3. GENETIC TECHNOLOGIES AND HEALTH CARE APPLICATIONS

The goal of health care is to reduce the burden of disease on individuals and society. Existing and emerging health care technologies can be used to predict, diagnose, prevent, treat, or avoid genetic diseases. Well-established methods — based on inheritance patterns, diagnosis of symptoms, and interpretation of metabolite patterns — have been making a valuable contribution to health care in Canada for several decades. These methods will continue to play an important role.

New technologies have the potential to revolutionize health care, making it possible to identify individuals genetically predisposed to disease.

We are now in the early stages of a new era of genetic knowledge and technology that could result in the next quantum leap in our understanding of the nature and function of the human organism and the genetic mechanisms of disease. New DNA technologies make it possible to see the genetic material, to identify the particular sequence of each gene, and to correlate specific genes with their normal function in the human organism. Similar to the discovery of the microscope and x-ray, the new genetic technologies have the potential to revolutionize health care by making it possible to recognize individuals who have or are susceptible to diseases with a genetic component.[60]

There are four approaches to controlling genetic disease: prevention, gene therapy, treatment, and avoidance.

The ultimate objective is to understand the series of events leading from the cause to the clinical manifestations of disease, and then to use the knowledge to prevent or treat the disorder. There are four potential approaches to reducing the burden of genetic disease: disease prevention, gene therapy, treatment of incipient or established disease, and avoidance. Prevention is the ideal, and one way it can be achieved is by reducing the mutation rate. Where this is not possible, the options include prevention of the disease by controlling the associated risk factors, gene therapy to offset or correct the mutation, or treatment to address the consequences of the mutation. Finally, for families at known risk, a number of approaches are available to avoid the birth of affected children.

Canada has been a pioneer in the development of genetic technologies and services.

Accurate prediction of risk and accurate diagnosis of genetic disease are important components of disease control. Genetic diagnosis, screening, counselling, and treatment are the foundations of genetic health services, and Canada has been a pioneer in developing diagnostic, screening, and treatment technologies, and in establishing disease registries.

DNA Technologies for Diagnosis of Genetic Disease

Diagnosis of genetic disease (see Box 11) is based on:

Diagnosis can be made at many levels.

- chromosomal structure and number;
- DNA sequence (using gene probes or markers);
- the amount, character, and function of the gene's protein product;
- any measurable metabolic or biochemical effects that are characteristic of the disorder;
- all associated clinical manifestations.

Diagnoses based on clinical signs have major drawbacks.

Diagnostic technologies based on metabolic products or clinical signs have a major disadvantage: by the time such diagnosis is possible, the disease may be established and irreversible harm done. Moreover, these diagnostic methods do not pinpoint the precise genetic cause of the disorder and are therefore frequently less useful in establishing prevention and treatment programs.

Box 11
Examples of Methods Used in Genetic Testing

Indirect Tests

Maladaptive genes produce metabolic changes that can sometimes be measured to indicate the presence of incipient genetic disease. The substances measured may or may not be involved in causing the disease but are nevertheless associated with its presence.

Example: Phenylketonuria is a single-gene disease that causes mental retardation unless treatment with a special diet begins shortly after birth. The disease results from a genetic defect that prevents the breakdown of phenylalanine. As a consequence phenylalanine builds up in body fluids.

There are mass screening programs in place across Canada to detect disorders of phenylalanine metabolism in newborns. The screening test measures the level of phenylalanine in a blood sample taken from the newborn.

Gene Product Tests

The proteins derived from maladaptive genes can be measured directly to identify some diseases. The test must differentiate the abnormal form or activity of the protein from its usual form or activity.

Example: People with sickle cell anaemia possess an abnormal form of haemoglobin that causes red blood cells to change shape when the oxygen supply in the blood is below a certain point (e.g., during ordinary physical movement). The changed shape causes the cells to clump together, blocking blood vessels and interfering with circulation. The results can be fatal.

The abnormal blood cells produced by the sickle cell gene can be recognized by their abnormal sickle shape.

Chromosomal Analysis

Some genetic diseases involve very large alterations in the genetic material. Reliable techniques for examining chromosomes have been available for more than 30 years. Aberrations in number or structure (e.g., large insertions, deletions, or rearrangements) of chromosomes can be observed.

