

**Table 1.** (Continued)

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Dec 1, 1999	Chromosome 22 is the first human chromosome to be completely sequenced. Biotechnology stocks skyrocketed.
Jan 10, 2000:	A day before the International Human Genome Conference, Celera announces using shotgun sequencing to cover 1.8x80% of the human genome, more cost effective and less time-consuming than HGP can do the work.
Jan 11, 2000	International Human Genome Meeting in San Francisco. Participants talk a lot about Celera. NIH and Celera enter into confidential negotiations to share data.
Mar 6, 2000:	NIH-Celera negotiation breaks down.
Mar 12, 2000:	U.S. President Bill Clinton and U.K. Prime Minister Tony Blair jointly announce that genetic data should be freely available. News media misconstrue their message. Biotechnology stocks crash.
Mar 13, 2000:	The U.S. Patent Office announces that Bill Clinton speech is misconstrued. It does not forbid patent applications.
April 6, 2000:	Venter and Waterston appear at a U.S. Congress Hearing. Celera announces completion of 90% of first human genome draft.
May 8, 2000:	To avoid the dilemma of January Celera announcement, HGP announce entering the second phase of sequencing a day before the Cold Spring Harbor Meeting.
June 26, 2000:	The U.S. and U.K. jointly announce completion of the first draft of the human genome.
Feb 12, 2001	Science publishes online the data from the private sector, Nature <sup>10</sup> publishes online data from the public sector.

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## 5 A Small Step For Genome, A Giant Step For Humankind

Deciphering the human genome has been an epic task. Scientists have used the most powerful computers and developed a new generation of automated machines to read the 3 billion chemical letters. The task has been likened to putting a man on the moon. But is it?

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<sup>10</sup> <http://www.nature.com/genomics>

While this metaphor is useful in political and funding purposes, the comparison does not convey the true significance of HGP. The moon shot affected a negligible number of people substantially and had only negligible effect on a substantial number of people. The impact of HGP will be substantial and it will affect a substantial number of people.

**Table 2.** Comparison and contrast of moon shot and the human genome project.

<b>Moon Shot</b>	<b>The Human Genome Project</b>
<ul style="list-style-type: none"> <li>• An interdisciplinary project involving scientists, engineers, legal experts, and social scientists.</li> <li>• The project could not have begun without concurrent advances in other fields. In this case, in engineering such as rocketry and material science.</li> <li>• A huge project that requires involvement of a nation or an international effort. This is a U.S. effort.</li> </ul>	<ul style="list-style-type: none"> <li>• Ditto. In this case, mostly wet bench scientists and computer scientists.</li> <li>• Ditto. In this case, high throughput instrumentation and computer technology.</li> <li>• Ditto. In this case, it is an international effort, involving 5 main and 11 contributing centers worldwide. Celera Genomics is a private enterprise.</li> </ul>
<ul style="list-style-type: none"> <li>➤ A project that will amount to nothing if the project is half-complete. It will serve no one any good to shoot a rocket half way up the sky and have it come through Earth’s atmosphere in a flurry. Though not a moon shot, the Superconducting Super Collider project is a case in point.</li> </ul>	<ul style="list-style-type: none"> <li>➤ A project that something will be learned even if the project should have to be abandoned. We will still obtain DNA sequences from which we can find genes.</li> </ul>
<ul style="list-style-type: none"> <li>➤ It affects the lives of very few, mostly those who go up to the moon.</li> </ul>	<ul style="list-style-type: none"> <li>➤ It will affect everyone, especially those who are genetically predisposed to diseases.</li> </ul>
<ul style="list-style-type: none"> <li>➤ This is a Cold War competition between the U.S. and the USSR, mainly politically motivated. A classified project.</li> </ul>	<ul style="list-style-type: none"> <li>➤ This is a peacetime effort. It is motivated by the goal to improve quality and productivity of life. A non-classified project.</li> </ul>
<ul style="list-style-type: none"> <li>➤ It opened up the stratosphere commons. To date, U.S. has six American flags on the moon to mark U.S. “territories”. This is an exploratory project.</li> </ul>	<ul style="list-style-type: none"> <li>➤ It opens up the biosphere commons, and a floodgate of patentability of biological commons. This is a deciphering project.</li> </ul>
<ul style="list-style-type: none"> <li>➤ It was funded primarily by the U.S. government. Direct benefits from the project will not be gained for a long time to come.</li> </ul>	<ul style="list-style-type: none"> <li>➤ It is funded both by the public and the private sectors. The private sector is interested in the information, an asset in the current prevailing knowledge-based economy.</li> </ul>

