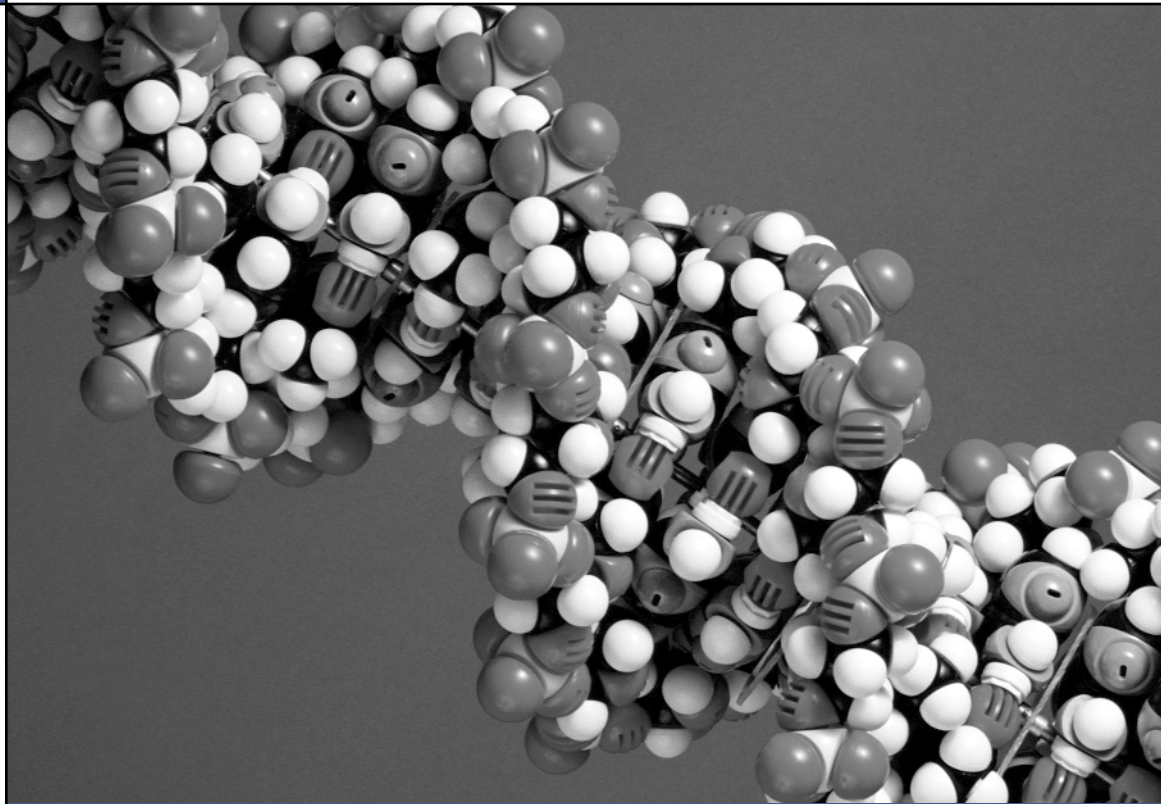


Managing “Big Science”: A Case Study of the Human Genome Project

New Ways to Manage Series



W. Henry Lambright
Professor of Political Science and Public Administration
and Director, Center for Environmental Policy and
Administration
The Maxwell School
Syracuse University

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The PricewaterhouseCoopers Endowment for
The Business of Government

F O R E W O R D

March 2002

On behalf of The PricewaterhouseCoopers Endowment for The Business of Government, we are pleased to present this report by W. Henry Lambright, "Managing 'Big Science': A Case Study of the Human Genome Project."

Professor Lambright's report is about both the past and the future. He traces the history of the Human Genome Project from its inception in the early 1980s to the present. It is a fascinating tale of scientific competition, politics, and the quest to understand the mystery of life itself. But the report is also about the future and what major national projects will look like in the decades ahead. The two biggest scientific undertakings of the 20th century—the Manhattan Project and Project Apollo—were centrally controlled national projects undertaken solely by the United States government. Large scientific projects in the 21st century will be far different.

In the future, predicts Professor Lambright, large-scale research and development projects are likely to cross agency lines, involve partnerships between the public and private sectors, and stretch beyond the United States. The Human Genome Project featured all three characteristics. If interagency, intersectoral and transnational partnerships are the wave of the future, Lambright also speculates that a new set of leadership skills will be needed by future government executives to manage such undertakings.

We trust that this report will be useful and informative to both those inside and outside of the scientific community. The approach described by Professor Lambright is clearly applicable to other national and international challenges, such as global warming, terrorism, and disease. New approaches and new organizational designs will be needed to successfully meet those challenges.

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EXECUTIVE SUMMARY

The Human Genome Project (HGP) is the largest scientific and technological enterprise in the history of biology. Costing in excess of \$3 billion and stretching over a decade and a half, HGP involved two agencies in Washington, a major funding organization in England, and scientists in six countries. It is universally seen as a success, although it will not completely finish its quest to sequence the chemical letters in the human genome until 2003. The project was always controversial, but its enormous significance has become increasingly obvious to science, medicine, business, and government.

