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Proposal for a
COUNCIL DECISION

adopting a specific research programme in the field of health:
Predictive Medicine: Human Genome Analysis
(1989-1991)

(presented by the Commission)

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PROPOSAL FOR A COUNCIL DECISION ADOPTING A SPECIFIC RESEARCH
PROGRAMME IN THE FIELD OF HEALTH :
PREDICTIVE MEDICINE : HUMAN GENOME ANALYSIS

CONTENTS	
0.	SUMMARY 1
1.	REASONS FOR PROPOSAL :
1.1	What is Predictive Medicine ? 3
1.2	The scientific basis for Predictive Medicine
1.2.1	The organization of genetic information: Mapping human genes 3
1.2.2	The occurrence of genetic disease 4
1.2.3	Technologies for mapping genes 6
1.2.3.1	Genetic linkage maps 6
1.2.3.2	Physical maps 7
1.2.3.3	Ordered clone libraries 7
1.2.3.4	Sequencing 7
1.2.3.5	Management of information and materials 8
1.2.4	Applications of gene mapping in Predictive Medicine
1.2.4.1	Diagnostic applications 8
1.2.4.2	Identification of genes associated with disease 9
1.2.4.3	Gene therapy 9
1.3	Social and ethical considerations 9
2.	THE PREDICTIVE MEDICINE PROGRAMME : HUMAN GENOME ANALYSIS 10
3.	JUSTIFICATION OF THE CONFORMITY OF THE PROGRAMME WITH THE OBJECTIVES AND METHODS OF THE EUROPEAN COMMUNITY
3.1.	Conformity with the objectives of the framework programme of research and technological development 12
3.2	Justification of the scientific content of the programme: the international challenge and European scientific cohesion 13
3.3	Relation to other Community research programmes 13
3.4	Precompetitive nature of the research 14
3.5	Management and evaluation 14
4.	IMPLEMENTATION AND FINANCIAL MEANS 15
4.1.	Networks of facilities 15
4.2	Research contracts 16
4.3	Training 16
4.4	Scientific Management 17
4.5	Commission Staff 17
4.6	Summary of Financial Means 17
	PROPOSAL FOR COUNCIL DECISION AND ANNEX 18
	FINANCIAL RECORD 26
	IMPACT ON SMALL AND MEDIUM-SIZED ENTERPRISES 30

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SUMMARY

Infectious disease is no longer the major cause of illness or death in the Western world. Instead, much disease has a genetic component : it may be the result of inheritance of a single defective gene (monofactorial) or of the interaction of multiple gene defects (multifactorial) with environmental factors. Many common and debilitating diseases such as coronary artery disease, diabetes and the major psychoses, fall into the latter category, i.e. the disease results from the exposure of genetically susceptible people to environmental factors. Predictive Medicine seeks to predict susceptibility to diseases with a view to their prevention and early diagnosis, as well as to improved prognosis and, eventually, treatment.

The human genome is the complete set of genetic material (deoxyribonucleic acid, or DNA) which embodies the instructions describing each human being. It is now possible to analyse, or map, the genome in such a way that one can "read" these instructions and, in so doing, locate the genes which, when altered, give rise to particular diseases. Along the way it will be possible to make fundamental new discoveries in biology and acquire new technology for medicine.

The Predictive Medicine Programme will contain the following strands :

- improvement of the resolution of the human genetic map, i.e. creation of a map of the human genome, consisting of DNA markers, which would enable researchers to locate genes easily and quickly;
- the setting up of ordered clone libraries, i.e. of collections of ordered sets of DNA fragments which fully represent the DNA present in the entire genome, selected chromosomes or chromosomal fragments;
- the improvement of advanced genetic technologies and, through a training programme, the spreading of these advanced technologies throughout the Member States.

The programme is a European response to the international challenges presented by the large-scale biological research projects in the United States (Mapping and Sequencing the Human Genome) and Japan (Human Frontier Science Programme). Although it is a programme of basic precompetitive research, both new information and new materials of potential commercial value will result; new technological processes will also be developed. These will all contribute to the development of Europe's biotechnology industry - often based in small and medium-sized enterprises.

As the title implies, the content of the programme will have the ultimate aim of identifying genes involved in disease, with a view to their isolation and structural analysis.

The enormous increase in genetic information - or rather the uses to which it may be put - does raise ethical questions. Aspects such as personal privacy must be weighed against general health care considerations; the ability to diagnose disease will outrun the possibilities of treating it. These and many other issues must be given serious consideration.

RESEARCH PROGRAMME IN THE FIELD OF HEALTH : PREDICTIVE MEDICINE- HUMAN GENOME ANALYSIS

1. REASONS FOR PROPOSAL

1.1 WHAT IS PREDICTIVE MEDICINE?

Fifty years ago the principal cause of morbidity and mortality was infectious disease but with the discovery of antibiotics, and improvements in hygiene and pest control, it is now a minor one in industrialized countries. Apart from the consequences of accident or war, much disease today has a genetic component which may be of greater or lesser importance. Over the past few years a great deal has been learned about those diseases which are due to the inheritance of a single defective gene, though in most cases we are still very far from a remedy.

However, when it comes to the common diseases such as coronary artery disease, diabetes, cancer, autoimmune diseases, the major psychoses and other important diseases of Western society, the position is far less clear. These conditions have a strong environmental component and although genetic factors are undoubtedly involved, they do not follow any clear-cut pattern of inheritance. Put another way, the disease results from the exposure of genetically susceptible individuals or populations to environmental causes; prevention will depend on reducing the levels of exposure either in populations or, more probably, in susceptible individuals. As it is most unlikely that we will be able to remove completely the environmental risk factors, it is important that we learn as much as possible about the genetically determined predisposing factors and hence identify high-risk individuals. In summary, Predictive Medicine seeks to protect individuals from the kinds of illnesses to which they are genetically most vulnerable and, where appropriate, to prevent the transmission of the genetic susceptibilities to the next generation.

1.2 SCIENTIFIC BASIS FOR PREDICTIVE MEDICINE

1.2.1 THE ORGANIZATION OF GENETIC INFORMATION: MAPPING HUMAN GENES

The human genome is the complete set of genetic material-deoxyribonucleic acid (DNA) - which embodies the instructions describing each human being. It is now within the realms of possibility to "read" these instructions in their entirety and, in doing so, to make fundamental new discoveries in biology, to learn to predict and ultimately treat genetic diseases, and to acquire new technology for medicine.