Table 2. (Continued)

➤ Private sector involvement was from the high tech sector to manufacture parts for the project, mostly from aerospace companies. Only the most advanced developed countries can spearhead in this project.	➤ Private sector involvement is from high-tech, medium-tech, and low-tech sectors. Almost any underdeveloped, developing, and developed countries can be a part.
➤ Highly capital intensive. Only a few qualify to be truly a part of the mission.	➤ Mostly labor intensive. It involves long hours, repetitive and laborious production-line effort.
➤ Being exploratory in nature, the end result is unknown.	➤ The end result is known, a huge sequence of about 3 billion letters.

### 5.1 Impacts and Implications — Deciphering the Rosetta Tablet

Knowledge of the human genetic sequence will help scientists understand more about the causes of human ailments and fashion powerful new treatments. But some fear the knowledge will be misused because the human genome can give scientists potent tools to manipulate human traits and behavior before society has sorted out the implications. Elbert Branscomb, Director of the Joint Genome Initiative, Walnut Creek, said, “For the first time we have rolled back the big stone and peered into the sepulcher with our tiny flashlights, reading the sacred script off the tablet.” Branscomb was apparently referring to the famous Rosetta Tablet found in 1799, which has consumed vast amount of energy of many a scholar to interpret the hieroglyphic texts.

#### 5.1.1 Genetic Engineering

Genetic engineering will allow us to correct misspelled individual words in *Encyclopedia Humanica*. In this regard, it is important to make a distinction between two very different kinds of genetic engineering:

1. Somatic genetic engineering — when we correct misspellings in *Encyclopedia Humanica*, the corrections will be made in the cells carrying out the particular function. The alterations will have been made in only the individuals and will not be passed into future generations.
2. Germline genetic engineering — when we correct misspellings in germ cells that create new individuals, we are rewriting *Encyclopedia Humanica* for the new traits will be passed on to future generations and the books will have been altered permanently.

Though genetic engineering has been a subject of debate because of its ethical implications, the full utility of genetic engineering will probably not be felt for a few decades.

## 5.1.2 Humpty Dumpty

As the genomes of yeast, nematode, fruit fly and many other organisms have been deciphered, and the first draft of the human genome has been completed, there is going to be a tidal wave of diagnostic tests that will tell patients their predisposition, but offer no therapeutic cure. The gap between diagnostics and therapeutics is no secret to biotechnology insiders. This is what the community calls the Humpty Dumpty dilemma.<sup>11</sup> This makes anxiety the most likely first byproduct of the genomics revolution.

