approval of the tests) long-term care insurers should only seek to rate applicants for risk of genetically complex disease if they could show that "*consumer-driven 'right to know' testing has become sufficiently common…for serious adverse selection to take place*".

51 The Implications of Genetic Testing for Employment', HGAC, June 1999

52 Macdonald AS, 1997. 'How will Improved Forecasts of Individual Lifetimes Affect Underwriting?', Philosophical Transactions of the Royal Society **352**, 1067-1075.

53 Genetic Tests and Future Need for Long-term Care in the UK, July 1999, CCC.

As far as those seeking insurance are concerned, one of the main fears is discrimination – i.e. the possible use of genetic test results to set unfair or unreasonable premiums. HGAC heard "*compelling anecdotal evidence*" that insurers currently set unreasonable premiums on the basis of genetic test results, but found "*no hard evidence that this was systematic*". It concluded "*there was a strong and persistent sense of unease among those who had provided genetic test results to insurers about the way that this had been interpreted…we therefore could not set aside perceptions of unacceptable discrimination as groundless*".

Perception of discrimination – irrespective of whether it is justified or not - is important for two reasons. Firstly, because it might dissuade those at risk of a treatable disorder from taking a genetic test. And secondly, because it might encourage people to seek 'over the counter' genetic tests if and when they become available. The main concern here is that people taking such tests might be reluctant to share the result with their GP, on the grounds that the GP might be obliged to disclose it to the insurance company's medical officer.

Overall however, HGAC found little evidence to suggest that discrimination was widespread. It noted that around 95% of applicants for life insurance in the UK are granted cover at standard rates. Around 4% are offered cover at higher premiums (at anything up to 2-3 times standard rates), and ~1% are refused cover. Insurers suggest that the competitive nature of the insurance market protects against discrimination: individuals who feel they have been unfairly or unreasonably dealt with can always seek terms from another company. Against this, GIG and other interest groups point out that consumers often find it difficult to assess the fairness / reasonableness of the terms offered, and that the complexity and diversity of different insurance products makes direct comparisons difficult. Many groups thus see an urgent need for the setting up of an independent appeals mechanism to improve public confidence in the insurance industry's handling of genetic tests. To this end, HGAC recommended "*the industry should consult with the Insurance Ombudsman and Consumer Protection Groups…to develop a robust independent appeals procedure*". Any such body should also seek to define an "*appropriate interpretation of normal sums assured for different types of product*".

Finally, because of the sensitive nature of genetic tests, patient interest and other groups have stressed the importance of arrangements to ensure the confidentiality of the results. One of the main concerns here is the possibility that disclosure of a genetic test result by one member of a family might allow an insurer to infer that another member of the same family is at increased risk. HGAC reviewed existing confidentiality arrangements and concluded that they were "*generally satisfied*" that the 'fire-walls' between records on different family members prevented linkages being made. However, it recommended that the Data Protection Registrar "*keeps under review the ways in which insurers collect and handle genetic test results*" in view of the industry's need to conduct long-term research into the actuarial significance of genetic tests.

5.3.6.2 Genetic Testing and Employment

Another area where newly developed genetic tests might find application is for use for employment purposes. From an employer's point of view, genetic test results might provide useful information in a number of areas. They might reveal whether a (current or prospective) employee:

- suffered from (or was predisposed to) a condition that might lead to prolonged sick-leave;
- suffered from (or was predisposed to) a condition that might place the individual themselves, or other employees, at risk in the workplace;
- was particularly sensitive to a specific feature of a work environment.

There is little evidence that genetic test results are currently being used by UK employers for any of these purposes. Indeed, in a recent report[54] HGAC identified only one such example: the Ministry of Defence (MoD) currently screens all applicants for air-crew training for sickle cell disease / carrier status. MoD regards those individuals with this disorder or carrying the trait as a potential risk to themselves and others because the low oxygen pressures encountered in flight may provoke a sickling crisis.

