Current & Future Technology Applications in Biotech

- Human Genome Project (HGP)
- Gene Therapy
- Cell Therapy
- Transplantation
- Pharmacogenomics
- Transgenics:
  - Animals
  - Plants
- Bioremediation & Environmental Applications
- Proteomics, Microarrays, and Analytical Applications
- Multisource Biotech
- Ethical Considerations
Project was extremely controversial since there was public funding of patented discoveries. The HGP was jointly funded by National Institutes of Health (NIH), Department of Energy, and the Wellcome Trust (a British philanthropy separate from Glaxo Wellcome [now GlaxoSmithKline]). Celera used a 'shotgun' sequencing approach while NHGRI used linear sequencing; Celera finished first but had more missing data.

**Human Genome Project (HGP)**

- Collaboration of the National Human Genome Research Institute (NHGRI) and Celera Genomics
- June 27, 2000: completed first 'draft' of DNA sequencing of human genome - 3.1 billion base pairs; sequencing needs repeating at least six times to assure sequence accuracy
- Genomic theory is that human DNA is 99.9% identical across all races and gender, but differences reside in SNP (single nucleotide polymorphisms) that account for hair, skin, body type, disease predisposition, etc.
- **Potential Targets?**
  - Original estimates of 100,000 genes were overstated; conservative estimates were 3,000 - 10,000 genes with about 482 potential drug targets
  - In 2002 (post-genomic era), revised estimates of drug targets was lowered to 272
  - Recent survey by Curagen predicts 58,000 genes with 8,000 potential targets broken out as:
    - 4,990 small molecules
    - 2,329 antibody targets
    - 794 protein therapeutics
Gene therapy delivery: viral vs. non-viral vectors - risks vs. benefits for either one. Non-viral vectors include liposomes and adipocytes. Technology developments may include other human cell lines, human cell components, or bacterial binding vectors.

PKU: Incidence of 1 per 12,000 white children. If not treated early can result in severe mental retardation. The disease is caused by a defect in a gene producing a liver enzyme. If detected early enough, the child can be placed on a special diet for their first few years, but this is very unpleasant and can lead to many problems within the family.

SCID: The first case was David, known as "the boy in the bubble" born in 1971; he died 12 years later after receiving a bone marrow transplant that, unknown to doctors, carried a silent Epstein-Barr virus. In contrast to David's story, Ashanti – who was born in 1986 with an autosomal recessive form of severe combined immune deficiency – spent her early years with every environmental microbe attacking her body. She was treated with a synthetic enzyme called PEG-ADA, which gradually decreased in efficacy, and in 1990 she became the first patient to receive gene therapy in an approved protocol. She is now almost 13 years old and living a normal life. Using a technique known as "non-myeloblative conditioning" means you don't wipe out the bone marrow — you just give one of the drugs used for a transplant, at a much lower dose, to make 'space' for engineered marrow to seize, expand, and grow better.

Parkinson's Disease: Preclinical testing in monkey and mouse models of using glutamate decarboxylase gene attenuated neuronal over activity resulting from dopamine depletion. Gene therapy technique uses adeno-associated virus to carry a gene called GAD into the brains of rats who have chemically induced Parkinson's. GAD is responsible for making GABA (gamma-amino butyric acid) - a putative neurotransmitter that is released by nerve cells to slow activity. Clinical trials slated to start soon - based on promising preclinical data; 12 advanced patients to be selected and monitored with PET, MRI, and clinical signs for a year.

Transplantation: gene therapy may prevent acute and chronic rejection of transplanted tissues by introducing either new genes that are important in preventing rejection (e.g., co-stimulatory blocking molecules or immunosuppressive cytokines) or antisense nucleic acids to block the production of rejection-associated molecules such as adhesion molecules. The delivery of genes by gene therapy vectors that encode foreign donor antigens (alloantigens) might also be an effective means of inducing donor-specific unresponsiveness (immunological tolerance) in the recipient, perhaps eliminating the requirement for potentially harmful whole-body immunosuppression.