Example: Down syndrome is usually caused by the presence of an extra copy of chromosome 21. To reach a diagnosis, cells from an individual are treated so the chromosomes can be seen and distinguished from one another when magnified and photographed. This process is called karyotyping.

Recombinant DNA Technology

This technology can be used to establish the presence of, or potential for, disease involving genetic alterations as small as a change in one nucleotide. Recombinant DNA tests rely on the fact that a single strand of DNA will bind to another strand if it contains the complementary sequence of nucleotides.

Genetic Markers

The presence of, or susceptibility to, a genetic disease can be ascertained through use of genetic markers, even when the mutation causing the disease has not itself been identified. Markers are characteristic nucleotide sequences that are associated with, but are not necessarily the cause of, the disease or susceptibility.

Example: Huntington disease is a neurological disorder whose symptoms begin in adulthood and include uncontrollable limb movements and mental deterioration. Diagnosis is now possible in some families before the symptoms of the disease appear. The risk of developing Huntington disease can be assessed by finding out whether a DNA sample from a person at risk for the disease binds to specific DNA strands containing the relevant genetic marker. A person with one parent affected by the disease has a 50 per cent chance of inheriting the disorder; currently available DNA testing may reduce the uncertainty over whether that person has inherited the disorder to 4 per cent.

(continued on page 40)

Diagnostic technologies based on knowledge of precise DNA sequences have several advantages. Because the DNA is present from the moment of fertilization, tests based on analysis of DNA can identify risk before the onset of any symptoms or damage. In addition, since an individual's full complement of genes is present in the nucleus of every cell, it is always possible to examine DNA, whereas the enzyme or metabolite of interest may not be present in all cells. The gene may be active only in certain tissues and at certain times; the gene products may be located in tissues that are difficult to sample, such as the eye or brain. However, there are still several useful applications for tests based on gene products and metabolites (e.g., the test for Tay-Sachs disease and screening for phenylketonuria).

Diagnostic techniques based on precise DNA sequences have several advantages.

Technology now exists to scan genetic material for the presence of specific mutations. If the DNA sequence of the mutation causing a disease (or a predisposition to a disease) is known, the mutation can be detected using a gene probe. If the precise mutation is not known it can often be inferred using a genetic marker.[61] The first disease-specific marker — for Huntington disease — was identified in 1983. There are now markers for several hundred genetic disorders and the list is growing rapidly (see Box 12). In contrast with methods that identify the mutation itself (direct methods), diagnosis by association with markers (indirect methods) requires family studies.

If the DNA sequence causing a disease is known, it can be detected using a gene probe.

If the precise mutation is not known, it can often be inferred using a marker.

Screening and Diagnosis

Genetic screening is a search in a population to help identify individuals who may have or be susceptible to a specific genetic disease, or be at risk for having children with the disease. Screening programs may be used as a part of diagnosis and health care delivery geared to individual needs. Screening can assist in prevention or treatment of disease, help provide reproductive options for those at risk of having children with serious genetic disease, and be used as a research tool to study genetic variation, or specific mutations and their causes and health implications.[62]

Genetic screening identifies those individuals in the population who may have or be susceptible to a specific genetic disease.

Screening is an initial step; more precise tests are required later for definitive diagnosis. A variety of screening technologies and programs exist, targeted to different disorders, age groups, and stages of disease (including carriers of genetic diseases, fetuses, newborns, pre-symptomatic individuals and individuals with symptoms).[63] There are disorders for which screening programs can be effectively applied on a national level (e.g., phenylketonuria) or on a subset of the population (e.g., the screening of the Ashkenazi Jewish population for Tay-Sachs disease). The types of screening programs and Canadian examples are outlined in Appendix 3.

Screening is an initial step. More precise tests are needed for definitive diagnosis.

Most screening tests at present measure enzyme or metabolic effects rather than changes in the DNA itself. For example, the disease phenylketonuria (PKU) results from an inability to metabolize phenylalanine, one of the essential amino acids. This inability can result from a number of different mutations in the relevant genes. The prognosis and treatment vary according to the specific mutation. Screening of newborn populations based on a chemical test that detects an elevated level of phenylalanine in the blood will identify all those with an elevated level. More detailed testing of the identified individuals will indicate the precise cause and, hence, the most appropriate treatment.[64]

Most current screening tests look for biochemical effects rather than changes in the DNA.