There is however evidence that an increasing number of UK employers are assessing the health of their existing or prospective employees. For instance, HGAC cited a Health and Safety Executive survey of 1,600 UK employer; it found that around 1 in 3 carry out pre-employment health assessments. At this stage, such assessments are usually designed to weed out unsuitable applicants or to limit an employer's liability (e.g. detecting pre-existing disorders to reduce liability for claims of work-related disease). Employers may also elect to assess their employee's health to meet legal / insurance / pension requirements, to identify work-related needs, or to offer advice on health promotion.

As noted previously, such assessment does not currently involve the use of genetic tests. But the pace of scientific and technological developments in this area makes it increasingly feasible that genetic tests could be used for such purposes in the not too distant future. This prospect raises similar questions to those posed by the use of genetic tests for insurance purposes: should individuals be compelled to take tests, disclose existing test results, and if so under what circumstances?

Such questions have been considered by the Nuffield Council on Bioethics[55] in 1993, by a working party of the Health and Safety Commission's (HSC) Occupational Health Advisory Committee (OHAC) since 1995 and most recently by the HGAC[56]. Among these bodies' main conclusions are:

- Genetic tests have not yet been shown to be reliable enough for use in current health screening / surveillance in the workplace.
- Individuals should not be required to take a genetic test for employment purposes, nor to disclose the results of genetic tests they have already taken. An exception to this would be if the test had been shown to provide clear evidence needed to assess a person's ability to perform a job safely or their susceptibility to harm from doing a job.
- Certain aspects of the workplace / work may meet health and safety requirements but pose specific risks to individuals with certain genetic characteristics. Under such circumstances, employers should offer a genetic test to assess such risks if a reliable test is available. The use of tests in this way should only be considered where: there is strong evidence of the link between the workplace and the condition to be tested for; the condition is one that seriously endangers the employee or third parties; the danger

54 'The Implications of Genetic Testing for Employment', HGAC, 1999.
55 'Genetic Screening – Ethical Issues' Nuffield Council on Bioethics, 1993.
56 'The Implications of Genetic Testing for Employment', HGAC, 1999.

cannot be removed/reduced by other means. If issues of public safety arise then employers may refuse to employ a person refusing to take such a test.

- All tests should be offered on a consensual basis; they should be accurate and reliable, and the results treated in accordance with Data Protection principles. Results should be interpreted carefully and communicated to the person tested; professional advice should be available.

5.3.6.3 Biological Sample Collections and Medical Information

The proposed UK-based population biomedical collection (Section 2) also raises a number of ethical, legal, ownership and commercial issues. During 1999, the MRC published interim guidance on two aspects relevant to such a collection: the use of human tissue/biological samples in research[57] and the use of personal information in medical research[58]. As far as the use of samples in research is concerned, the guidance covers issues such as:

- Ownership – UK law is unclear as to whether anyone can 'own' samples of human tissue or whether donors of tissue have any rights over 'their' samples. The guidance thus focuses on custodianship (the right to control the use made of samples) rather than legal ownership *per se*. It recommends that samples be treated as gifts, with donors giving consent for their donations to be used in research, effectively transferring responsibility for samples to a custodian.
- Custodianship – while principal investigators will have day to day responsibility for the management of samples, formal responsibility for custodianship of a collection should rest with institutions rather than individuals.
- Commercial exploitation – the guidelines acknowledge that the involvement of the commercial sector is of critical importance in turning knowledge from research into health benefits. They thus allow for commercial access to sample collections from MRC-funded research where this is consistent with the MRC's mission. But they note that it is not appropriate for any one company to be given exclusive access to publicly-funded sample collections.
- Confidentiality/anonymisation – data collected on individuals and from research done on donated samples are covered by the Data Protection Act 1998 so long as they can be linked to an identifiable individual. The MRC guidelines recommend that "*data should be stored, processed and analysed in a form that does not allow individuals to be identified unless there is a strong ethical or scientific justification for not doing so*".
- Data sharing – the value of a sample collection/database is maximised by allowing access to a wide variety of users. But the guidelines note that arrangements should be made to ensure that any copies of data generated by users are returned to the custodian after a suitable period of time.
- Consent – the guidance recommends a two-stage approach to seeking consent from donors to use samples in medical research. First, consent should be sought for the specific experiments already planned. Second, donors will be asked to give broader consent to store the sample and use it in certain types of research in the future. It is important that the donor understands the type of research and the possible impact it might have on them in the future (see below).
- Feedback – experiments on tissue samples may yield information that has health implications for the donor. The extent to which such information can – or ought to - be

