19. Genetic Technology

19.2 Genetic Technology Applied to Medicine

Paper 4

Question Paper

1 The gene *BRCA1* is expressed in breast tissue and in several other tissues of the body. *BRCA1* codes for a tumour suppressor protein. This protein is involved in either repairing damaged DNA, or in triggering the death of a cell if DNA cannot be repaired.

Some mutations in *BRCA1* are associated with an increased risk of developing breast cancer.

(a) State **one** reason why a doctor would recommend that a person has genetic testing for a mutation in the gene *BRCA1* **and** explain why this mutation would put the person at a greater risk of breast cancer.

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(c) Genetic screening shows that in the UK:

- 1 in 400 females have a mutated allele of *BRCA1*
- 70% of females with a mutated allele of *BRCA1* will develop breast cancer by the time they are 80 years old.

In 2022, the population of females in the UK was 3.5×10^7.

Calculate the number of females in the UK population in 2022 who it is estimated will develop breast cancer by the age of 80 years old. Give your answer in standard form.

Show your working.

number of females = ... [2]

(d) One advantage of genetic screening is to determine which drugs should be selected to treat cancer.

A study was carried out on women with breast cancer who had been treated with a DNA-damaging drug that kills tumour cells.

The women had all been tested for *BRCA1* mutations. One group had a *BRCA1* mutation and the other group did **not** have a *BRCA1* mutation.

The researchers used data to assess the probability of survival for the women in each group of the study after treatment with the drug.

Fig. 5.1 shows the probability of survival for a time period of up to 180 months.

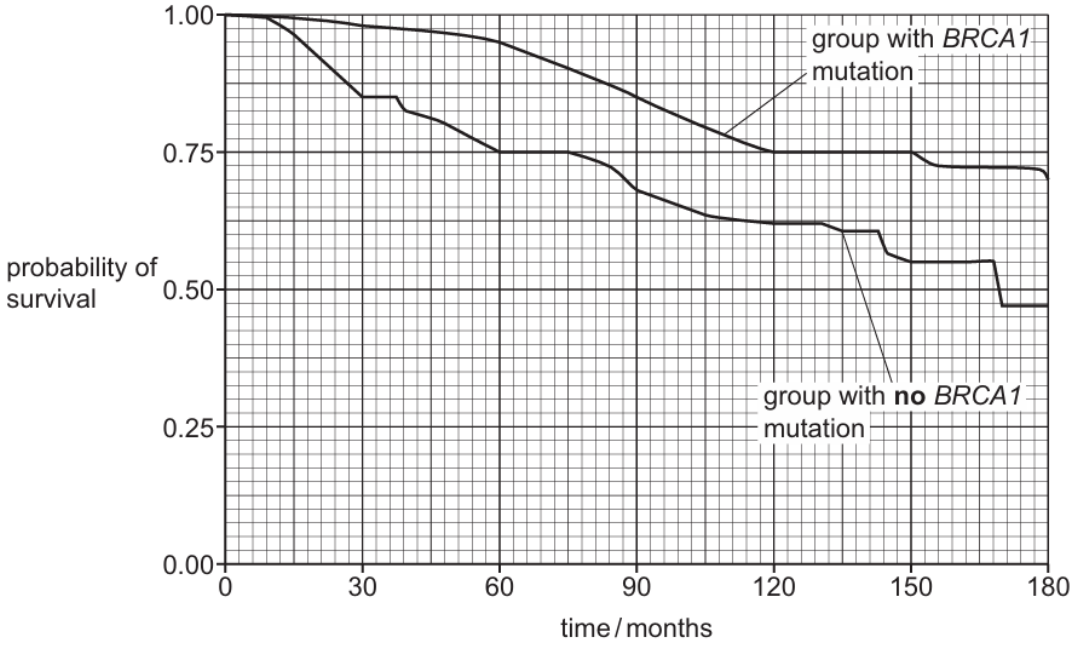


Fig. 5.1

The researchers suggested the hypothesis that the DNA-damaging drug is more effective in women with a *BRCA1* mutation.

Discuss whether the results in Fig. 5.1 support the hypothesis suggested by the researchers.

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2 The treatment of many diseases has been improved by the use of genetic technology in medicine.