Box 11 (continued)

Gene Probes

These work on the same principle as genetic markers but use strands of DNA that contain the actual sequence of the genetic mutation that causes the disease.

Example: Haemophilia A results from an inability to make factor VIII, a protein involved in blood clotting. Several genetic mutations causing haemophilia A have been identified and diagnosis using gene probes is now possible.

Box 12 Mutant Genes and Genetic Markers

Examples of disorders for which mutant genes have been characterized:

Cystic fibrosis
Duchenne muscular dystrophy
Haemophilia A
Phenylketonuria
Premature coronary artery disease
Retinoblastoma
Sickle cell anaemia
Tay-Sachs disease
ß-Thalassaemia
Von Willebrand disease

Examples of disorders for which genetic markers are available:

Adult-onset polycystic kidney disease
Familial Alzheimer disease (in some families)
Fragile-X mental retardation
Huntington disease
Myotonic dystrophy
Neurofibromatosis
X-linked retinitis pigmentosa

Box 13 Phenylketonuria Newborn Screening: An Example of the Effectiveness of Genetic Health Services

- The major effect of phenylketonuria (PKU) is mental retardation. Twenty-five years ago it accounted for 1 per cent of admissions to institutions for the retarded in Canada.
- About one in 10 000 newborns has PKU.
- A liver enzyme (phenylalanine hydroxylase) is deficient in a person with PKU. This enzyme converts phenylalanine, a substance absorbed from food, into other products. If phenylalanine is not converted, it accumulates in body fluids and causes brain damage. These effects can be prevented by a diet controlling the intake of phenylalanine. Diagnosis in the first month of life and continuous treatment thereafter prevents mental retardation.
- Women with PKU give birth to mentally retarded babies in the vast majority of cases unless they maintain a phenylalanine-controlled diet throughout pregnancy. Elevated phenylalanine levels in the mother interfere with the development of the child she carries.
- There is currently a register of women with PKU in Quebec and a study of the long-term effects of dietary interventions during pregnancy on the children of these women is under way.

Baby G was her parents' first child. She was born before newborn screening programs for PKU were established in Canada. At six months she showed delayed development, and at nine months uncontrollable seizures began. Investigations revealed she had phenylketonuria. Today at age 28 she is very retarded and requires custodial care.

(continued on page 42)

The ability to screen for and diagnose diseases with a genetic determinant is improving as a result of our growing knowledge of DNA sequences and gene-disease links.

Prevention

Genetic diseases can be prevented by reducing the mutation rate, controlling the risk factors, or compensating for the defective gene.

Prevention of genetic disease can be achieved in a number of ways.[65] All measures that will reduce the mutation rate constitute primary prevention; they include control of exposure to ionizing radiation and chemical mutagens. Secondary prevention addresses interacting risk factors for genetically predisposed individuals (e.g., controlling diet for those at risk for heart disease). Another form of secondary prevention compensates for the defective gene. For instance, the special diet given to patients with PKU is low in phenylalanine to prevent metabolic imbalance and associated brain damage (see Box 13).

However, our current knowledge is not sufficient to prevent most multifactorial diseases.

Our present understanding of the cause of mutations and of interactions between genetic predisposition and environmental risk factors in multifactorial disease is not yet sufficient to prevent most diseases. But the knowledge we do have already has some useful applications. For example, new knowledge about a risk factor (familial hypercholesterolaemia) for heart disease shows that a serious predisposition can be treated to reduce the occurrence of heart disease or improve the prognosis once the disease is present.[66]

Gene Therapy

Gene therapy involves correcting the defect in the genetic material.

Gene therapy for genetic disease is the attempt to correct the intrinsic defect in the genetic material. Correction of a genetic defect is a complex process.[67] The DNA sequence of the functional gene must be known and the genetic material available. A vector or agent is needed to deliver an effective dose of the therapeutic sequence to repair the natural condition, while doing no harm. The therapeutic DNA sequence must be introduced at the correct location in the overall DNA sequence, without causing damage to the DNA. The therapy must result in the desired effect in the right tissues at the right time.

There are two forms of gene therapy; one involves inserting the DNA sequence into germ line cells, whereas the other uses non-germ line (or somatic) cells. Changes to germ line cells can be passed along to subsequent generations. Changes to somatic cells affect the individual receiving the therapy, but the changes are not transmitted to offspring.