57 "Human Tissue and Biological Samples for Use in Research", Interim Operational and Ethical Guidelines, MRC, November 1999.

58 'Personal Information in Medical Research', Draft MRC Guidelines, MRC, September 1999.

fed back to the donor depends on factors such as whether and how the data are anonymised, and the clinical relevance of any test performed (results from early research are unlikely to be of great predictive or clinical value in the first instance). To date, no clear consensus has emerged on whether it is appropriate to feed back research results to individuals; the MRC plans to monitor developments in this area.

Use of personal information in medical research raises a number of similar issues; MRC draft guidelines have identified 11 key principles to guide research in this area (**Box 5.11**). Initiatives such as the MRC/Wellcome Trust UK-based population biomedical collection require the recruitment of large numbers of people to donate samples, divulge information, etc. – their success will thus depend to some extent on public attitudes to such exercises. In this context, the MRC and Wellcome Trust are currently undertaking a public consultation exercise to ensure that the public's views are taken into account when details of the biomedical collection are finalised. This exercise will include interviews with a wide range of groups including doctors and other primary health care workers, members of the public, special interest and religious groups, people from various ethnic backgrounds, as well as individuals at risk of (or affected by) genetic disorders. Key issues that the consultation will address include:

BOX 5.11 USE OF PERSONAL INFORMATION IN MEDICAL RESEARCH - KEY PRINCIPLES

- Personal information of any sort which is provided for health care, or obtained in medical research, must be treated as confidential. Normally, clinical researchers must ensure they have consent to hold or use personal information, and in most clinical research this is practicable.
- When consent is impracticable, confidential information can be disclosed for medical research without consent: if it is justified by the importance of the study; if there is no intention to contact individuals (except to seek consent) or reveal findings to them; if there are no practicable alternatives of equal effectiveness; and if the infringement of confidentiality is kept to a minimum. The decision about whether a study is sufficiently important is not for the investigator alone - it must also be referred to a Research Ethics Committee for independent assessment.
- Research must be planned with confidentiality in mind. Regardless of the strength of the justification for conducting the study, the design must minimise the amount of information used without or before consent, and the numbers of people who have access to it.
- All medical research using personal information - from any source - must be approved by a Local Research Ethics Committee or Multi-Centre Research Ethics Committee.
- Hospitals and practices involved in research must have procedures for making patients aware that their information is used for research, and explaining the reasons and safeguards. If patients object to their information being passed to others and have discussed this with their doctor, their objections must be respected.
- All personal information must be encoded or anonymised as far as is reasonably possible, and as early as possible in the data processing.
- Responsibility for disclosing patient information lies with the holder of the information.
- Personal information must be handled only by health professionals or staff with an equivalent duty of confidentiality.
- Researchers must have in place procedures to minimise the risk of their research causing distress. Researchers must also be aware that, despite their best efforts, occasional untoward events may occur and plan for how to deal with these.
- Principal investigators must take responsibility for ensuring that training, procedures, supervision, and data security arrangements are sufficient to prevent unauthorised breaches of confidentiality.
- At the outset, researchers must decide what information about the results should be available to the people involved in the study once it is complete, and agree these plans with the Research Ethics Committee (but must also be prepared to reconsider if there are unforeseen findings from the study).