Neuronal Repair: Damage to the central nervous system is debilitating and can be life threatening. Each year, approximately 600,000 people suffer a stroke, and some 10,000 more damage their spinal column as a result of fractured vertebrae. Most of these individuals—there are 4.4 million stroke survivors and about 200,000 spinal cord injury survivors in the United States alone—will have a lifelong neurological deficit. The estimated lifetime cost for the care of a single 25-year-old quadriplegic is over $2 million, without taking into account lost earnings, shortened life span, and reduced quality of life. Research to date suggests that adult stem cells from adipose tissue may have potential application in the area of neuronal regeneration.
Bone Repair: Bone-fixation devices are currently made of metal or biological products, such as demineralized bone powder. There are no cell-based therapeutic products for fracture repair on the market. Studies are under way to determine if adult stem cells from adipose tissue can form biologically functional bone in animals.

Cartilage Repair: Adipose-derived adult stem cells have been shown to produce the proteins needed for cartilage formation in a laboratory setting. Studies are now under way to determine if they can differentiate into functional cartilage cells (chondrocytes) in living animals.

Cellular Carriers for Gene Therapy: Gene therapy is still in its infancy, but it has potential applications in all reversible genetic diseases. Preliminary data indicate that adult stem cells from adipose tissue can express foreign genes, thus suggesting, in principle, that they can serve as cell-based carriers for gene therapy. By manipulating the adipose-derived adult stem cells ex vivo, it may be possible to avoid many of the adverse effects seen with virus-based gene therapy approaches.
Gene Therapy: Future Applications

**Year 2010**
- Genetic testing will be available for 25 common conditions such as colon cancer.
- Interventions will be available to decrease a person’s risk of most of these genetic diseases. For example, patients found to be at high risk for colon cancer will be told to undergo regular colonoscopies beginning at age 25.
- Gene therapy will prove successful for several conditions.
- Most doctors will begin practicing genetic medicine.
- Pre-implantation diagnosis will be widely available.
- The limitations of genetic testing will be fiercely debated, such as what is appropriate?
- Effective legislative solutions to medical records privacy will be in place in the United States.
- Access to genetic screening and therapies remains inequitable, especially in the developing world.

**Year 2020**
- Gene-based designer drugs will be available for common conditions such as diabetes and high blood pressure.
- Cancer therapy will be targeted to the molecular fingerprint of the tumor.
- Pharmacogenetic applications will be standard practice for the diagnosis and treatment of many diseases.
- Geneticists will learn how to perform germ-line gene therapy without affecting other genes and hence human germ-line therapy will be declared safe and ethical.
Gene Therapy: Future Applications

Year 2030
- Genes involved in aging will be fully catalogued.
- Clinical trials will be underway to extend maximum human lifespan.
- Use of a full computer model of human cells will replace laboratory experiments.
- The complete genomic sequencing of an individual will be routine, cost less than $1,000.
- Major anti-technology movements will be active in the United States and elsewhere.

Year 2040
- Complete genome-based health care will be the norm.
- Individualized preventive medicine will be available and largely effective.
- Illness will be detected earlier, before symptoms develop, by molecular surveillance.
- Gene therapy and gene-based drug therapy will be available for most diseases.
- The average lifespan will reach 90 years.
- The debate about the role of humans in taking charge of their own evolution grows louder. Who is to decide what is a good characteristic or trait?
- Genes involved in aging will be fully catalogued.
- Clinical trials will be underway to extend maximum human lifespan.
- Use of a full computer model of human cells will replace laboratory experiments.
Ethical issues concern mainly use of fetal tissues and xenografts from non-human primates as well as current political debate on the use of stem cells from embryonic sources. Safety is an essential consideration of any new therapy and regulatory considerations for cell therapy are those for biological preparations. The federal government has approved the use of federal funds for the study of stem cells, but expenditures are restricted to research on embryonic cell lines derived before August 9, 2001. A larger source of cell lines is essential for productive research. Many of the cell lines in existence on August 9, 2001, are of poor quality or are under tight commercial control and patent protection, in some cases by companies with proprietary interests. Most or all of the embryonic stem cell colonies have been mixed in the laboratory with mouse cells for the purposes of early-stage research. The mice from which the feeder cells were obtained were not raised according to safety standards set by the Centers for Disease Control and Prevention. There are concerns that the ethnic and racial diversity of the cell lines may be limited. The Institute of Medicine has warned that over time, cell lines in tissue culture change, typically accumulating harmful genetic mutations. Furthermore, researchers are unsure if these cell lines were developed from embryos donated with appropriate informed consent. Without such assurances, scientists could be in danger of being sanctioned by the ethics committees at their universities or research institutions.