No proven gene therapies are available yet.

No proven gene therapies are available to cure genetic disease at this time. Intensive research will undoubtedly yield somatic cell gene treatments for some disorders. Potential applications include, for example, treatment of sickle cell anaemia and thalassaemia by reintroducing treated cells into bone marrow. Repair of germ line cells is unlikely in the foreseeable future, and for many diseases gene therapy may never be a viable option.

In September 1990 a four-year-old American girl became the first person to undergo somatic cell gene therapy in an attempt to treat a genetic disorder (severe combined immune deficiency disease). Research involving such treatment is under consideration for a number of other disorders.[68]

Box 13 (continued)

Her sister, R, was born three years after G. On the third day of her life, genetic testing showed that R also had phenylketonuria and treatment was started on the same day. Today, R is a university graduate and leads a normal, healthy life.

Canada has been in the vanguard for universal newborn screening, early diagnosis, and treatment of PKU. Through a national food bank for genetic patients, treatment is available for this disease and many others like it. Mental retardation due to PKU has virtually disappeared in Canada since the inception of newborn screening and access to treatment.

Box 14
Tay-Sachs Disease: Prenatal Diagnosis and the Choice for Healthy Children

- Tay-Sachs disease is a degenerative disorder that affects the neurological system, leading to blindness, mental retardation, and death in early childhood.
- In the general population the disease is rare, occurring once in approximately 400 000 births. But it is much more frequent in specific populations. Approximately one in 30 individuals of Ashkenazi Jewish descent carries one copy of the gene that causes the disease when present in a double dose. One in 3600 infants from this group has the disease. Tay-Sachs disease has also turned up with higher than average frequency in the French Canadian population.
- Studies of the Tay-Sachs gene have shown there are several different mutations causing the disease. Two different mutations occur in the Canadian Jewish population. Another mutation that has not been identified in Jews occurs in French Canadian families with a history of Tay-Sachs disease; and there are yet other mutations in French Canadians.

Mr and Mrs S's first child was a healthy boy. Their second born (B) was also a boy. At six months, B could not sit and his head was enlarging. He died in early childhood of Tay-Sachs disease: paralyzed, mute, blind, wasted, with a head too large for his body. There is no treatment for Tay-Sachs disease.

When the enzyme deficiency in Tay-Sachs disease was discovered in 1969, it became possible to identify carriers of the Tay-Sachs gene. Two large screening programs were established in Canada in the early seventies. Follow-up studies show that screened persons have positive views about the procedure. Carrier couples have used prenatal diagnosis to deal with the risk of having an affected child.

After Mr and Mrs S lost B they wanted to have another healthy child. Two pregnancies were monitored and both the fetuses had Tay-Sachs disease; the parents had the option to terminate and they did. They tried once again. Mrs S carried an unaffected fetus to term and delivered a healthy girl. She is now 12 years old. Meantime, the incidence of Tay-Sachs disease in Canada has fallen strikingly in the past two decades.

Gene therapy entails a risk to the individual receiving the therapy and a potential long-term risk to the species. All attempts to treat disease through gene transfer should be subject to guidelines equivalent to the Medical Research Council guidelines for both research involving human subjects and gene therapy research.[69] All proposed research and treatment technologies will have to be carefully evaluated.

Gene therapy poses a potential risk to individuals.

Treatment

When prevention is not possible, the identification of individuals at genetic risk or at the stage of incipient, instead of established, disease can lead to a better prognosis through earlier diagnosis and treatment, as in the case of some familial cancers. Understanding the cause of disease helps to tailor the treatment to the specific problem; this is true for pneumonia and equally true for heart disease, leukaemia, hypertension, and numerous other disorders. At present, there are relatively few effective treatments. This scarcity partly reflects the lack of knowledge about the cause and course of most genetic diseases.[70]

Earlier identification of susceptible individuals may improve treatment and prognosis.

Avoidance

The term avoidance is used to cover technologies and strategies to avoid the birth of children with serious genetic disorders. Avoidance strategies include deciding not to have a family, prenatal diagnosis (with the option of terminating the pregnancy if the fetus is affected), and alternative methods of having children, such as adoption, artificial insemination, or other reproductive technologies.[71]

Technologies and strategies are available to help avoid the birth of children with serious genetic disorders.