Source: "Personal Information in Medical Research", Draft MRC Guidelines, MRC, September 1999.

- Levels of awareness of the use of human biological samples in medical research in general and in genetic research in particular.
- What are the main sources of information / understanding about samples collections (national or local press, television, radio, books, work, etc.)?
- Are people generally positive or negative in their attitude towards large scale sample collections that include personal medical information? What do people see as the main benefits and dangers of such collections?
- How do people understand, recognise and value the motivations of scientists involved in such research?
- Do attitudes vary to different types of samples (e.g. blood, surgical wastes, saliva, skin)?
- Attitudes towards donating samples for medical research. Under what circumstances / conditions would people be likely to donate samples and allow access to personal medical information? What information do people need / want in reaching such decisions?
- Trust – what institutions / professions do people trust to be the guardians of samples / information (e.g. doctors, charities, researchers, government institutions)?
- Regulation – what controls need to be in place to build public trust / confidence?
- What concerns and / or ethical issues do people currently have (or see on the horizon)?
- What are peoples' attitudes towards the commercial use of samples and the commercial exploitation of discoveries arising from research on such samples?

5.3.6.4 Research into Other Ethical, Legal and Social Implications

In addition to the specific issues of employment and insurance, human genome research will have wider implications for individuals, families and society as a whole. This has been acknowledged by genome research-funders in the US and the UK. In the US, the National Institutes of Health (NIH) and the Department of Energy (DoE) commits between 3-5% of their annual research budgets to the study of ELSI issues. Since ELSI programmes were first set up in the early 1990s, US research has focused on 4 main areas[59]:

- Privacy and fairness in the use and interpretation of genetic information. Issues here include privacy and confidentiality of genetic information, consent to disclosure and purposes for which it might be used (e.g. insurance, employment, criminal justice, education, adoption, military), discrimination and stigmatisation, and philosophical / conceptual aspects (e.g. personal identity, genetic determinism).
- Clinical integration of new genetic technologies. Among the main concerns in this area are that new genetic tests might be offered before their impact on individual's lives and health have been fully understood. Key issues include the education of health practitioners themselves, the delivery of appropriate genetic counseling, ensuring informed consent and maintaining professional standards.
- General issues surrounding the conduct of genetics research. One of the main concerns is that the risks and benefits to individuals taking part in genetics research are often not fully known; ensuring participants give informed consent is thus difficult. Another concern is the potential conflict between the need to disseminate results for research purposes on the one hand, and protecting the privacy of participants on the other.
- Public and professional education. The rapid pace of developments in genome research means that very few people, from health practitioners to ordinary members of the public,

59 see http://www.ornl.gov/hgmis/resource/elsi.html

understand the implications of such advances. Education is seen as an essential component in fully realising the potential of recent advances in genetics research.

UK research into such issues has been more pragmatic; rather than funding research into some of the more philosophical aspects of the debate, the focus has been on those social and ethical implications that are relevant to public policy. For instance, the Wellcome Trust funds such projects through its Medicine in Society Programme, which is funded to the tune of £15M over five years. This encompasses a Biomedical Ethics Programme focused on genetics and neuroscience issues. The overall aims of the programme are to:

- support research into the social, ethical and other consequences of advances in biomedicine;
- build / enhance national capacity in this area;
- ensure that the research is relevant to public policy and that the results are communicated effectively to those making such policy.

To date, the Trust has funded a number of innovative projects relevant to the area of human genetics. These include:

- A public debate jointly organised with the MRC on 'designer babies' in 1998;
- An on-going study on how people in clinical genetics deal with moral dilemmas;
- Production of a touring play (in conjunction with the Office of Science and Technology) designed to promote debate among young people on the social and ethical impact of advances in genetics and genetic testing. The Trust has supplied further support to adapt the play for television.
- Various consultation / education exercises designed to feed back public opinions into the policy process. These include (qualitative) social research into public attitudes to cloning[60], and on-going research into attitudes to pre-implantation genetic diagnosis and gene therapy.