HESC implanted in mice can produce teratomas containing tissue of all these germ lineages, demonstrating retention of the ability of their pluripotent state. Using specific cell markers, the stem cell differentiation can be characterized and tracked to ensure continued regeneration of specific differentiated cells. Differentiation of HESCs to multipotent progenitors and then to more restricted cells - identified by genotypic and phenotypic markers - has been shown. Examples include differentiation to more mature lineages, such as astrocytes (characterized by G-FAP), neurons (characterized by beta-tubulin), and oligodendrocytes (characterized by GAL-C). Tyrosine hydroxylase-producing cells (suggestive of dopaminergic neurons) have been generated. The derived neurons express action potentials, which indicate functional activity. Transplantation studies in Parkinsonian rats are ongoing. HESC-derived hepatocytes show morphological similarity to endogenous hepatocyte cells and express albumin, alpha 1-trypsin, CK18, CK19, lack alpha-fetoprotein production. These cells also produce glycogen. Analysis of basal metabolic activity shows the cells are inducible in response to toxic compounds and stable with maintenance of expected activity.
The number of companies involved in cell therapy has increased remarkably during the past few years. More than 200 companies have been identified to be involved in cell therapy and more than 141 of these are profiled in the report. Important collaborations in the area of cell therapy are shown. Collectively, the current value of markets for cell therapy technologies is about $18.2 billion and is expected to increase to $32.1 billion by the year 2005 and $78 billion by the year 2010. The largest expansion will be in diseases of the central nervous system and cancer. Skin and soft tissue repair as well as diabetes mellitus will be other major markets.

The concept of using adult stem cells from adipose tissue for these purposes is novel, yet practical. Adipose tissue is abundant and easily accessible as the "waste" generated by liposuction, the procedure many people undergo to remove unwanted fat. No other tissue-harvesting procedure, with the exception of blood donation, has such an abundant source and can be obtained by such relatively noninvasive and low-risk methods.

Cell Therapy: Potential Applications

- Therapeutic Applications
  - Nervous System: Paralysis, Parkinson's Disease, etc.
  - Cancer
  - Cardiac Disorders: Myocardial infarction and heart failure
  - Diabetes mellitus
  - Diseases of bones and joints
  - Genetic disorders
  - Wounds of the skin and soft tissues

- Stem Cell Sources
  - Embryonic stem cells are among the first to appear as a fertilized egg develops. They have the ability to develop into most of the specialized cells in the human body including blood, skin, muscle and nerve cells. They also have the capacity to divide and proliferate indefinitely in culture.
  - Adult stem cells collected from adipose tissue (via liposuction): two pounds of fat will yield about 500 million adult stem cells in 2 weeks—cells that can then be used immediately or cryopreserved in a manner that maintains their potential to grow and differentiate.
  - Their use is politically charged in the US, causing restrictions on development of new cell lines. In August 2001, President Bush restricted federal funding for any stem cell research to already established lines – via the Human Embryonic Stem Cell Registry. Although federal funding does not impact private development of these lines.
Organ Transplants. Introduction of immunosuppressive molecules into allografts via gene therapy.

- Gene transfer and gene therapy techniques are being developed to introduce immunosuppressive molecules into allografts in order to prolong allograft survival and produce tolerance. Investigation of transfer technologies, screening of candidate molecules, and definition of the cellular and molecular consequences of gene transfer are current areas of active investigation.

Bone marrow transplantation (BMT)

- Clinically feasible method for permanently replacing deficient Arylsulfatase A (ARSA) activity in Metachromatic Leukodystrophy (MLD) patients by migration of donor bone marrow derived cells into disease target organs.