Each human being has two sets of 23 chromosomes along which are arranged an unknown number of genes (a sequence of bases in DNA which codes for one protein), the best total estimate of which is 50,000 to 100,000. Each gene is composed of DNA, which is a

thread-like substance made up of nucleotides (a purine or pyrimidine base attached to a sugar and phosphate group), and generally found as two strands wrapped around each other in the form of a double helix. The two strands are held together by bonds between base pairs of nucleotides. The linear pattern of nucleotides in the genome is known as the DNA sequence and its length is measured in base pairs of DNA. The human genome contains about 3,000 million base pairs.

A variation in this hereditary set of instructions occurs when there is a mutation, or change in the sequence or number of nucleotides in one or more genes. The challenge is to find the genes which, having mutated, give rise to a particular disease. Logically, this must be achieved by first locating the position of the genes along the chromosomes and then defining the sequence of nucleotides that determine normal genetic characteristics; only by defining the normal genetic structure can the abnormal then be recognized. Such a genetic map is the equivalent of a dictionary since it provides a unique ordering of the genes. We need only think of the problem of looking up a word without a dictionary or of finding a book in a library without a catalogue. Having access to this "human gene dictionary" is thus absolutely fundamental to the speed with which we can analyse human genetic variation and to our understanding of the complex ways in which genes interrelate to determine human development.

1.2.2 THE OCCURRENCE OF GENETIC DISEASE

Genetic variation giving rise to disease can be present in all body cells, including the germ (egg and sperm) cells, and can be transmitted from one generation to the next. Other variation is present only in somatic (non-sexual) cells and has consequences only for that person. Many types of cancer arise as a result of mutations of the latter type.

In broad terms, disease involving inherited genetic factors can be divided into three categories :

- single gene defects (monofactorial) which show simple Mendelian inheritance patterns. Most of these conditions are rare in themselves but since there are many of them, they represent in total a substantial burden of disease. Currently some 4,200 single gene defects are recognized and manifest in 2.5% of all liveborn in Western European populations;
- multiple gene defects (multifactorial), in which multiple genetic and environmental factors are involved. Many common debilitating diseases fall into this category;
- abnormalities of chromosome number and structure, as in Down's syndrome.

The incidence of some diseases which are due to single gene defects is given in Table 1; that of some common diseases of multifactorial origin is in Table 2.

Table 1 : Occurrence of some single gene defect diseases in Europe

Disease	Occurrence related to number of births	Prognosis
Cystic fibrosis	1/2,500	Life rarely exceeds 20 years
Sickle cell disease	1/6,000*	Variable seriousness, often lethal
Phenylketonuria	1/15,000	Favourable if early diagnosis
Lesch-Nyhan Syndrome	1/16,000	Kidney and brain disturbance, generally lethal
Beta-thalassemia	**	Life rarely exceeds 20 years
Duchenne muscular dystrophy	1/7,000***	Myopathy after the age of four, fatal outcome around 20 years
Immunodeficiencies	****	High death rate

* Infrequent in Europeans, sickle cell disease (a haemolytic anaemia) may have a frequency exceeding 1/100 in some African populations, 1/400 in Caribbean islanders and 1/2,500 in black Americans.

** Infrequent in Northern Europe, beta-thalassaemia (another haemolytic anaemia) is widespread in the Mediterranean basin, with a maximal occurrence in Cyprus (1 to 2/100).

*** Linked to the X chromosome, this disease occurs only in boys, with a frequency of 1/3,500 (1/7,000 for all births).

**** The occurrence of genetic immunodeficiencies is low.

Table 2: Common chronic diseases with a multifactorial genetic component

Disease	Frequency in general population	Frequency in 1st degree relatives of affected persons
Peptic ulcer	1/25	1/10
Rheumatoid arthritis	1/50	1/20
Diabetes mellitus:		
insulin-dependent	1/500	1/33
insulin-independent	1/50	1/10
Ischaemic heart disease <65 yrs	1/50	1/10
Severe manic-depressive psychosis	1/100	1/6
Epilepsy (grand mal)	1/200	1/25

1.2.3 TECHNOLOGIES FOR MAPPING GENES

There are different ways of constructing maps of the human genome. In its most simple form gene mapping means assigning a gene to a specific chromosome. The first such assignment, made in 1911, was of the gene for colour-blindness to the X chromosome and this depended on the observation that males and not females were affected. In the same way, several other X-linked genes were discovered but some fifty years passed before the development of new techniques allowed the assignment of genes to the other 22 pairs of chromosomes. Even then there was no way of locating genes whose product was unknown until, in the 1970s, recombinant DNA technology provided a new approach. This approach, called reverse genetics, depends on first localizing a disease gene to a particular chromosome by its association with genetic markers (identifiable regions on a chromosome) within families exhibiting the disease. This process is expedited by the availability of genetic linkage maps for each chromosome.

1.2.3.1 GENETIC LINKAGE MAPS

A genetic linkage map shows the distance between genes, and other genetic markers, on the basis of the frequency with which they are inherited together. Genes that are close together on a chromosome usually stay together, or linked, during the division of egg and sperm cells, a process during which some parts of the chromosomes recombine. The distance along genetic maps, represented by recombination frequency, is measured by how often a particular gene is inherited separately from some marker and is expressed in centimorgans. If a gene and a marker on the same chromosome are separated only 1% of the time, the distance between them is 1 centimorgan and this distance is on average 1 million base pairs of DNA, although there will be major differences from this depending upon which chromosome region is under consideration. Such observations are made by studying the cosegregation of genetic markers within families, and very large pedigrees are required to establish linkage relationships between genetic markers with sufficient reliability. For example, currently about 600 individuals in 40 large families have been used to establish a linkage map to the 9 centimorgan level. An improvement to between 1 and 5 centimorgans will necessitate an expansion of the total number of large families by a further 20.