(b) (i) Leber Congenital Amaurosis (LCA) is an inherited eye disease. In LCA, the photoreceptor cells in the retina die at an early age. This causes impaired vision (reduced eyesight) in children, which can progress to blindness.

Mutations in different genes cause different forms of LCA. One form of this disease, LCA2, is caused by a mutation in the *RPE65* gene. Gene therapy has been used to treat LCA2.

Outline how an inherited eye disease, such as LCA2, is treated with gene therapy.

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(ii) Suggest why the eye is a suitable organ for gene therapy.

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(c) LCA10 is a different form of LCA caused by a recessive mutation in the *CEP290* gene. This gene codes for the protein CEP290, which is involved in the correct functioning of photoreceptor cells in the retina.

The mutation in *CEP290* causes an error to be made when the primary transcript is spliced to form messenger RNA (mRNA). The abnormal mRNA that is formed has an extra sequence of RNA nucleotides, known as exon X, between exon 26 and exon 27. Exon X contains a STOP codon.

Fig. 3.1 compares the effect of the mutation in *CEP290* with the normal gene expression.

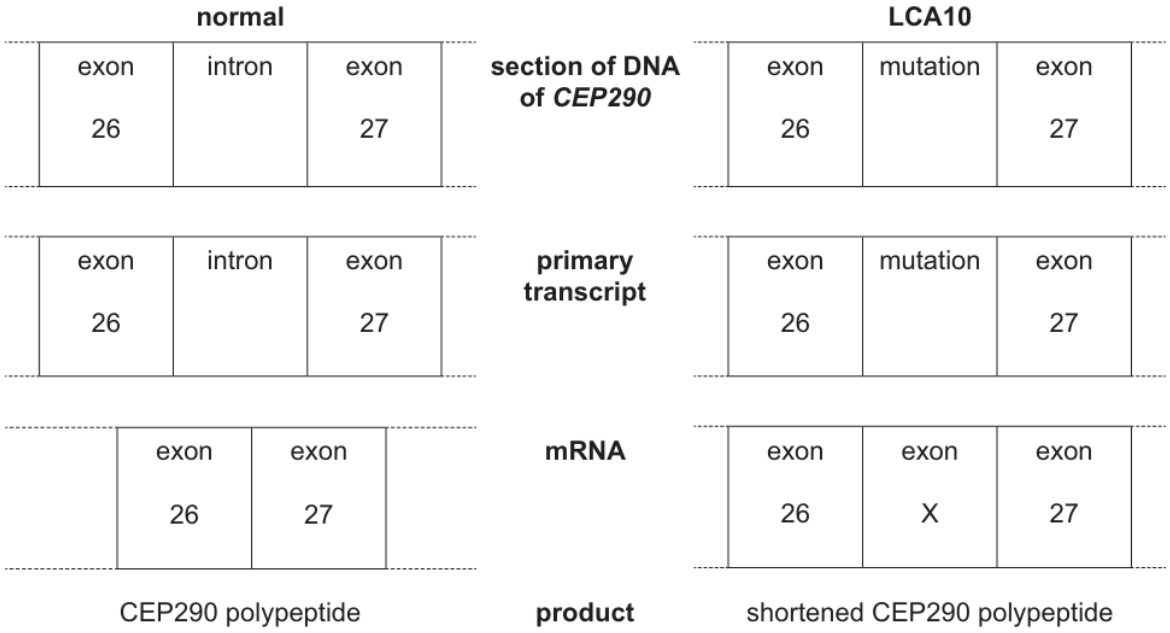


Fig. 3.1

In 2022, research was carried out into possible treatment of LCA10 using genetic technology.

(i) A human clinical trial investigated a treatment of LCA10 using a short RNA nucleotide sequence known as Sepofarsen.

Sepofarsen binds to the section of the primary transcript containing the *CEP290* mutation so that normal splicing occurs and functional CEP290 protein is synthesised.

- People in the clinical trial received regular treatment with Sepofarsen to the eye with the greatest loss of vision (treated eye) for a period of 12 months.
- Changes in the light perception (visual acuity) of both eyes were measured using a vision chart.
- A negative change in the visual acuity score shows an improvement in visual acuity.

Fig. 3.2 shows the results of the clinical trial over 12 months.