5.4 RESEARCH ISSUES

5.4.1 Gene Therapy and Inadvertent Germ-Line Modification

Germ-line modification was one of the main issues considered by the Clothier Committee, set up by the Government in November 1989. It noted that such modification could prevent the transmission of defective genes to subsequent generations, but concluded "*There is insufficient knowledge to evaluate the risks to future generations. We recommend, therefore, that gene modification of the germ line should not yet be attempted*".

Since then, there has been widespread consensus that gene therapy should be restricted to modifying somatic (non-sex) cells. While this consensus still holds, recent years have seen concerns about the possibility of inadvertent modification of germ cells. The worry is that some of the DNA sequences delivered during somatic gene therapy will not be taken up by the target tissue, but instead be distributed around the body. If some of the DNA is taken up by germ cells, there is the possibility that it might affect a permanent genetic change that could be passed on to future generations. In some cases it is possible to design trials to minimise this possibility. For instance, in gene therapy where the 'target tissue' is blood cells, these can be removed from the body, treated, and then reintroduced. But in many gene

60 'Public Perspectives on Cloning', The Wellcome Trust.

therapy trials the DNA sequences are administered topically (e.g. to nasal or lung cells in CF trials), and distribution to non-target tissues is inevitable.

In general, there is little evidence from research on which to base an assessment of the risks of inadvertent germ line modification. On the one hand, studies using highly sensitive DNA amplification techniques have been able to detect transient distribution of DNA sequences to non-target tissues in humans. Other studies in mice have detected adenovirus vectors in the testes / ovaries of mice for up to 1 month after (intravenous) administration. However, none of the 800 or so offspring born to such mice showed evidence of germ-line transmission. Nor is there any evidence of inadvertent germ line modification from research trials of gene therapy in humans. Theoretical estimates (e.g. taking into account the efficiency of gene transfer obtained with current vectors) of the likelihood of such modification occurring have put the risk as low as 1 in 100 billion billion. A GTAC working group in 1998[61] noted that 'conventional' (small molecule) drugs were also capable of causing inadvertent germ line changes. It concluded that there was no reason to consider gene-based treatments differently to drug-based treatments (although there is less information available on the risks associated with the former). Overall, it considered that it would not be possible to reduce the risks of inadvertent germ-line effects to zero.

5.4.2 In Utero Gene Therapy / Stem Cell Transplantation

Some genetic disorders (e.g. Hurler's, Krabbe's and Gaucher's diseases) result in serious illness or death at the pre- or neonatal stage. Where such disorders can be diagnosed before birth, in utero gene therapy offers the potential for the birth of a healthy baby. The potential use of gene therapy at this stage was reviewed in a report published by GTAC in 1998[62]. It identified two main approaches:

- stem cell transplantation (SCT);
- in utero gene therapy.

Stem cells are immature cells that are capable of replicating themselves, and of generating other cell types (muscle, blood, brain cells, etc.) as they multiply. While a detailed discussion of this rapidly moving area is outside the scope of this report[63], stem cells have the potential to be used for a variety of therapeutic purposes. The GTAC report concentrated on the potential for using blood stem cells to treat inherited disease in utero and highlighted a number of advantages to such an approach. For instance, there is no need to 'match' the donor cells because the foetal immune system has not developed to the stage where it will reject foreign cells. Indeed, exposing the foetus to foreign cells may allow a 'tolerance' to develop, which means that further treatment (after birth) may be conducted free of the risk of rejection. In addition, the mechanics of accessing the foetal blood supply for transplantation are relatively straightforward.