Recombinant DNA technology introduced a new dimension to genetic linkage mapping. Scientists discovered that restriction enzymes - the tools used to recognise a particular, short DNA sequence and cut it at that site - sometimes failed to cut the DNA of some people in the expected places. As a result, fragments of a different length were produced and these variations were inherited. Known as restriction fragment length polymorphisms (RFLPs), they are used as reference points along the genome

To identify RFLPs generated from very large pieces of DNA, it is necessary to use radioactively labelled, single-stranded sequences of DNA called DNA probes, which form base pairs (hybridize) with complementary sequences in the RFLP markers. Some useful probes for RFLP mapping are fragments of genes, others are complementary to a new generation of markers, "variable number tandem repeats", which make use of the clusters of repetitive DNA sequences found, in varying numbers, throughout the human genome.

1.2.3.2 PHYSICAL MAPS

A physical map of the human genome shows the actual distance, measured in base pairs of DNA, between genes or markers. Various low resolution methods of physical mapping are known which are dependent upon dividing single human chromosomes into several fragments. However, they locate only very large pieces of DNA, into which either a few or thousands of genes might fit. Mechanisms for finding a gene of interest in long stretches of DNA remain primitive.

New methods of separation of very large DNA fragments produced by restriction enzymes which cut at very rare sites allow the construction of long-range restriction fragment maps, which have a considerably higher resolution and bridge the gap between the single gene and the entire chromosome.

1.2.3.3 ORDERED CLONE LIBRARIES

Development of higher resolution physical maps is extremely valuable in helping to locate genes of medical importance. Also, for physical mapping projects, it is necessary to have access to large stocks of DNA and clone libraries can provide such a source.

Cloning is making multiple copies of a DNA fragment by incorporating it into a self-replicating molecule which can then be introduced into a host cell. Libraries are collections of cloned DNA fragments from a common source. To construct a physical map, the order of the cloned DNA fragments relative to one another along the chromosomes must be known. The goal is to create a complete set of overlapping clones, whose order is known, to cover the entire human genome. Once the physical relationship between cloned fragments has been established, their nucleotide sequence can be determined.

1.2.3.4 SEQUENCING

The ultimate physical map will be the total DNA sequence of the human genome. Although it is feasible to consider sequencing the genome, to determine the total sequence of 3,000 million base pairs in a reasonable time would require a very considerable improvement in existing techniques.

However, there is a case for first sequencing those regions of the genome which are believed to be clinically or scientifically important. These would include chromosome regions in which clinically important genes are either expressed - i.e. transcribed into messenger ribonucleic acids (mRNAs) which are in turn translated into proteins - or serve some regulatory function. One method which has been proposed is first to sequence DNA copies (cDNA) of cellular messenger RNA transcripts, with a view to using that information to identify which genes are expressed in the genome.

1.2.3.5 MANAGEMENT OF INFORMATION AND MATERIALS

The production of higher resolution genetic and physical maps will each generate an enormous amount of data; establishing the correlations between them will generate even more. In both cases there will also be a considerable requirement for the distribution and collection of materials, e.g. probes, DNA clones. The efficient management (and integration) of the information and of the handling of materials will be of prime importance, and argues for the identification of a number of central facilities each to become the centre of a research network.

1.2.4 APPLICATIONS OF GENE MAPPING IN PREDICTIVE MEDICINE

1.2.4.1 DIAGNOSTIC APPLICATIONS

Tests for genetic disorders are generally used in prenatal diagnosis of abnormalities such as Down's syndrome or in screening the newborn for conditions amenable to treatment, such as phenylketonuria. They are also used in screening adults (often from particular ethnic groups) for increased risks of transmitting genetic disease to the next generation - for instance, by identifying carriers of diseases such as sickle cell anaemia, beta-thalassaemia, Tay-Sachs disease, etc.

Most of the currently available tests are based not on identifying the abnormal gene(s) but on detecting the gene product; hence they are limited to some 200 disorders where a gene product or biochemical marker is known, a small number in comparison to the 4,200 known single gene defects. Other limitations to this approach lie in the inaccessibility of some tissues to sampling (eye, brain) and the probability that the disease will have manifested itself - perhaps irreversibly - by the time that the genetic defect is detected. Tests which directly detect the genetic lesion in the DNA overcome many of these limitations.

In the last five years, 400 or more genetic disorders have been mapped to a particular chromosome; of these, some 40 have been defined in depth and include Huntington's disease (chorea), cystic fibrosis and Duchenne muscular dystrophy. In each of these cases, a diagnosis can be made by a DNA-based test without knowing the gene's product or function. Further, the test can be used for preclinical diagnosis of a disease of late onset

(such as Huntington's), for prenatal diagnosis and for detecting carrier status.

1.2.4.2 IDENTIFICATION OF GENES ASSOCIATED WITH DISEASE

Importantly, detection of the gene by reverse genetics can lead to our understanding its function and its role in the pathology of the disease concerned. Examples where this has already occurred include Duchenne muscular dystrophy, chronic granulomatous disease (a white blood cell disorder) and retinoblastoma (a form of eye cancer). It can be expected that in the coming years many other disease genes will be isolated, including those involved in such disorders as colon carcinoma and severe mental retardation. The availability of a higher resolution genetic linkage map would simplify considerably the identification of the genes involved in many common diseases which, as mentioned above, are caused by multiple gene defects. Computational methods exist which permit the subpartitioning of genetic linkage data and identification of those genes contributing to multiple gene defects.

This information, when combined with that derived from overlapping clone libraries, will permit the rapid isolation and structural analysis of the genes concerned. Improved prediction of disease susceptibility will result. One of the most important disease categories is that involving heart and vascular disease.

1.2.4.3 GENE THERAPY

It is hoped that eventually it may be possible to correct a defective gene by inserting normal DNA directly into a cell - a process known as gene therapy. This ultimately depends on the discovery of safe methods of inserting the DNA and of a means of ensuring that the DNA corrects the target defect without producing any other adverse effects. Gene mapping will not have any direct effect on the prospects for gene therapy but the knowledge gained about the function of genes may have an indirect benefit.

1.3 SOCIAL AND ETHICAL CONSIDERATIONS

Information about human genetic make-up will increase enormously in the course of mapping the human genome; simpler, faster and less costly methods of screening for genetic susceptibility to disease will be developed. This will provide the possibility of therapeutic intervention to prevent the manifestations of disease. As genes are identified which are associated with an increased risk of common diseases, such as heart disease, diabetes and arthritis, population screening will become a possibility. In Western Europe, where there is a steadily ageing population and an associated ever-increasing cost of health care, the prospects both of cheaper testing and of earlier intervention making possible a decrease in morbidity are very attractive ones.