- Hematopoietic stem cells (HSC) are efficiently transduced by lentiviral vectors in the absence of stimulation, allowing for the maintenance of full engraftment capacity, self-renewal and normal lineage specification.
### Organ Transplant Statistics

<table>
<thead>
<tr>
<th>Organ Type</th>
<th>Waiting in the U.S. *</th>
<th>Number of Transplants Performed in US in 1998 **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>4,063</td>
<td>2,345</td>
</tr>
<tr>
<td>Heart / Lung</td>
<td>224</td>
<td>47</td>
</tr>
<tr>
<td>Kidney</td>
<td>44,031</td>
<td>12,346</td>
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<tr>
<td>Lung</td>
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<tr>
<td>Liver</td>
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<td>4,487</td>
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<tr>
<td>Pancreas</td>
<td>823</td>
<td>248</td>
</tr>
<tr>
<td>Kidney / Pancreas</td>
<td>961</td>
<td>973</td>
</tr>
<tr>
<td>Intestine</td>
<td>117</td>
<td>69</td>
</tr>
<tr>
<td>Pancreas Islet Cell</td>
<td>182</td>
<td>N/A</td>
</tr>
<tr>
<td>Total Patients</td>
<td>67,050</td>
<td>21,197</td>
</tr>
</tbody>
</table>

- Over 1,000 people added to national waiting list each month; a person every 15 minutes
- 14 people die per day waiting for organ transplants; in 1998 over 5,171 patients died while waiting
Numerous partnerships have already been established such as the Roche/Affymetrix alliance and collaborative development efforts between Abbott Diagnostics and Pyrosequencing. Although the FDA has cleared only two products for in vitro diagnostic (IVD) use, additional pharmacogenomic products will become available in the clinic within the next one to two years; tests used in psychiatry, diabetes, and asthma will likely have a longer development time frame.

The following examples demonstrate how knowledge of a patient’s genetic profile may be used to provide a personalized medication or dose:

- Patients with a mutation in the gene coding for CYP2D6 will show little or no analgesic effect from codeine. Codeine is metabolized to its active metabolite, morphine, by CYP2D6.
- Patients suffering from Alzheimer’s disease who have the E4 subtype of the gene coding for apolipoprotein E (apoE E4) are less likely to benefit from the drug tacrine. ApoE E4 affects cholinergic function in the brain.
- Trastuzumab, a monoclonal antibody, binds to a product of the HER2 gene to treat breast tumors that overexpress HER2. Tamoxifen, on the other hand, is not used in women whose tumor does not express the gene for the estrogen receptor.
- Cholesteryl ester transfer protein (CETP) functions in the metabolism of high-density lipoprotein (HDL). A genetic variant of the gene coding for CETP is correlated with higher CETP plasma levels and lower plasma levels of HDL. One study showed that pravastatin slowed the progression of coronary atherosclerosis in men who carried this genetic variant.
- Women who carry the blood-clotting variant factor V Leiden and were taking oral contraceptives were shown in one study to have a dramatically increased risk of developing cerebral-vein thrombosis.
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency, the most common inherited enzymopathy, leads to hemolysis after ingestion of oxidant medications (antimalarials, sulfonamides, some analgesics and nitrofurans). Without G6PD, the red blood cells are not protected from oxidative damage and hemolytic anemia results.
- Patients taking desipramine or imipramine (metabolized to desipramine) may develop toxic plasma concentrations if there is a mutation in the gene coding for CYP2D6. CYP2D6 leads to the conversion of desipramine to an inactive metabolite.
It was not until the 1980s that direct transfer of foreign DNA into plant cells was convincingly demonstrated. The technique used, gene transfer using the soil bacterium Agrobacterium tumefaciens and the production of crown galls, is still the most commonly used technique. Crown galls are undifferentiated tumors of plants that are caused by infection by A. tumefaciens and can be propagated in the lab. It was eventually discovered that Agrobacterium contains plasmids that attach to plant DNA and transfer genes to the plant chromosomes. Once researchers realized that the plasmids were doing natural genetic transfer, it was a fairly simple matter to create artificial transgenic plants, though not necessarily to transfer desired genes. There are now nine other direct DNA transfer methods, many of them difficult to use or inefficient (including one technique that, in its earliest version, involved shooting DNA coated metal pellets into plant cells using an actual handgun).

There are now many genetically modified plants, the most famous of which include the FlavrSavr tomato, Roundup-ready corn, and golden rice. In his final chapter, the author discusses problems with the biotech revolution, including costs to Third World farmers, possible ecological impacts, the public’s general distrust of large multinational companies involved in biotech, and the fears of Europeans that transgenic plants would change the flavor or texture of their cuisines. While this discussion is clearly biased in favor of the benefits of plant biotech, the author is very fair and open about the failures of the Green Revolution (the last effort of developed countries to improve Third World agriculture) and understands the lingering skepticism of farmers and others about the potential benefits of this new revolution.
Anti-GMO lobby group GE Free New Zealand attacked the decision saying said the risks of genetically modified organisms getting into the food chain or crossing into other species was too great. Genetic modification is a controversial issue in New Zealand where the economy is heavily dependent on agricultural produce and markets itself as having a green, pristine environment. The recently re-elected, Labor-led coalition government plans to lift a ban on the commercial release of genetically modified organisms next year, a stand that caused the environmentalist Green Party to refuse to join Labor in power.