To date, the UK is the only country to have issued guidance on in utero gene therapy. The GTAC report concluded that this area did not raise any new ethical issues other than those already recognised in other in utero interventions or in existing uses of gene therapy. In general, GTAC concluded that in utero gene therapy could only be considered if the disease or disorder treated were "*life threatening, or associated with severe disability and for which no*

61 "Hitting the Target with Gene Therapy", GTAC Workshop, November 1998.
62 "Report on the Potential Use of Gene Therapy In Utero", GTAC, 1998.
63 See POSTnote 141 'Stem Cell Research', June 2000.

suitable treatment is available after birth". In order to be ethical, the risks of all physical procedures would have to be known, with consent being solely a matter for the pregnant woman.

The Committee drew attention to concerns over the potential for inadvertent germ line modification posed by in utero gene therapy, and noted that these would have to be fully addressed in any proposals presented to GTAC for such treatment. With this in mind, it made a distinction between SCT with stem cells that have been genetically altered outside the body (ex vivo), and the use of gene therapy in the foetus itself. It believes that SCT in utero using cells modified ex vivo poses no higher risks of germ line modification than procedures it has already licensed (e.g. ex vivo modification of stem cells prior to bone marrow transplantation) in infants. In contrast, GTAC concluded that the direct application of gene therapy in utero was "*unlikely to be acceptable for the foreseeable future in view of the safety and ethical difficulties*".

5.4.3 Safety of Gene Therapy Vectors

The death of an American man taking part in a gene therapy trial at the University of Pennsylvania in September 1999 has focused attention on the safety of the adenovirus vectors used in some gene therapy trials. The patient had a liver disease, and researchers feared that this might have been connected to an exaggerated response to the adenoviral vector used in the gene therapy trial. This case prompted the US National Institutes of Health (NIH) to call for more information on adverse reactions in patients participating in gene therapy trials involving adenoviral vectors. It subsequently found evidence of several hundred potential serious adverse reactions in some 70 trials over 7 years. However, the significance of such events is not clear since it is difficult to distinguish between an adverse reaction to a therapy and a worsening of a patient's disease condition.

GTAC has conducted a survey of gene therapy research involving adenoviral vectors in the UK. It established an *ad hoc* working group – consisting of members from GTAC, other regulatory bodies, industry and academia - to analyse data derived from the audit with a view to establishing a code of practice. At the time of the survey, 69 patients with advanced cancer had been recruited into 11 adenoviral gene therapy trials in the UK. The working party published a report[64] in June 2000 that made recommendations concerning:

- patient surveillance and monitoring;
- administration of the virus through the hepatic artery (which is considered to present a greater theoretical risk to the patient);
- the need for accurate standardisation of dose;
- suitability of patients selected for adenoviral therapy (the working party recommended that only patients whose disease is severe or life threatening should be recruited into dose escalation studies);
- reporting of serious adverse events / reactions
- public awareness and sharing of information.

GTAC and the DH also have plans for a study to provide long-term follow up of all patients enrolled in gene therapy trials in the UK. The study will entail audit and health monitoring of patients, and will begin in summer 2000.

64 'Report of the GTAC Adenovirus Working Party', GTAC, June 2000

5.4.4 Pharmacogenetics

5.4.4.1 Clinical Trials and Surveillance

As outlined in Section 4.2, genome research and pharmacogenetics will allow drugs to be 'matched' to patients. Such developments will have a number of implications for pharmaceutical companies, regulators and patients alike. For a start, researchers organising clinical trials may be able to select only those patients who will benefit from a drug, and exclude those who may suffer an adverse reaction to it. This means that fewer patients will be needed in the trials to demonstrate efficacy; companies may thus be able to design smaller, cheaper and faster clinical trials. While this has obvious benefits for the pharmaceutical industry, there may be implications that need to be considered by regulatory bodies.