This enormous increase in genetic information does raise ethical questions. Improvements in diagnosis and risk prediction will

inevitably precede the development of therapeutic remedies, creating a growing gap between diagnosis and treatment. The information about an individual's genetic constitution will be more precise, more detailed and more easily obtained; it will benefit individuals by informing them about health risks but it could also be used to their detriment by third parties such as employers or insurance companies. Further ethical considerations will arise from the increased range of prenatal diagnoses which will become easily available - parents may seek to choose the sex of their children, for instance. These questions do not arise directly from the information which is collected but from the uses to which it is put. This implies that, independently of the technical possibilities and benefits offered by human genome analysis, it is vital that politicians and Society as a whole consider seriously the dilemmas presented. Aspects such as personal privacy, including the right of the individual to know or not to know, must be weighed against general health care considerations.

Dialogue and information transfer on the social consequences and ethical aspects of such research will be organised, in a systematic manner, with the various interested parties.

There is a unanimous opinion that, also for ethical reasons, there must be a rejection of any possibility of modifying the genetic constitution of human germ cells, even for purely therapeutic reasons; this topic will be excluded from this European Community research programme.

2. THE PREDICTIVE MEDICINE PROGRAMME : HUMAN GENOME ANALYSIS

The framework programme⁽¹⁾ originally stated that the technical content of the Predictive Medicine Programme would "mainly be oriented towards better knowledge of the human genome, immunity techniques (applicable to cancer, autoimmune diseases, infections), genetic engineering processes aiming at repairing DNA defects (e.g. in congenital diseases of genetic origin) and development of diagnostic test kits (e.g. for AIDS)". Since a choice has to be made, it seems appropriate to concentrate endeavours on definition of the human genome.

The programme will have these aims :

1) To achieve a high-resolution genetic map (at 1 to 5 centimorgan level) of the human genome. This will require an increase from 40 to 60 in the number of large families currently under study in Europe, the extra 20, where possible, to be families known to have a genetic modification of medical interest; the setting up of a network of 10 to 15 European laboratories with both the interest in and the capability of working with material from these families; the establishment of

¹ Framework Programme for Community Activities in the field of Research and Technological Development (1987-1991).
OJ N° L 302, 24.10.1987, p. 1-23.

one or two centres which would provide DNA prepared from the families to the members of the collaborating network, and also maintain and distribute to them a collection of the necessary probes; and consideration of the role of computing facilities both to enable participants to handle the collection and reduction of these data and also to carry out the preparation of the map.

2) To set up collections of ordered DNA clones either from the entire genome or from selected chromosomes. These ordered clone libraries, which might be produced in several centres, will require the establishment of facilities for maintaining the stocks of cloned DNA fragments, and for distributing DNA - free of charge - to a network of European laboratories interested in matching genetic material to these cloned fragments. A related project could be the sequencing of cDNA clones isolated independently and mapping them with an ordered clone library.

3) To improve advanced genetic technologies, with the further aim of spreading them more evenly among European laboratories. Examples are: production of new biochemical reagents (restriction enzymes), procedures for labelling DNA probes, amplification of genes, vectors for the transfer of human genes, methods of cloning long DNA segments, development of software to help sequencing, development of new strategies for sequencing, and creation of overlapping clone banks. The best way to support this kind of work is by research contracts, with priority given to collaborations between laboratories in different Member States working on a common subject, and also to those where there is participation by industrial laboratories. Communication between the contracting laboratories will be so managed as to achieve a collaborative research network.

In the process of improving the genetic map and creating the ordered clone libraries, due attention will be given to those chromosomes or chromosome regions known to contain the genes responsible for specific genetic diseases, especially where this will optimize the use of existing family material. There is also a need to learn more about the location and function of the currently unknown groups of genes involved in the multifactorial disorders which form the major part of the burden of disease and where risk prediction is particularly important. A pragmatic approach will be adopted to maintaining a suitable balance between these objectives, and to avoiding unnecessary overlaps with other genome analysis programmes.

A European pilot network for the prevention of one particular disease taken as a model would be a valuable goal for medical research in the Community, but this kind of project would need careful preparation (both in choice of target and of methods), and the setting up of a large-scale programme would be premature. However, the Predictive Medicine Programme could support the organization of a collaborative action for the preparation of a more detailed project. The development of an extensive European network might be an objective for the follow-up to this

programme. Diseases of particular interest in this respect might be cystic fibrosis and phenylketonuria.

3. JUSTIFICATION OF THE CONFORMITY OF THE PROGRAMME WITH THE OBJECTIVES AND METHODS OF THE EUROPEAN COMMUNITY

3.1 CONFORMITY WITH THE OBJECTIVES OF THE FRAMEWORK PROGRAMME OF RESEARCH AND TECHNOLOGICAL DEVELOPMENT

The Predictive Medicine Programme involves both technological research and training actions which will contribute to the achievement of many of the aims listed in the framework programme.

1) The activity "Quality of life" includes the Predictive Medicine Programme in its "Health" line. This aspect is obvious, because the development of Predictive Medicine will decrease the prevalence of many diseases which are very distressing for the patient and his family, (incapacitating or painful chronic diseases, often with a fatal outcome), as well as being socially very expensive for the Community.

2) The goal "to promote scientific research and technological development at Community level in order to strengthen the scientific and technological basis of its industry" is also explicitly addressed by the programme, which aims to promote advanced technologies with a high added value (e.g. DNA probes for diagnostic kits). Informed estimates of the potential European market for DNA probes in the next decade suggest that it is worth between 1,000 and 2,000 million ECU/year.

3) The goal of "participation of small and medium-sized enterprises" will also be met because most of the high technology enterprises which are able and willing to collaborate in the programme are in this category.

4) The goal of "harmonious development of the Community with a view to strengthening its economic and social cohesion" is especially important in this field, where the state of scientific development differs widely between Member States. The provision of a large number of grants for intra-Community exchanges of scientists, together with obligatory trans-national collaboration, will aim at promoting greater contact between individual scientists and at technology transfer to the currently less advanced laboratories in Member States.

For the future, a follow-up to this programme might include the launching of a large-scale operation concerning one of the main diseases of children (coordinated action including research, forecasting, prevention and treatment). This would be the best way to convince Europeans in general that the creation of a "Europe of health" is not merely a matter of public relations but a living reality.