Transgenic animals have the potential for dramatically reducing animal use,” stated transgenics pioneer Gordon in his plenary lecture (at the 1997 CAAT [Center for Alternatives to Animal Testing] Conference). “Mice can be modified in order to be made susceptible to viral infections usually limited to primates, so that the testing of vaccines such as the polio vaccine can be adapted to rodents. Disease models can be created with foreknowledge of the specific genetic change underlying the disease state. This advance has the potential of reducing the screening of animals for spontaneous mutations that mimic human disease, and the experiments required to characterize such spontaneous mutations.”

Transgenics: Animals

- Chief applications include:
  - generation of organs for transplant with reduced rejection rates
  - animal lines for generating ‘humanized’ proteins and antibodies
  - ‘improved’ attributes (e.g., more meat, milk, eggs, etc.)

- Estimated market for animal-derived transgenics is $30 B by 2010, such as:
  - Chickens: Ability to produce proteins in eggs
  - Goats: Genzyme Transgenics developing cloned goat lines for production of antibodies, proteins, clotting factors [antithrombin III], etc. in milk. Cost of production is said to be $105/gram vs. $500-$1500/gram per conventional methods.
  - Cattle: New Zealand scientists slated to create transgenic cattle for multiple sclerosis study (as of 10/1/02). See political fallout in notes below. A particular problem with cattle is the potential for BSE/TSE infection.

- Politics
  - Some factions that once radically resisted all animal experimentation are now more circumspect in the applications for science vs. sheer exploitation.
  - Also, political and news highlights have improved animal care and justification for uses.
  - However, animal ethicists are conflicted over the utility of genetically modified animals. For example, transgenic animal models have the potential for reducing overall animal use by employing more elegant evaluations.
  - Firms that use transgenic animals should be very sensitive to the negative politics and potential litigation surrounding products from this area.

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Shaken by experiences including its disastrous mission in Somalia, the US has concluded that it lacks appropriate weapons for peacekeeping and other "military operations other than war". To address this problem, the US has embarked on a program to develop new non-lethal weapons to control both armed enemies and civilians. Militaries and domestic law enforcement agencies in the United States and elsewhere are closely following this research and, in some instances, are participating. The non-lethal weapons research detailed here raises questions about protection of civil liberties, particularly freedoms of thought and expression, and US compliance with arms control agreements including the Chemical Weapons Convention and Biological and Toxin Weapons Convention. The first report, on calmatives and malodorants (Backgrounder #8), was published in July 2001. The third report will be published later in 2002 and will address new crowd control technologies.

In the United States (and other countries), heavily polluted sites are a common legacy of military and industrial operations. To address environmental problems including radiation, hydrocarbon, and chemical contamination, a number of US military projects seek to develop microbes to remove pollutants. For example, the explosive TNT (2,4,6-Trinitrotoluene) is both a pollutant and a component of many weapons. Bioremediation studies have identified several microbes that degrade TNT (10) and, reportedly, TNT inoculated with one of these loses 50% of its explosive charge every seven days, (11) a rate that would quickly render infected stores useless.

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**Bioremediation & Environmental Applications**

- **Non-military applications include:**
  - 30 years ago, first patent on a genetically engineered organism was for a microbe that could degrade oil (for use in oil spills). Since then, only limited development in commercial bioremediation outside of military applications and thin profit margins of environmental firms.
  - Purifying stormwater runoff prior to adding to natural water streams.
  - Purifying and degrading animal waste (e.g., hog lagoons) prior to other treatments.
  - Reducing heavy metal content in drinking water and waste effluent.
  - Use in artificial marshland habitats for clarifying water.
  - The few such non-military projects are a Stanford University effort to make a single microbe to remediate both carbon tetrachloride and heavy metals, and Michigan State University research on a genetically engineered microbe to degrade polychlorinated biphenyls (PCB).