**Table 3.** Human chromosomes and the associated diseases.<sup>12</sup>

<b>Chromosome Number</b>	<b>Diseases</b>
Chromosome 1	Alzheimer's disease, Glaucoma, Prostate cancer,
Chromosome 2	Colon cancer, Memory, Muscular dystrophy
Chromosome 3	Colon cancer, Dementia, Lung cancer
Chromosome 4	Ellis-van Creveld syndrome, Huntington's disease, Parkinson's disease
Chromosome 5	Colorectal disease, Diastrophic dysplasia, Spinal muscular atrophy
Chromosome 6	Dyslexia, Epilepsy, Schizophrenia
Chromosome 7	Cystic fibrosis, Diabetes, Obesity
Chromosome 8	Burkitt lymphoma, Hemolytic anemia, Werner syndrome
Chromosome 9	Chronic myeloid leukemia, Malignant melanoma, Tangier disease
Chromosome 10	Cowden disease, Hermansky-Pudlak syndrome, Jackson- Weiss syndrome,
Chromosome 11	Albinism, Diabetes, Sickle-cell anemia
Chromosome 12	Darier disease, Inflammatory bowel disease, Rickets
Chromosome 13	Breast cancer, Pancreatic cancer, Retinoblastoma
Chromosome 14	Alzheimer's disease, Goiter, Leukemia/T-cell lymphoma
Chromosome 15	Angelman syndrome, Juvenile epilepsy, Marfan's syndrome
Chromosome 16	Chron's disease, Familial Mediterranean fever, Polycystic kidney disease
Chromosome 17	Breast cancer, Cataract, Muscular dystrophy
Chromosome 18	Niemann-Pick disease, Pancreatic cancer, Tourette's syndrome
Chromosome 19	Arteriosclerosis, Diamond-Blackfan anemia, Myotonic dystrophy
Chromosome 20	Bubble-boy disease, Creutzfeldt-Jakob's disease, no immunity to viruses

<sup>11</sup> This is attributed to Eric Shulse, director of the molecular diagnostics unit at PE Biosystems, Foster City, who said "You know Humpty Dumpty is crashed, that's your diagnostic, but it's a lot harder to put Humpty Dumpty back together again."

<sup>12</sup> Genome by Matt Ridley, National Institutes of Health, Department of Energy Joint Genome Institute (JGI).

**Table 3.** (Continued)

Chromosome 21	Amyotrophic lateral sclerosis, Down syndrome, Usher syndrome.
Chromosome 22	Chronic myeloid leukemia, DiGeorge syndrome, Ewing's sarcoma
X Chromosome	Colorblindness, hemophilia, Gout
Y Chromosome	Gonadanal dysgenesis

### 5.1.3 Single Nucleotide Polymorphism

The first draft of the human genome will show genetic sequences that are considered normal. The next step, already underway in public and private laboratories, is to look for the many slight differences in the genetic codes of any two humans. This is called single nucleotide polymorphisms or SNPs. SNPs will help explain why some people, and not others, are susceptible to complex diseases likely caused by the interplay between environmental factors and genetic factors. Drug giants are already talking about using SNPs to tailor remedies to individuals, i.e., personalized medicine, and thereby lessen the side effects coming from one-size-fit-all medicine.

### 5.1.4 Patentability of Biocommons

The patent office interpreted the Chakrabarty decision<sup>13</sup> as permitting gene patents. The logic is that if living organisms can be patented, small pieces of chemicals isolated and purified from them should be patentable. Isolated and purified are the key words. After the Chakrabarty decision, biotechnology firms raced to isolate, purify, and patent genes. For example, genes that produce insulin, growth hormones and blood production factors have been granted patents. Today, hundred of genes have been patented, both by private firms and universities. As John Doll, chief of the biotechnology division at the U.S. Patent and Trademark Office in Washington, DC explains, "The 100,000 or so genes (we now know that this estimate of the number of human genes is way too high) in the human body are clumped inside the nucleus of every cell. Envision a piece of steel wool, made up of filaments wound round and round. The entire steel wool would be the human genome. A gene would be a single tiny snippet. It is not just floating around. Man goes in, clips it out of the genome, isolates it, gives it to us and says this is what it does."<sup>14</sup>

The rush to decipher the human genome has triggered a money-making free-for-all akin to the claim-jumping disputes of the Gold Rush era. The only difference is that instead of racing to the land office, gene hunters stake their claims at the U.S.

<sup>13</sup> Sidney A. Diamond, Commissioner of Patents and Trademarks, petitioner, v. Ananda M. Chakrabarty et al., *65L ed 2d 144*, June 16, 1980, 144–47.

<sup>14</sup> Tom Abate, "Gene-patent opponents not licked yet, debate about human genome far from over", *San Francisco Chronicle*, March 20, 2000, pp. B1.