3.2 JUSTIFICATION OF THE SCIENTIFIC CONTENT OF THE PROGRAMME: THE INTERNATIONAL CHALLENGE AND EUROPEAN SCIENTIFIC COHESION

The justification of the scientific content of the programme was set out in the discussion of the scientific basis for Predictive Medicine (cf. 1.2). It is argued that the ability to understand normal genetic function, and hence to recognize the abnormal and then predict disease susceptibility, rests on having access to a "human gene dictionary", i.e. a detailed map of the position of the genes on the chromosomes. This involves improvement of the genetic map and the physical map, and the setting-up of ordered clone libraries of the human genome - in the short-term perhaps of either selected chromosome regions or genes. The total sequencing of the genome, which is the next logical step, is still a remote goal because existing techniques are too slow to allow the sequencing of the 3,000 million base pairs in an acceptable time; a start could, however, be made on sequencing the cDNA.

The Predictive Medicine Programme would thus enable Europe to accept the challenge of remaining a vital international scientific force in human genetics.

The United States (US) report "Mapping and Sequencing the Human Genome"⁽²⁾ is a wide-ranging plan which includes the genetic map, the physical map, an ordered DNA clone library and, ultimately, sequencing. This impressive and prestigious programme - it has been compared to the "Apollo" project in the field of space - has captured the imagination of many scientists and politicians. For Japan, the "Human Frontier Science Programme" is a proposal for an international research programme in basic biology and the development of associated key technologies. At the time of writing the content of this programme has not been agreed, but it may well include a commitment to human genome analysis and/or the development of fast automatic DNA sequencing equipment.

Whatever view one may have of these projects, the European Community cannot remain indifferent. Furthermore, in the case of the American programme, active European participation is explicitly sought. The Predictive Medicine Programme provides the means for Europe to participate in an exciting project in one of the most advanced sectors of biological research.

3.3 RELATION TO OTHER COMMUNITY PROGRAMMES OF RESEARCH

Within the framework programme, the Predictive Medicine Programme will be coordinated with the following specific Community programmes of research and technological development, in order to avoid overlap and to ensure coherence of research efforts:

2 "Mapping and Sequencing the Human Genome", Report of the Board of Basic Biology Commission on Life Sciences, National Research Council. National Academy Press Publisher, Washington D.C., 1988.

- The "Medical and Health Research" Programme 1987-1991, and especially its area I.1.4 "Early detection and diagnosis of Cancer" which is closely related to the genetic field through the topic of oncogenes. Both programmes form an important part of the "Europe against Cancer" Programme,⁽³⁾.
- The "Advanced Informatics in Medicine in Europe" (AIM) programme, especially its Action Line II "Strengthening Europe's position in Medical and BioInformatics (MBI) and health care", which could give support for the development of effective communication and information processing within the proposed networks.
- The biotechnology programmes, especially the programme BRIDGE, being prepared at present, with which it would be carefully coordinated in respect of expression vectors, gene transfer and, more generally, the genetic engineering of animal and human cells.
- The "Environmental Protection" Programme, especially its research areas : "Environment and Human Health" and "Genetic Effects of Environmental Chemicals".
- The "Radiation Protection" Programme, especially its mutagenesis area.
- The "Stimulation" Programme, especially its "Biocommunication" area.

The programme will also benefit from synergy with other activities of the Community in the field of Information Technology and Telecommunication (IT&T).

3.4 PRECOMPETITIVE NATURE OF THE RESEARCH

The programme is one of basic precompetitive research. However, both new information and new materials of potential commercial value will result. It is generally agreed that all the mapping and sequence information should be freely available but that associated technological developments - of instruments, equipment, reagents or software - should be protected in the usual way by patents, copyright, etc.

3.5. MANAGEMENT AND EVALUATION

The existing CGC on Medical and Health Research should deal with the Predictive Medicine Programme and will advise the Commission in the manner defined in the Council decision creating CGCs. The programme will be submitted to evaluation procedures in accordance with the "Community plan of action relating to the

3 Decision of the Council and of the representatives of Member States of 7 July 1986, concerning an action programme of the European Communities against cancer. O.J. N° C 184, 23.7.87, p.19.

evaluation of Community research and development activities"(4). The CGC may wish to obtain specialized advice and meet in variable configurations; it may also wish to set up a Working Party to advise the Commission on the management of the Predictive Medicine Programme.

4. IMPLEMENTATION AND FINANCIAL MEANS

After the approval of the Medical and Health Research Programme, 15 million ECU remain on the sub-activity "1.1 Health" of the framework programme for the implementation of the Predictive Medicine Programme. Four main chapters of expenditure are proposed, for two networks (human genetic map and ordered clone library of the human genome), research contracts for work in advanced genetic technologies, and training grants. In addition there would be overheads and staff expenses. The indicative budget distribution is:

<u>CHAPTER</u>	<u>MODE OF ACTION</u>	<u>BUDGET</u> (Million ECU)
Improvement of the human genetic map	Support to a network of centralized facilities	4.0
Ordered clone library	As above	4.0
Research on advanced genetic technologies: e.g. reagents (restriction enzymes), gene detection, gene vectors, cloning, computer software, cDNA cloning and sequencing.	Research contracts	3.5
Grants (particularly post-doctoral, 100 scientist-years)	Grants	2.5
Scientific management, including evaluation		0.45
Staff		0.55
	TOTAL	15.0

4.1. NETWORKS OF FACILITIES

Progress with the human genetic map and the creation of ordered clone libraries of the human genome will be achieved most effectively by building on existing laboratories through the creation of networks. Efficient management, both of information and of biological materials, will be of prime importance for both.

4 Communication to the Council concerning a Community plan of action relating to the evaluation of Community research and development activities for the years 1987 to 1991.
O.J. N° C 14, 20.1.87, p.5.

actions, and it is proposed therefore to identify a central laboratory in each case to act as the focus for management, i.e. to become the centre of a network of laboratories.

Four million ECU will be used for the development of a European network for the improvement of the human genetic map, and another four million ECU for setting up a network of laboratories concerned with an ordered clone library of human DNA. These sums amount to approximately 10% of the sums suggested in the report of the US Office of Technology Assessment as appropriate for the US Human Genome Project. Although modest, at least in the exploratory phase of these activities, Europe's contribution to the international effort will be a significant one.