At this time, families faced with a high risk of serious genetic disorder in their offspring often regard prenatal diagnosis as the best option available to them for having healthy children (see Box 14). Technologies for prenatal diagnosis, although not available for all genetic disorders, are more advanced than technologies for prevention or treatment. However, some women choose not to undergo prenatal diagnostic testing. One reason is that the procedure may damage a normal fetus. Currently, the additional risk of losing the fetus is about one in 200 during amniocentesis and a little higher during chorionic villi sampling procedures.[72] Some who refuse the test do not want to be faced with a decision about terminating their pregnancy. Others simply do not consider it an option because of their views on pregnancy termination.

Prospective parents who are at risk often consider prenatal diagnosis their best option.

Prenatal testing may be refused for fear of damaging the fetus.

Factors affecting the willingness of women to undergo prenatal diagnosis include the degree of risk that the diagnostic procedure will harm the fetus, the accuracy of the diagnostic test, the probability that the fetus has the disorder, and the severity of the disorder and its health implications.[73]

The attitudes toward prenatal diagnosis highlight the need to develop diagnostic procedures that are less invasive and thus pose less risk to the fetus. Also required are methods that provide genetic information earlier in the pregnancy, perhaps even before fertilization. The ultimate objective is to remove the need for prenatal diagnosis by finding cures for genetic diseases.

There is a need for prenatal diagnostic procedures that give earlier results with less risk to the fetus.

Box 15
Thalassaemia: An Example of the Need for Continuing Research into Genetic Disease

- Thalassaemia is the most common identifiably genetic disease in the world. Approximately 3 per cent of the human population carries a thalassaemia gene.
- People inheriting one thalassaemia gene (carriers) have a harmless mild anaemia (thalassaemia minor). People inheriting two thalassaemia genes have a fatal anaemia (thalassaemia major).
- Current treatment for people with thalassaemia major includes blood transfusions and treatment to remove the resulting excess build-up of iron in the body's tissues. These measures prolong life into the third decade. In the future, gene therapy involving insertion of normal genes into bone marrow may prolong life further and reduce the need for treatments, which are painful.
- Thalassaemia genes have been perpetuated in human populations because they confer a selective advantage: they protect carriers from malaria.

At 27 years, H is the oldest person with thalassaemia in Quebec. His parents came to Canada from a malarial region of Europe. H recently married. He and his wife advocate the simple test that identifies persons carrying a thalassaemia gene. Carrier couples receive genetic counselling, and have the option of prenatal diagnosis to avoid having a child with the disease (a 25 per cent risk). The Quebec thalassaemia screening program now screens 80 per cent of high school students in the communities at high risk. The Quebec program is the largest on the continent and among the most effective in the world at avoiding thalassaemia disease. Meantime, H is waiting for advances in treatment or gene therapy.

Use of avoidance-related technologies requires careful consideration of the ethical implications. A caring society will also ensure that the availability of prenatal diagnostic technology does not diminish efforts to develop better disease treatments and therapies (see Box 15).

Counselling

Counselling provides information and support; the primary responsibility of the counsellor is to the patient.

The purpose of genetic counselling is to provide the medical and genetic facts, to describe the risk of recurrence of disease and the options to avoid recurrence, and to assist the individual or family in coping with this information.[74] The Canadian approach to counselling recognizes the autonomy of the client and the primary responsibility of the counsellor to the client, rather than to the species or future generations.[75]

Additional guidelines are needed to deal with some difficult counselling issues.

The Canadian College of Medical Geneticists has a good general policy relating to counselling,[76] but more comprehensive guidelines dealing with specific topics, such as confidentiality and full disclosure, are needed. The report of the U.S. President's Commission, *Screening and Counseling for Genetic Conditions* (1983), provides an excellent outline of specific topics from which additional guidelines particular to the Canadian context could be developed as required.[77]

Current Technology Limitations

The use of genetic diagnostic technology does have its limitations.

The use of DNA-based diagnostic technology is growing but has, and probably always will have, limitations because of the complexity of the human genome and the consequences of natural genetic variation. Whereas some mutations (e.g., sickle cell anaemia) are common and the related test can be applied across a large population, most mutations are less common, even rare. In cases where the mutation is not yet known, the patient must be studied in the context of his or her family. For this, other family members must be available and willing to cooperate.