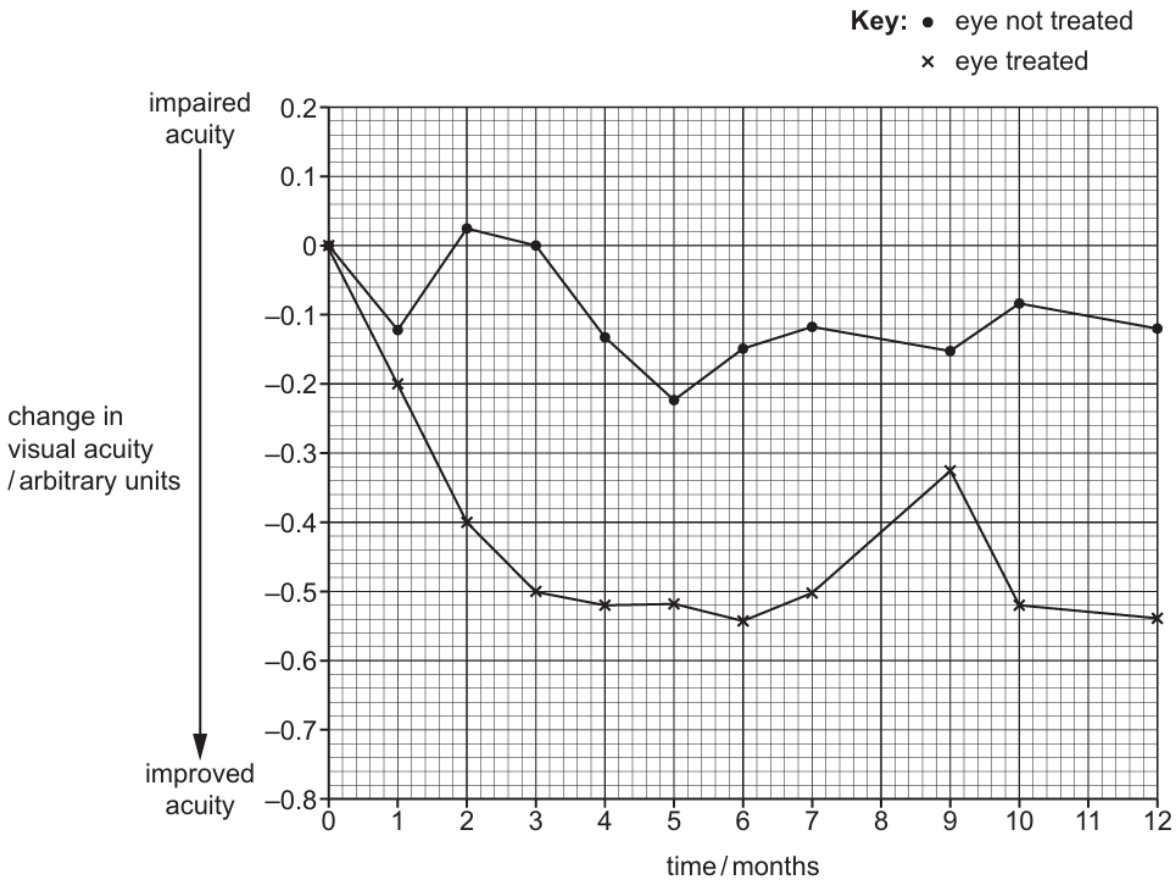


Fig. 3.2

Describe the results of the clinical trial data shown in Fig. 3.2.

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3 **(a)** Recombinant human proteins can be used to treat disease.

(ii) From the 1920s until the 1970s, insulin obtained from the bodies of animals was used to treat diabetes. From the 1970s, recombinant human insulin was used instead.

Explain the advantages of using recombinant human insulin to treat people with diabetes.

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(b) Insulin is composed of two polypeptide chains, the A chain and the B chain, that are linked by disulfide bonds.

Variations in amino acid sequence occur:

- in the insulin molecules of different animals
- in new versions of human insulin that have been engineered to control blood glucose concentration more effectively than normal recombinant human insulin. These new versions of human insulin are called analogues.

Table 4.1 shows the amino acid positions where variation occurs in different animal and human analogue insulin molecules. The dashes indicate a missing amino acid.