4.2 RESEARCH CONTRACTS

The basic research on advanced genetic technologies in the programme will be funded through cost-shared and marginal cost contracts with public and private institutions in the Member States. The contribution to research contract funding from the Community budget is estimated at 3,500,000 ECU. This figure is based on an estimate of 20 research contracts on advanced technologies, of about 150,000 to 200,000 ECU per contract (for three years) according to the size of the project. It corresponds to the expected response from European laboratories in the field. In the selection process, priority will be given to proposals involving a number of Member States and/or participation by private enterprises. The management of communication between the various contracting laboratories will be a first step towards the establishment of a European network in molecular genetics. Although the sum involved in each contract may seem small, the impact will be amplified by the complementarity of the programme to national research efforts. It should be noted that no single European country would be able to develop the complete range of research facilities and networks described above.

4.3. TRAINING

An average estimate of the requirements for training in the period under consideration is about 100 scientist-years, i.e. 2,500,000 ECU. Two aspects deserve special consideration:

- (i) Steps must be taken to ensure that those Member States which currently lack a capability in the techniques of modern molecular genetics are given the opportunity to acquire it;
- (ii) Only if there are very compelling reasons will scientists be permitted to train outside the proposed European networks; in order to smooth the path for the transfer of technology, and for the return of the individual newly-trained scientist, it is expected that 30 to 50% of such a scientist's time will be spent introducing the new techniques into his own laboratory setting.

4.4. SCIENTIFIC MANAGEMENT

Budgetary provision of 450,000 ECU is considered necessary for the external scientific management of the programme. This assessment, based upon an analysis of current annual needs in similar programmes, covers the expenses of meetings, participation in symposia, travel and subsistence costs of experts and Commission staff, visits to laboratories participating in the programme (two visits to each contracting laboratory, i.e. about 50 visits in the course of the programme), and the convening of six workshops during the same period. Funds are also included for the preparation of a follow-up to the present programme (studies and preparatory meetings) which might include inter alia the setting up, as mentioned previously, of a large network of research, forecasting, prevention and treatment for one of the major genetic diseases of children.

The cost for scientific management amounts to 3% of the total budget requested for the programme, including the cost of evaluation.

4.5 COMMISSION STAFF

Expenditure of 550,000 ECU for a staff of two is considered necessary for the execution of the programme. This estimate includes new staff only, i.e. one official of category A (93,000 ECU/year) and one of category C (37,000 ECU/year), inflation being estimated at 4% per year; this estimate includes only the minimal requirements necessary for the management of the programme.

4.6 SUMMARY OF FINANCIAL MEANS

	(Million ECU)
Networks of facilities	8.0
Research contracts	3.5
Training	2.5
Scientific management	0.45
Staff	0.55
	<hr/>
TOTAL	15.00

PROPOSAL FOR A COUNCIL DECISION

Adopting a research and technological development programme in
the field of health : Predictive Medicine :
Human Genome Analysis : (1989-1991)

THE COUNCIL OF THE EUROPEAN COMMUNITIES

Having regard to the Treaty establishing the European Economic
Community, and in particular to Article 130 Q (2) thereof,

Having regard to the proposal from the Commission⁽¹⁾,

In cooperation with the European Parliament⁽²⁾,

Having regard to the opinion of the Economic and Social
Committee⁽³⁾,

Whereas Article 130 K of the Treaty stipulates that the framework
programme shall be implemented through specific programmes
developed within each activity;

Whereas by its Decision of 28 September 1987⁽⁴⁾ the Council has
adopted a framework programme of Community research and
technological development (1987-1991), in which it provided for
activities to be undertaken in the field of health;

Whereas, for the evaluation of each specific programme and the
selection of Community actions, the framework programme sets out
criteria among which is that of contributing to the strengthening
of the economic and social cohesion of the Community, consistent
with the pursuit of scientific and technical quality;

Whereas two successive pluriannual programmes of research and
training of the European Economic Community in the field of

1 OJ N°

2 OJ N°

3 OJ N°

4 OJ N° L 302, 24.10.87, p.1.

biotechnologies⁽⁵⁾, of which the second is still in progress, have shown the possibility and usefulness of a Community action promoting the utilization of modern biology for scientific and industrial purposes;

Whereas the biotechnology programme presently in progress does not include some fields of research important for human health and the quality of life, for the industrial development of biotechnologies with medical aims and for the control of the increase of social and health expenses;

Whereas the framework programme has foreseen in its activity "Quality of life" under the "Health" line 1.1, the "Initiation of new activities relating to the development of predictive medicine";

Whereas, as a result, a specific research and technological development programme is necessary in the field of predictive medicine and, in particular, that it is necessary to:

- develop the basic technologies concerning the study of the human genome, as a prerequisite to a large number of developments in biotechnology for health, and to ensure the distribution of these technologies widely in European laboratories, and
- improve the resolution of the human genetic map and to refine the physical map by the creation of ordered clone libraries, as a basis for locating genes of medical importance and for a better general understanding of gene function;

Whereas the carrying out of the above-mentioned goals require the undertaking at Community level of actions aiming at:

- filling some existing gaps in scientific and technological knowledge, gaps which prevent the full development of the resources of modern biotechnologies in the medical field, and
- promoting, through concerted actions between private and public laboratories, European transnational cooperation aimed at speeding up the implementation of technologies already available while promoting European scientific areas which will encourage new approaches to be developed;

5 OJ N° L 375, 20.12.1981, p.1;
OJ N° L 83, 25.3.1985, p.1.

Whereas the Scientific and Technical Research Committee (CREST) was consulted on the following measures,

HAS ADOPTED THIS DECISION:

Article 1

A specific research and technological development programme for the European Economic Community in the field of Predictive Medicine : Human Genome Analysis, as defined in the Annex, is hereby adopted for a period of three years commencing on 1 January 1989.

Article 2

The amount deemed necessary for the execution of the programme is 15 million ECU, including expenditure on a staff of two persons.

Article 3

Detailed rules for the implementation of the programme are set out in the Annex.