In many cases, genetic testing is based on linked genetic markers. But the presence of the marker does not mean that the disease-causing mutation is present. The frequency with which the marker and the disease-causing mutation are found together depends on the proximity of the marker to the gene.

Even if a specific mutation is present, it is not always possible to predict whether the individual will develop the related illness or how serious the disease will be.

Even evidence that the mutation is present does not necessarily mean that the individual will develop the illness. Moreover, while some genetic diseases have a predictable outcome, others vary in their severity, age at onset, and prognosis. For example, expressions of the gene for neurofibromatosis vary from a few coffee-coloured skin spots to major tumours and seriously handicapping systemic involvement. These differences may arise from the effects of other genes or from environmental factors that either amplify or suppress the effect of the neurofibromatosis mutation. Differences may also reflect the fact that a number of different mutations are "lumped together" as a single condition.

Even in disorders where the specific mutation and subsequent effects are well known, it does not necessarily follow that an effective treatment is available. At present, the ability to identify an individual at risk for genetic diseases exceeds the ability to prevent or effectively treat the disease. This limitation is likely to continue for some time and implies that knowledge of

Our ability to identify susceptible individuals may continue to exceed our capacity to prevent or treat their diseases.

presymptomatic genetic disease or risk of disease is not necessarily beneficial. Although the genetic technologies hold great promise, we do not know yet how successful researchers will be in developing technologies to prevent or treat most genetic diseases. In 50 years we may have significantly more cures and treatments. Or we may primarily have more and better diagnostic and predictive capability.

Some disorders will remain difficult or impossible to treat for the foreseeable future.

The genetic diseases receiving the greatest attention from researchers are the classic, single-gene, inherited disorders and common disorders. The classic, single-gene disorders are of interest because diagnostic and treatment technologies should be easier to develop, at least in theory. Common disorders are of interest because their technologies have the potential for wide application. Genetic tests and therapeutics for the majority of genetic diseases, which are neither classic nor common, may be a long time coming.

Uncertainty

Genetic tests are most useful when they translate uncertainty into certainty.

The risk of occurrence of disease is often expressed in terms of probability. Such risk statements cause difficulties in several ways. Tests that simply indicate a probability of the disorder being present, or a degree of risk, are of less help to the person who must decide on a course of action than tests that confirm the presence or absence of the disorder. Uncertainty is generally undesirable; certainty — even of having a disease — has its advantages if courses of action are available. As well as pertaining to whether an individual has a disorder, certainty can refer to the conditions under which a susceptible individual will develop the disorder, or to the disease outcome. The better the information, the more informed the choice the individual can make.

Risk statistics may be difficult for a patient or family to understand.

But understanding a risk, and then going one step beyond that to accept or reject the risk, is difficult for most people. Numerous factors influence how an individual interprets risk of disease.[78] Our understanding of risk statistics and our attitudes toward the disease are major variables.

An individual's perception of risk is affected by the manner in which risk information is presented.

The manner in which probability is presented also affects an individual's perception of risk. The following two statements, which describe the same degree of risk, can be viewed quite differently by prospective parents: "There is one chance in four that your child will be born with a genetic disease," versus "There are three chances out of four that your child will not have this disease."

The development of better predictive technologies will help reduce the uncertainty. We need technologies that turn uncertainty into clear statements about the presence or absence of the disorder, or the predisposition to the disorder. However, some uncertainty will still remain over whether individuals susceptible to a particular disease will actually get the disease. There is also a need to help individuals to understand the meaning of risk and to assess the trade-offs associated with uncertainty.

Prerequisites for Use of Technologies

The objective of genetic health care should be to deliver reliable and cost-efficient services.

All technologies delivered in Canadian health care systems should provide reliable and cost-efficient services. Decisions about provision of a specific health technology are influenced by the prevalence of the related disease in the

population, the severity of the disorder, social attitudes, ethical considerations, treatment options, the availability of other technologies, and costs.

To be useful, genetic technologies must first indicate reliably whether the mutation is present or absent. The technology must offer the individual real benefit in terms of disease prevention, treatment, avoidance, or planning. The number of useful applications of genetic technologies is growing.

Services should offer a real benefit in terms of disease prevention, treatment, avoidance, or planning...

A major component of a compassionate health care system is its care and support for individuals who are either sick or at risk of developing a disease. Efficacious genetic technologies and services are, and should continue to be, evaluated and delivered in the context of a caring society.