Table 4.1

amino acid position	type of insulin					
	human	**cow**	**pig**	**cat**	**short-acting analogue**	**long-acting analogue**
A8	threonine	alanine	threonine	alanine	threonine	threonine
A10	isoleucine	valine	isoleucine	valine	isoleucine	isoleucine
A18	asparagine	–	asparagine	histidine	asparagine	asparagine
A21	asparagine	asparagine	asparagine	asparagine	asparagine	glycine
B3	asparagine	asparagine	asparagine	asparagine	asparagine	–
B28	proline	proline	proline	proline	lysine	proline
B29	lysine	lysine	lysine	lysine	proline	lysine
B30	threonine	alanine	alanine	alanine	threonine	threonine
B31	–	–	–	–	–	arginine
B32	–	–	–	–	–	arginine

(i) Cats with diabetes can be successfully treated with insulin injections. Cat insulin is **not** available, but vets can choose from the other types of insulin shown in Table 4.1.

Identify the type of insulin that is most suitable for treating cats.

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4 Medicine is defined as the diagnosis, treatment and prevention of disease.

Outline the different ways in which genetic technology can be applied to medicine, with reference to named diseases.

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5 Adenosine deaminase (ADA) deficiency is an immune system disorder caused by a recessive autosomal mutation.

Severe combined immunodeficiency caused by a lack of ADA is called ADA-SCID.

(b) In 2016 gene therapy to cure ADA-SCID was approved in Europe. The gene therapy involves three main steps.

- Blood (haematopoietic) stem cells are taken from the bone marrow of the person with ADA-SCID.
- The functional gene and its promoter are inserted into the blood stem cells.
- A single infusion (injection) of the gene-corrected cells is given to the patient.

(i) Explain why a single infusion of gene-corrected stem cells is enough to cure the disease.

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(iii) A modified retrovirus is used to insert the new gene into the DNA of the blood stem cells.

State **two** ethical considerations of using a retrovirus for gene therapy.

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6 **(a)** Genetic technology involving the creation of recombinant DNA can be used to treat different human diseases. These include diseases such as diabetes that may have multiple causes and inherited disorders that are caused by a single gene.

Outline **two different** ways of using recombinant DNA technology to treat these diseases.

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single gene disorder .....

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7 Gene therapy can be used to treat some genetic disorders. An appropriate vector is chosen to carry the normal allele into the target cell. Three types of vectors commonly chosen are naked DNA, viruses and liposomes.

(a) A trial of gene therapy to treat cystic fibrosis used a viral vector. The viral vector caused a primary immune response with the production of memory cells.

Explain why the production of memory cells prevents the gene therapy from working in long-term chronic conditions such as cystic fibrosis.

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(b) With reference to the three types of vectors that are commonly used, discuss the challenges in choosing appropriate vectors for use in gene therapy.

Do **not** include problems associated with an immune response in your answer.

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8 Mitochondrial complex I is a large enzyme complex that forms part of the electron transport chain. The enzyme is composed of many different polypeptides.

The genes coding for these polypeptides are located either in mitochondrial DNA (mtDNA) or in nuclear DNA. Mutations in these genes can lead to the production of an enzyme that does not function efficiently. This results in a disease known as mitochondrial complex I deficiency. If severe, this can lead to death in early childhood.

(c) Genetic screening can be carried out on people with symptoms of mitochondrial complex I deficiency.

Previously 7 mtDNA genes and 37 nuclear genes were sequenced. Some of the people tested did not have mutations in any of these genes. As a result, another gene was sequenced in these people and was found to be mutated.

This led to the suggestion that genetic screening should sequence a larger proportion of the genome for people suspected of having this disease.

Discuss the **ethical** reasons for and against sequencing a larger proportion of the genome for people suspected of having mitochondrial complex I deficiency.

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9 Sickle cell anaemia is a non-infectious chronic disease. If not treated, sickle cell anaemia can be painful and life-threatening.

Sickle cell anaemia is caused by a base substitution mutation in the gene coding for the β-globin polypeptide of haemoglobin. This leads to a change in the primary structure of the polypeptide, as valine is present instead of glutamine. This results in abnormal sickle-shaped red blood cells, which stick together in blood vessels.

Symptoms of sickle cell anaemia include painful attacks when red blood cells block capillaries in tissues and organs.

(b) Sickle cell anaemia is an autosomal recessive inherited disorder:

- allele Hb^A codes for the normal β-globin polypeptide
- allele Hb^S codes for the sickle-cell polypeptide.