Article 4

1. In the second year of the programme implementation, the Commission shall undertake a review of the programme and it shall report to the Council and to the European Parliament on the results of this review, together, if necessary, with any proposals for modification or prolongation.
2. An evaluation of the results achieved shall be conducted by independent experts and shall be published in the form of a communication to the Council and to the European Parliament.
3. The above-mentioned reports shall be established having regard to the objectives and evaluation criteria set out in the Annex to this decision and in conformity with the provisions of Article 2(2) of the framework programme.

Article 5

1. The Commission shall be responsible for the execution of the programme and shall be assisted in its implementation by the Management and Coordination Advisory Committee (CGC) on Medical and Health Research, set up by Decision 84/338/Euratom/ECSC/EEC⁽⁶⁾.

6 OJ N° L 177, 4.7.1984, p.25

2. The contracts entered into by the Commission shall regulate the rights and obligations of each party, and in particular the methods of disseminating, protecting and exploiting the research results.

Article 6

In conformity with Article 130N of the EEC Treaty, the Commission is authorized to negotiate agreements with non-member States and international organizations, particularly with non-member States taking part in European cooperation in the field of scientific and technical research (COST) and with countries which have concluded scientific and technical framework cooperation agreements with the Community, with a view to associating them fully or partially with the programme.

Article 7

This Decision is addressed to the Member States.

Done at , 1988

For the Council,

The President.

ANNEX

for a specific research programme in the field of health :
Predictive Medicine : Human Genome Analysis

1. OBJECTIVES

Use and improvement of new biotechnologies for risk-forecasting, early diagnosis, prevention, prognosis and treatment of some human diseases, and for a better understanding of the mechanisms of heredity.

2. CONTENT

Precompetitive Community research , setting up and reinforcement of networks of European laboratories, and training intended to allow the use of modern biotechnologies for the improvement of risk-forecasting, early diagnosis, prevention, prognosis and treatment of some human diseases (in particular hereditary diseases and cancers).

2.1 IMPROVEMENT OF THE GENETIC MAP OF MAN

Establishment of a Europe-based network, with a worldwide extent, for the collection of the DNA of large families, in order to provide free of charge to research scientists well-characterized genetic material and a set of probes to determine the location of the relative positions of genes on the chromosomes. Possible provision of computer facilities to handle the data.

2.2 SETTING UP OF AN ORDERED CLONE LIBRARY OF HUMAN DNA

Setting up of a European network of laboratories working on establishing overlapping cloned libraries, and support for limited sequencing of cDNA.

2.3 RESEARCH ON THE IMPROVEMENT OF ADVANCED GENETIC TECHNOLOGIES

New biochemical reagents (restriction enzymes, etc.). Improvement of methods for the detection and localization of genetic markers (techniques for labelling DNA probes, amplification of genes, etc.). Development of new vectors for the cloning of large DNA fragments and of procedures for the transfection of chromosomes. Development of model systems for the reproducible and stable expression of medically important genes both in vivo and in vitro. Development of new computer software for the collection and manipulation of data from genome sequencing and mapping.

2.4 TRAINING

Setting up a training programme to assist with the technology transfer of molecular genetics methods to Member States in which these techniques are currently underdeveloped and, in particular, the transfer of techniques into the clinical field.

3. IMPLEMENTATION

The programme shall be implemented through cost-shared or marginal cost contracts, support to centralized facilities and networks, training contracts, training grants, courses, consultations with national experts, organization of study-group meetings, participation in seminars and symposia, and publications.

The Commission participation may range from about 50% in the case of cost-shared contracts and may reach 100% in other cases.

Participants may be research institutions, universities, private enterprises, or combinations of them, located in Member States or in the third countries referred to in Article 6.

Projects must be carried out by participants from more than one country, and include at least one participant from one Member State.

- 7 -
EVALUATION CRITERIA

The Community plan of action relating to the evaluation of Community research and development programmes⁽⁷⁾ states that the milestones and objectives for each research programme have to be set out in verifiable and, where appropriate, quantitative form. These are listed below:

1. The long-term objective of this programme is to contribute to the fight against human diseases arising from genetic variation (including genetic diseases sensu stricto and many common diseases with a genetic component, such as heart disease and cancer), through forecasting the risk, early diagnosis, prevention, improvement of prognosis and, ultimately, therapy. The Commission proposes to achieve this objective by :
 - the management of a network of laboratories set up around European facilities for (a) the improvement of the human genetic map and (b) the setting up of ordered clone libraries of human DNA, either of the complete genome or of selected chromosomes, together with cDNA sequencing;
 - the launching of a programme of precompetitive research contracts on advanced genetic technology;
 - the setting up of a programme of training to increase the distribution of modern genetic technologies in Europe, and to improve technological know-how in European laboratories.
2. The primary short-term objective is that the programme should succeed in establishing the above-mentioned European networks of laboratories in the field of:
 - the human genetic map
 - ordered clone libraries of human DNA and cDNA sequencing
 - advanced genetic technologies.These objectives should be verifiable in 1990-1991.
3. Particular objectives to be attained within three years of the programme implementation are as follows:
 - 3.1 Concerning the human genetic map:
 - the present total of 40 well-studied large families which form the basis for the genetic map should be increased to 60 families;
 - genetic material from these families, and DNA probes, should be made available free of charge to interested European laboratories;

7 OJ N° C 14, 20.1.87, p.5

- a central facility should be set up to pool the results and establish an improved genetic map at the 1 to 5 centimorgan level;
- 3.2 The strategies for setting up ordered clone libraries of human DNA should be compared and an approach defined; facilities for maintaining the stocks of cloned DNA fragments should be established and the available clones dispatched free of charge to interested European laboratories.
- 3.3 Substantial improvements should be obtained in the following advanced genetic technologies:
 - New reagents, such as restriction enzymes,
 - Methodology for cloning large DNA fragments and for the transfection of chromosomes,
 - Gene vectors adapted to human cells in vitro,
 - Methodology for the detection of a particular gene in a cell (examples : how to make the use of DNA probes and gene amplification easier),
 - Localization, cloning and sequencing of new genes, especially those which are disease-related,
 - New computer software for the storage, collation and analysis of DNA sequence data.
- 4. In addition, the programme should ensure that the following general criteria are met:
 - 4.1 That throughout the execution of the programme, the projects should have taken adequately into consideration the complex ethical aspects of human genetics, avoiding any manipulation of human germ cells, and any risk to the environment.
 - 4.2 That medical developments are actually or potentially facilitated by the results obtained.
 - 4.3 That potential opportunities for commercial developments are obtained.
 - 4.4 That the overall technological level of the participating European laboratories has been increased.
 - 4.5 Taking account of the results of Community, national or private sector research activities in human genetics, the evaluation panel shall consider whether the Predictive Medicine Programme has contributed to the application of the results of the said activities in regions of the Community other than those in which the research was conducted.