...and should always be delivered in the context of a caring society.

Technology Assessment and Economic Implications

In conjunction with the development of genetic technologies, there is a need for effective review protocols. Any introduction of new genetic tests and treatments for clinical purposes should involve a technology assessment that takes into consideration benefits, safety, ethical implications, and economic consequences, as well as technical matters. Primary requirements for any technology are efficacy and reliability. For genetic tests sensitivity, specificity, and predictive value should be carefully assessed (see Box 16).

Proposed genetic services should be assessed with consideration to safety, efficacy, ethical and economic implications, as well as technical considerations.

The cost implications of new technologies and services have to be considered carefully. Effective cost assessments provide a framework for making decisions on allocation of health care funds. Key elements in economic evaluations include:[79]

- well-defined questions that can be answered by the assessment;
- selection of an appropriate form of evaluation;
- consideration of a comprehensive range of alternative technologies or services;
- evidence of the effectiveness of the technologies or services being compared;
- identification of the range of costs and benefits of each alternative;
- measurement of the costs and benefits in appropriate units;
- adjustment of costs and benefits to reflect their monetary value at the time they are realized;
- an allowance for uncertainty in costs and benefits and estimation of the degree of uncertainty.

There are a number of key elements that must be addressed in economic analysis.

Long-Term Implications

Will genetic technologies have a significant effect on the characteristics and health of future generations? There is no easy answer. The technologies have potential long-term implications through prevention and treatment of genetic disease, and through identification and control of mutation-causing agents.

Consideration should be given to the long-term implications of genetic technologies.

As a species we have for thousands of years encountered — and sometimes introduced — new selective forces in the evolutionary equation. All medical care alters natural selection by assisting individuals in overcoming the effects of disease and leading normal and healthy lives, be it with hearing aids, insulin, or

Box 16
Sensitivity, Specificity, and Predictive Value of Screening Tests

Test Result	Disease Categories of an Apparently Well Population	
	Target Condition Present	Target Condition Absent
Positive	A True Positives: Individuals with the condition and with positive test results	B False Positives: Individuals without the condition but with positive test results
Negative	C False Negatives: Individuals with the condition but with negative test results	D True Negatives: Individuals without the condition and with negative test results

An ideal test would detect only individuals with the condition and would identify all such individuals. Measures of a test's validity include:

Sensitivity = [A/(A+C)] = the probability that the test will correctly identify individuals with the condition.

Specificity = [D/(B+D)] = the probability that the test will correctly identify individuals without the condition.

Positive Predictive Value = [A/(A+B)] = the probability that a person with a positive test will manifest the condition.

Negative Predictive Value = [D/(C+D)] = the probability that a person with a negative test will not manifest the condition.

The closer that each of these measures is to 1.0, the more useful the test.

kidney transplants. Improvements in health care are increasingly postponing death and in that sense are resulting in preservation and transmission of "maladaptive" traits.

Genetic techniques that interrupt the transmission of dominantly inherited diseases will abruptly reduce their incidence. But effective treatment of diseases that would otherwise result in death prior to reproductive age will increase the frequency of the gene in the population. The situation is more complex for recessively inherited disorders. The incidence of such diseases may decrease rapidly through counselling, prenatal diagnosis, or curative treatment, but the number of individuals who are carriers could increase.[80] However, it would take many generations for the number of carrier-carrier matings to rise significantly, allowing time to work toward treatment or prevention of the disorder.

The technologies may reduce the incidence of both dominantly and recessively inherited diseases but increase the number of carriers.

The implications to health in the carrier of "silent" genes vary with the gene, and are still largely unknown. Carriers can have a health advantage. Carriers for blood diseases such as thalassaemia and sickle cell anaemia are resistant to falciparum malaria; this advantage has helped maintain these mutations in human populations. In other cases carriers may be at a health disadvantage. For example, carriers for ataxia telangiectasia appear at increased risk for breast cancer.[81]

The health implications of carrier status vary from gene to gene.

Identification of mutagenic agents in the environment may lead to long-term improvements in human health. Regulations for the control and use of potential mutagens will help maintain an environment compatible with present and future health, and are in the interests of the human race.

Identification and control of potential mutagens may lead to long-term improvements in human health.