Patent & Trademark Office (PTO). A patent will provide them a 20-year monopoly on any drug or therapy that comes from the gene.

**Table 4.** Names of institutions holding patents on genes as of Y2000.<sup>15</sup>

<b>Institutions</b>	<b>Number of Patents</b>
U.S. Government	388
Incyte Genomics	356
University of California	265
SmithKline Beecham	197
Genentech	175
Eli Lilly	145
Novo Nordisk	142
Chiron	129
American Home Products	117
Isis Pharmaceuticals	108
Massachusetts General Hospital	108
Human Genome Sciences	104
University of Texas	103
Institut Pasteur	101

The PTO now faces a backlog of 30,000 biotechnology patent applications. Many of the gene patent applications involve genes which were discovered using machines and their functions are not known. Some observers argue that if monopoly is given over a machine-discovered gene of unidentified function, the patent holder can demand royalties from researchers who put the gene to work. This might discourage their innovation. After years of bickering from various sectors, the PTO is now proposing to change the rule. To win a patent, applicants will have to describe a “substantial, specific and credible” use for their gene. Using this guideline, the huge backlog of 30,000 patent applications can essentially be categorized into three classes:<sup>16</sup>

1. The first class includes genes isolated in the laboratory (i.e., wet biology) whose purpose is likely to be known. Wet biology has been used to patent genes for more than twenty years. There is no controversy over this class.
2. At the other extreme is a class which includes “naked” DNA sequences. These are machine-generated gene discoveries. The functions of the genes are not known. The new guideline rules them out.

As the controversy over “nakedness” festers, biotechnology companies get smarter and overcome the legal rhetoric by employing software to analyze the structure to deduce functions of machine-discovered genes. These “naked” sequences now

<sup>15</sup> Source: PricewaterhouseCoopers.

<sup>16</sup> Tom Abate, “Call it the gene rush — Patent stakes run high”, *San Francisco Chronicle*, April 20, 2000, pp. A8.

become “*in silico*” sequences because their functions are deduced via computational means. A third class of patent applications begin to arrive on the scene:

3. In the middle ground between wet-biology discovered gene patent applications and machine-generated gene patent applications is the large number of applications that are machine-discovered genes but they are not “naked” DNA sequences because their functions have been computationally derived.

The crux of the matter is that the recent huge increase in the number of applications is due largely in part to speed of *in silico* analyses. Though the exact number of applications falling into the third category is unknown, it is easy to infer that the majority of the 30,000 applications do fall into this murky area.

### 5.1.5 Ethical, Social, and Legal Issues

Just as genetic knowledge can be used to better medicine, the project is fraught with potential perils. The knowledge can also be misused. On top of the list is genetic privacy. What is to stop employers, insurers, or anyone else from using genetic information in decision-making, leading to discrimination or genetocracy. This incidentally has become a main issue in the U.S. Y2000 Presidential Campaign.

Then there is the issue of perfect babies. The concept of what is perfect and what is abnormal are often merely reflections of the cultural stereotypes and prejudices of ourselves and our society.<sup>17</sup> The whole definition of normal could well be changed — the issue becoming not the ability of the child to be happy, but rather our ability to be happy with the child.<sup>18</sup> That is, our ability to be happy with the child’s expected height, eye color, intelligence level or weight, rather than the child’s expected welfare if it is genetically predisposed to diseases.

## 6 What Is In Store?

Most common people misunderstand that once the first draft of the human genome is complete, the work is done. Quite the contrary, the completion is just a milestone marking the beginning of efforts to unravel the secrets of the book of life.

### 6.1 Gaps Filling

The human genome project aims at determining the sequence of the euchromatic portion of the human genome. This portion excludes certain regions consisting of long stretches of highly repetitive DNA that encode little genetic information.

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<sup>17</sup> Andrew Kimbrell, *The Human Body Shop: The engineering and marketing of life*, (Harper Collins, San Francisco, 1993).

<sup>18</sup> Geoffrey Cowley, "Made to order babies", *Newsweek*, Winter/Spring 1990, pp. 98.