One such issue is that of adverse drug reactions. Some of these are so rare, that even large clinical trials involving thousands of patients may not detect them. There are concerns that a move towards smaller clinical trials might result in more such reactions being overlooked. One option here would be to integrate pharmacogenetics into the regulatory system, linking it up with the surveillance system that monitors adverse reactions to prescribed drugs. For instance, it has been suggested that DNA samples could be taken as a matter of routine from each patient prescribed a new drug. Analysing the samples from a patient showing an adverse reaction to the drug would allow any associated genetic polymorphisms to be identified. Drugs tested in this way would only be authorised for use in particular genetic sub-groups of patients. Monitoring such sub-groups for rare adverse drug reactions might reveal further genetic variations relevant to the drug in question. In this way, the 'genetic definition' of the sub-group for each drug could be continually fine-tuned.

Such a system has a number of potential advantages. It would enable data to be collected from much larger numbers of patients (hundreds of thousands) than is possible in formal clinical trials. It may also prove to be a more sensitive, rapid and cost-effective way of characterising rare adverse drug reactions. However, the application of pharmacogenetics to allow smaller clinical trials and develop a better surveillance system for rare adverse drug reactions would require careful consideration by regulatory bodies at both UK and EU levels.

5.4.4.2 Regulation of Pharmacogenetic Tests

Much of the public debate on 'genetic testing' has focused on tests that identify genetic features associated with particular diseases. Such tests raise many ethical issues. For instance, they may inform difficult reproductive decisions or have implications for other family members. Debate on such tests has thus focused on issues such as the need for informed consent, data protection, and the appropriateness of offering tests for diseases where no effective treatments are available. This has led to regulations designed to protect the patient and their family.

To what extent should similar regulations apply to tests offered for pharmacogenetic purposes? This question arises because the type of information yielded by such tests is different from that obtained by tests designed to detect genetic disease[65]. Pharmacogenetic testing yields information on an individual's genetic polymorphisms to predict how he or

65 AD Roses, 2000. "Pharmacogenetic and Future Drug Development and Delivery", Lancet, **355**, 1358-61.

she will react to a drug. It reveals nothing about the underlying genetic basis of any disorder the individual may have and cannot thus be used to infer anything of significance about that individual's family members. Because of this, the pharmaceutical industry is keen to ensure that pharmacogenetic testing is regulated separately from disease-specific genetic tests.

GLOSSARY

ABI	Association of British Insurers
ACGT	Advisory Committee on Genetic Testing
AGSAG	Advisory Group on Scientific Advances in Genetics
BAC	Bacterial Artificial Chromosome
BSHG	British Society for Human Genetics
CCC	Continuing Care Conference
CEGEN	Confidential Enquiry into Genetic Counselling by Non-geneticists
CF	Cystic Fibrosis
CMGS	Clinical Molecular Genetics Society
CPA	Clinical Pathology Accreditation
DH	Department of Health
DNA	Deoxyribonucleic Acid
EST	Expressed Sequence Tags
GAIC	Genetics and Insurance Committee
GIG	Genetics Interest Group
GTAC	gene Therapy Advisory Committee
HFEA	Human Fertilisation and Embryology Authority
HGAC	Human Genetics Advisory Commission
HGC	Human Genetics Commission
HGP	Human Genome Project
HUGO	Human Genome Organisation
IPR	Intellectual Property Rights
IVF	In Vitro Fertilisation
MRC	Medical Research Council
NCB	Nuffield Council on Bioethics
NHSHTAP	NHS Health and Technology Assessment Programme
NICE	National Institute of Clinical Excellence
NSC	National Screening Committee
PCR	Polymerase Chain Reaction
PGD	Pre-implantation Genetic Diagnosis
PND	Pre-Natal Diagnosis
RCP	Royal College of Physicians
RCPath	Royal College of Pathologists
RNA	Ribonucleic Acid
SCT	Stem Cell Transplantation
SGD	Single Gene Disorder
SNP	Single Nucleotide Polymorphism
STS	Sequence Tagged Site
TIGR	The Institute of Genomic Research
UKGTN	UK Genetic Testing Network
US DoE	US Department of Energy
US NIH	US National Institutes of Health
USPTO	US Patent and Trademarks Office
YAC	Yeast Artificial Chromosome

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