Another broad area with potential long-term implications is the development and use of genetically engineered material. Genetic engineering technologies have applications in diagnosis and treatment of disease, but there are serious potential hazards associated with genetically engineered material. In recognition of these hazards, some national and international guidelines and regulatory controls for responsible research, use, and handling of such materials have been put in place (see Box 17). Upgrading of guidelines and controls as appropriate to ensure safe practices must continue.

Development and use of genetically engineered materials also have potential long-term implications.

Guidelines for Screening and Testing

There is a need for guidelines to ensure that genetic screening programs and testing are appropriate and effective. Conditions that should be met by genetic screening programs include:

- that the objectives be clearly defined (whether for effective medical intervention, for family planning, for research, etc.);
- that screening be part of an integrated program that includes counselling, diagnosis, medical management, follow-up, outcome evaluation, and so on;
- that the genetic tests be sensitive, reliable, precise, and predictive;
- that the decision to be tested be based on individual consent (or parental consent in the case of minors), and that all services be available on a voluntary basis, with the exception of some screening programs for minors. In the case of certain serious, treatable disorders for which screening and treatment pose no significant risk, the state may intervene and waive the need for parental consent to ensure that universal screening and access to

Genetic screening programs should meet certain conditions.

Box 17
Guidelines and Regulatory Controls for Genetically Engineered Materials

- Research involving recombinant DNA technology and materials is covered by laboratory biosafety guidelines developed jointly by Health and Welfare Canada and the Medical Research Council. The guidelines recognize that it is impossible to predict all the potential engineered organisms or products used or produced in the course of research. Potential risks associated with recombinant DNA research should be assessed on a case-by-case basis by the biohazards committee at the laboratory proposing to undertake the research. Containment levels appropriate to the level of hazard should be adopted.

- The Medical Research Council guidelines on gene therapy research address long-term implications.

- Therapeutic and diagnostic products have potential long-term implications both because of their intended use and because of the possibility that engineered materials might be released into the environment during the manufacturing process. The licensing of pharmaceuticals, including those involving recombinant DNA in the process or final product, is controlled under the Canada Food and Drugs Act. Licensing takes into consideration safety and efficacy of the product, but does not deal with the issue of environmental release during commercial production.

- The development of commercial products to diagnose genetic disorders may involve use of recombinant DNA materials. Under the Medical Devices Regulations (Canada Food and Drugs Act), the Bureau of Medical Devices must be notified regarding the sale of such products. No information is required regarding safety, efficacy, or environmental implications.

- The environmental release of genetically engineered material is covered in biotechnology regulations currently (1991) being formulated under the Canadian Environmental Protection Act. The regulations will apply to new products, including genetically modified organisms, intended for deliberate environmental release or large-scale production. Release of engineered organisms could also be controlled through development of industry-specific provincial pollution control regulations and guidelines; no such regulations or guidelines are currently in place.

- Many research and commercial applications of recombinant DNA fit readily into existing regulatory mechanisms. Some regulatory modifications are under way to address new issues. However, new products and applications will continue to arise. Biotechnology-related products, processes, and issues that do not readily fit into the existing assessment and control mechanisms are dealt with through the Interdepartmental Committee on Biotechnology, which addresses safety and control requirements for new issues.

early, effective treatment are available. In such cases there is a duty to inform parents;
- that the results and effects of all screening programs be reviewed and evaluated, and that programs be modified as appropriate;
- because screening programs for specific ethnic groups could be used, or perceived to be used, in a repressive or stigmatizing manner, public education should emphasize that everyone is at least a carrier of genes with the potential to adversely influence health status, and that each population has its own particular genetic risks;
- that guidelines for screening programs be adopted by consensus, disseminated, and updated when necessary.

The CCMG has adopted professional and ethical guidelines for delivery of genetic services.

The Canadian College of Medical Geneticists (CCMG) has adopted professional and ethical guidelines for the delivery of genetic services.[82] In conjunction with the Society of Obstetricians and Gynaecologists of Canada, the CCMG has also developed recommendations related to the delivery of prenatal diagnosis of genetic disorders. Comprehensive guidelines will be required to deal with specific issues. For instance, in the case of prenatal diagnosis, a report of the Royal College of Physicians of London could serve as a model for the development of Canadian guidelines. (The report's recommendations are provided in Appendix 4.)