People who are heterozygous (Hb^A Hb^S) have sickle cell trait (SCT). For a child to inherit sickle cell anaemia (Hb^S Hb^S), both parents must have SCT.

A genetic screening program is available for sickle cell anaemia and SCT:

- when a mother is screened and found to have SCT, the father is then screened
- if the mother becomes pregnant, the fetus is screened for both sickle cell anaemia and for SCT
- the test is done either by amniocentesis or by chorionic villus sampling, both of which carry a small risk of the pregnancy failing.

(i) Outline **two** advantages of genetic screening for sickle cell anaemia and SCT.

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10 Domestic goats are small, herbivorous animals that provide milk for human use. Goats' milk is an important source of food for people living in rural China. Xinong Saanen and Guanzhong are the names of two varieties (breeds) of goat common in China.

In these breeds, there is genetic variation at nucleotide position 5752 of a gene coding for a growth factor. At this position there is either a cytosine (C) or a guanine (G) nucleotide. Some individuals are homozygous for the allele containing C at this position (**CC**), some are homozygous for the allele containing G at this position (**GG**) and some are heterozygous (**CG**).

Table 2.1 compares the mean milk yield of the first milk-producing period (first lactation) and the next milk-producing period (second lactation) for Xinong Saanen goats of each genotype.

Table 2.1

genotype at position 5752	mean milk yield / kg	
	first lactation	second lactation
CC	679	940
CG	622	858
GG	616	834

(c) Goats can be genetically modified to produce human proteins in their milk.

In 2009, an anti-clotting protein produced in this way was approved for use as a drug in people who lack the protein.

State **one** ethical advantage and **one** ethical problem of producing medicinal drugs from the milk of genetically modified goats.

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11 Therapeutic proteins are used to treat disease. The first purified therapeutic protein used was insulin, in 1922. The insulin was extracted from animal pancreases. Since 1982 most insulin has been made by recombinant DNA technology.

(a) Explain the advantages of producing human therapeutic proteins, such as insulin, by recombinant DNA technology.

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12 **(a)** A severe reduction of blood flow to the brain causes cells to die. This is called a stroke. The after-effects of a stroke can range from recovery to permanent brain damage and death.

A new emergency gene therapy treatment for people who are at risk of brain damage from a stroke was tested in mice.

- The human granulocyte colony-stimulating factor, hG-CSF, is a protein that stimulates the production of stem cells in bone marrow.
- mRNA coding for hG-CSF was obtained and used to make cDNA.
- This cDNA was inserted into an adeno-associated virus (AAV) vector and given in eye drops to mice just after they experienced a stroke.

(i) Explain what is meant by *gene therapy*.

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(ii) Describe the roles of reverse transcriptase and DNA polymerase in making cDNA for hG-CSF.

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(iii) The AAV vector used was unable to replicate itself within the target cells.

Suggest why the researchers chose a vector that could not replicate.

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(b) A study was carried out to investigate the effect of the gene therapy described in **(a)**. Four groups of mice were used.

- Group **A** mice had a stroke. They received eye drops containing AAV vector carrying cDNA for hG-CSF **once** only.
- Group **B** mice had a stroke. They received eye drops containing AAV vector carrying cDNA for hG-CSF **four** times.
- Group **C** mice had a stroke. They received eye drops containing AAV vector carrying the *GFP* gene coding for green fluorescent protein, instead of the cDNA for hG-CSF, **once** only.
- Group **D** mice did not have a stroke. They were not given any eye drops.

(i) Explain why the mice in group **C** were used in the study.

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(ii) Explain why the mice in group **D** were used in the study.

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(c) Table 5.1 summarises some results from the study and shows:

- the percentage of mice surviving
- the percentage of brain volume occupied by fluid-filled space
- the score on a behavioural test in which normal mice score 0.5 and brain-damaged mice score nearer to 1.0.

Table 5.1

mouse treatment group	percentage of mice surviving	percentage of brain occupied by fluid-filled space	behavioural test score / arbitrary units
A	63	3.6	0.67
B	100	3.0	0.67
C	25	5.2	0.90
D	100	3.0	0.50

Use the results in Table 5.1 to evaluate the benefits of gene therapy treatment, with AAV vector carrying the gene for hG-CSF, for **people** who have a stroke.

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