FINANCIAL RECORD

PREDICTIVE MEDICINE PROGRAMME

1. RELEVANT BUDGET HEADING

- Post: Line 7312

- Title: Specific research and technological development programme in the field of health - Predictive Medicine.

2. LEGAL BASIS

Article 130 of the Treaty,
Council Decision.

3. DESCRIPTION OF ACTION AND OBJECTIVES

3.1 Description

Community programme (1 January 1989-31 December 1991) for research and training in predictive medicine, carried out by means of implementation of laboratory networks, research and training contracts, consultancies by experts, organization of workshops, contribution to symposia, and studies.

3.2 Objectives

The objectives of the programme are the following: Community research and technological development in molecular genetics to achieve a better understanding of genetic disease and hence improve the prospects for diagnosis and therapy.

4. JUSTIFICATION OF ACTION

The choice of predictive medicine as one of the targets for Community efforts in health matters takes into account three elements:

- The priority to be given to advanced technologies, and particularly to modern biotechnologies, the importance of which for European economic development is an indisputable fact.
- The seriousness of the human and social aspects of some diseases - in particular the common diseases which result from a combination of genetic factors interacting with the environment.
- The economic importance of health expenditure, which is constantly increasing in Europe and is a serious problem for the governments involved.

These three elements come together in the definition of a research action programme in the field of biotechnologies to be applied to predictive medicine: this field covers diseases often of long duration, socially expensive and very distressing in human terms, where it is now possible to anticipate their early detection. This will lead to their prevention and eventual treatment, through using the resources of modern biotechnology while stimulating European industry.

5. FINANCIAL INCIDENCE OF ACTION ON EXPENDITURES

(including costs for staff and expenses for administrative and technical management)

Million ECU

5.1. Total cost over the whole of the expected duration 30

5.2. Participation in funding:

- From the Community budget 15

- From national budgets and other sectors at national level 15

5.3. Multiannual Schedule of Commitment Appropriations and Payments from the Community budget

5.3.1. Commitment Appropriations

	1989	1990	1991	TOTAL
Staff	0.14	0.20	0.21	0.55
Administration	0.20	0.12	0.13	0.45
Contracts and training grants	1.66	6.68	5.66	14.00
Total	2.00	7.00	6.00	15.00

5.3.2. Payments

	1989	1990	1991	1992	1993	TOTAL
Staff	0.14	0.20	0.21	-	-	0.55
Administration	0.20	0.12	0.13	-	-	0.45
Contracts and training grants	0.46	2.98	5.36	4.10	1.10	14.00
Total	0.80	3.30	5.70	4.10	1.10	15.00

5.3.3. Methods of calculation

5.3.3.1. Staff expenditure

The staff requirements for the implementation of this programme are:

1 category A staff, (*)

1 category C staff. (*)

The above-mentioned calculation of staff expenses is based on the following annual figures for 1989-1991: 93,000 ECU for an A post, 37,000 ECU for a C post, inflation being allowed for at 4% per year. Expenditure for missions of Commission staff, for national experts and auxiliary staff are also included under this heading.

5.3.3.2. Expenditure for administrative and technical operation

This heading covers the expenses of meetings, participation in symposia, and travel and subsistence costs of experts, as well as the publication and dissemination of results and information, together with the cost of scientific and technical assistance whenever it proves necessary for the implementation of the programme.

5.3.3.3. Expenditure in respect of contracts

The budget foreseen for contracts and training grants (14 million ECU) should permit the conclusion of research and development contracts (for a total amount of 11.5 million ECU) with an average length of 2.5 years (the duration of the programme being three years, but allowance being made for the period of the call for proposals and the period of administrative negotiation), and for a variable amount according to the subject of the research.

With regard to training contracts and the short-term training grants, the method of calculation is based upon an average cost of 29,000 ECU per year per scientist. It is foreseen that approximately 20-22 training contracts and 10-15 short-term training grants will be allocated each year. The total amount devoted to training actions will be 2.5 million ECU.

6. Financing of expenditure

The appropriations required to cover the Community's contribution to this project are to be entered in the Community's future budgets.

(*) 6 months in 1989.

7. Type of Control

- Administrative control by the Director-General for Financial Control (DG XX) as regards budget implementation, and by the Contracts Division of DG XII.
- Scientific Control by the responsible officials in DG XII assisted by the CGC.
- Audit by the Court of Auditors in accordance with the provisions of the Treaty.
- Evaluation in accordance with the Community plan of action. See also the Evaluation Criteria in the Annex to the Council Decision.

8. Financial Record

Summary

Action : Research and technical development in Predictive Medicine.

	Expenses (Million ECU)	Staff		
		A	B	C
		(Number of posts)		
TOTAL:	15.	1	-	1.

STATEMENT ON THE IMPACT ON SMALL AND MEDIUM-SIZED ENTERPRISES,
COMPETITIVENESS AND EMPLOYMENT

Although not primarily aimed either at the support of small and medium-sized enterprises or at the solution of the problems of industrial competitiveness and employment, the Predictive Medicine Programme should nevertheless have some positive results in this respect:

1. The improvement in advanced genetic technologies should lead to worthwhile developments:
 - The production of new reagents (such as restriction enzymes) could provide a good opportunity for the commercialization of high added value substances.
 - The obtaining of new DNA probes, and the simplification of their practical use, should permit the development of new diagnostic kits. Informal estimates of the potential market for DNA probes in the next decade in Europe indicate that it is worth between 1,000 and 2,000 million ECU/year.
 - New techniques for gene amplification might also give rise to development of commercial kits.
2. Most of the high technology enterprises which are both able and willing to collaborate belong to the category of small and medium-sized enterprises, and should be stimulated by the implementation of the programme.
3. In the longer term, the Predictive Medicine Programme can be considered as a valuable contribution to an alternative approach to the problem of steadily increasing health expenditure in European society, and this should ultimately result in an increase in the competitiveness of the Community.