- **Military applications (development of offensive weapons that destroy materials):**
  - Raises serious arms control concerns for the Biological and Toxin Weapons Convention (BTWC) and, because of the environmental dangers such organisms pose, for the Cartagena Biosafety Protocol, the principal international agreement on movement of genetically modified organisms. The United States is the world leader in the development of genetically engineered anti-material organisms and a federal law prohibits their military use. The enforcement of this law is weak and under threat.
  - Genetically engineered anti-material agents ("GAMAs") are part of a second tier of biotechnological products that may be abused in warfare.
  - Major focus is on cleaning up radioactive waste.
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Proteomics, Microarrays, and Analytical Applications

- Technologies that constitute molecular diagnostics:
  - first-generation amplification like DNA probes and fluorescent in situ hybridization (FISH),
  - second-generation biochips and microfluidics,
  - next-generation signal detection such as biosensors and molecular labels
  - discovery of therapeutic molecules,
  - screening and diagnosis of patients, and
  - optimization of drug therapy.

- Diagnostic uses in cancer
  - identification of proteins and biochemical pathways involved in carcinogenesis
  - elucidation of the information flow of the cell or “software” of protein pathway networks and circuitry (Why does a cell go berserk?)
  - For example, the SELDI ProteinChip® Array technology forms the basis of a clinical proteomics platform designed to expedite discovery, validation, and characterization of cancer biomarkers at all stages of cancer progression. Being able to detect cancer progression early in turn allows for the possibility of more effective treatment.
There is a very real risk in medicine that biotechnology advancements will only be available to a select class of patients that can afford it. This class separation—already seen with AIDS therapy unavailable in developing countries—is a lightning rod for civil unrest, protest, and acts of terrorism as well as sabotage against the governments controlling the property and manufacturers. As costs rise, there will be more acts of intellectual property infringement, counterfeit drugs, smuggling, and other means to capitalize on the "haves" vs. the "have nots."

Multisource Biotech

- Multisource biotech grows more compelling due to:
  - Cost constraints of socialized medicine formularies and government subsidization
  - Improved analytical prowess allowing accurate SAR (structure-activity relationships)
  - Improved manufacturing processes that increase safety (e.g., viral validation, replacing animal-origin material with recombinant-derived material, improved screening) or improved process reliability
  - Clinical history with a variety of recombinant biotech product classes
- Limited primarily by politics and economics:
  - No regulatory pathway recognized that allow two different manufacturers to compare products other than in head-to-head clinical trials.
  - Patent reform is key to identifying discrete areas held by innovator technology vs. patents that overreach the breadth and scope of what's been demonstrated (e.g., ever-greening, Festo decision, etc.)
- Approvals will be more circumspect than generic drug applications and should allow for a tiered approach of demonstrating comparability. Where differences are noted, the comparator needs supporting data why that wouldn't impact purity, potency, safety, and efficacy.
- Labelling will be a critically reviewed area since most innovators will fight any use of analytical comparisons to be stretched to clinical safety and efficacy.
Ethical Considerations

- **Stem Cells**: What is "life" and what ethical considerations should be applied to the sanctity and reverence of that concept?
  - A major debate over the use of embryonic stem cells is that they are cultured from the aborted fetuses, although some use in vitro fertilization cells as well. Religious leaders vehemently maintain conception is the beginning of "life" and despite legal availability of abortion (which they also protest), the harvesting of cells is an anathema to their beliefs.

- **Pharmacogenomics**: ethical issues abound regarding the data and its applications.
  - What is normal? Is a predisposition to a disability or disorder the same as the real thing? If not, who decides and how are those handled by families and insurers?
  - Are disabilities diseases? If so, do they need to be cured or prevented? Who will pay for this?
  - Does searching for a cure demean the lives of individuals presently affected by disabilities?

- **Gene Therapy: Somatic vs. Germ Line**
  - If this is performed in the adult cells of persons known to have the disease, is that more or less ethical than germ line gene therapy (which is done in egg and sperm cells and prevents the trait from being passed on to further generations)?
  - In cases of somatic gene therapy, the procedure may have to be repeated in future generations. However, what about the unknown risks to future generations?
  - Preliminary attempts at gene therapy are exorbitantly expensive. Who will have access to these therapies? Who will pay for their use?