The project has traversed five stages and is now in a sixth. The first stage, conceptualization, 1980-86, was the time when the idea of HGP was debated and evolved. The second, adoption, came in 1986-90. It was the time when the Department of Energy (DOE) moved ahead and was soon challenged by the National Institutes of Health (NIH). It wound up with HGP a joint "national" project. The third stage, 1990-93, was when the first leader of HGP, James Watson, captured control of the project for NIH and designed both the scientific and organizational strategy for its implementation. This stage ended in a crisis for HGP when Watson resigned in a dispute with the NIH director.

In the fourth stage, 1993-98, a new leader, Francis Collins, took command of HGP. He initially maintained the Watson approach, but sought to speed the project, which he saw as falling behind schedule. HGP grew in funding and performers.

However, it was increasingly challenged by J. Craig Venter, an outspoken scientist formerly in NIH who had moved to the private sector. Venter fervently believed his approach to genome sequencing was better than that of HGP.

The fifth stage, 1998-2001, was another time of crisis for HGP. Venter became president of a new firm, Celera, and challenged HGP to what was widely perceived as a race to sequence the human genome. Collins reoriented HGP in dramatic fashion, altering scientific and organizational strategy. The controversy escalated, as did the acrimony, public visibility, and political pressures surrounding it. President Bill Clinton, Prime Minister Tony Blair, and DOE became involved in various ways. In the end, Venter and Collins reached a truce and, in a White House ceremony, they were both declared "winners." An interim but very substantial goal was achieved—90 percent of the human genome sequence—that was recognized universally as a success. The two sides published papers (separately), assuring each a share of scientific glory in 2001.

In the present sixth phase, 2001-2003, the final touches are being put on the human genome by HGP. The HGP project is expected to end in 2003; meanwhile, HGP is transitioning to research on applications of the human blueprint that has been created.

The following factors were critical to the success of HGP: 1) a clear goal; 2) a flexible organiza-

tional structure; 3) political support; 4) competition; and 5) leadership. The fifth was the most important because it pulled the other factors together and made the most of them when it counted.

A major implication for the future lies with the partnership model of R&D that HGP's organization revealed. Partnerships across agencies, sectors, and nations are likely to be the wave of the future for large-scale public efforts at the frontier of knowledge. As a result of the HGP partnership, the first chapter of the human genome revolution is coming to a successful end, and the next step is under way.

The Human Genome Project Today

On June 26, 2000, President Bill Clinton, joined via teleconference by British Prime Minister Tony Blair, proclaimed a momentous event in history: "the completion of the first survey of the entire human genome."¹ The human genome represents a blueprint of a person, and has been likened to an instruction manual. It has also been called the Holy Grail of biology. Nicholas Wade wrote: "It provides the basis on which to understand the human body almost as fully and precisely as an engineer understands a machine. From that understanding, physicians can hope to develop new ways to fix the human machine and in time to correct most—perhaps almost all—of its defects."²

However, on June 26, 2000, at the White House ceremony, politicians, scientists, administrators, media, and others were not contemplating the future, good or ill. They were celebrating the moment. It had taken a decade and a half to get there, huge amounts of money, and an army of researchers and technicians spread over six countries. Responsible for reaching this epochal event was a large-scale federally funded project of international scale—and a private company, Celera, which inspired a race between public and private sectors to sequence (order the chemical letters of) the genome. The public-private contest was intended to end at this White House fete, where it was officially called a tie. In February 2001, the federal Human Genome Project (HGP) and Celera separately published their findings, at virtually the same time, thus gaining an equal share in scientific credit. The quest to decode the human genome was regarded universally a success.

The focus of this study is the governmental project, although the story of the private activity is interwoven, as it well deserves to be. Our principal interest is in what makes government programs work—critical factors in success, as well as failure. The aim is to look at the HGP as a result not only of science, but also of public management. It is to look at the forces—technical and political—that impact on management decisions. HGP has been likened to other great technical projects, such as the Manhattan Project and Project Apollo. While far smaller in scale than these, HGP is still huge. The figure \$3 billion is generally used as its cost, measured over project lifetime. This figure includes about \$2 billion from the National Institutes of Health and \$1 billion from the Department of Energy.³ The full reality is several hundred million more, since the Wellcome Trust, a huge philanthropy in England, became joint sponsor after the U.S. genome project was under way. In addition, other governments have contributed. However, at \$3 billion for the U.S. portion, HGP is easily the biggest science project ever in the biological field.

What is really the reason to compare HGP with other major monumental efforts in science and technology, like the Manhattan Project and Project Apollo, is that it represents "Big Science" in pursuit of a major breakthrough in technical capability. The Manhattan Project opened up the atom for use. Apollo made human space travel possible. And HGP will enable man to develop new methods of prevention and cure for a host of illnesses. Such breakthroughs do not come every day, year, decade, or century. They do not come easily. Hence, the



Photo courtesy of Associated Press.

J. Craig Venter, President Bill Clinton, and Francis Collins at the White House, June 26, 2000.

projects that bring them about stand out from most large-scale science and technology efforts that abound in the United States and abroad. They are worthy of serious study and an effort to derive lessons for government administration and policy.

That is the purpose of the present analysis, for HGP is a remarkable instance of successful public enterprise. The role of private enterprise was also extremely interesting and important. It shared the platform when success was proclaimed. However, this study concentrates on the public venture and the role of the private activity in affecting what public managers did. HGP, whatever its bumps along the way, wound up achieving its objectives and was speeded in doing so by private competition.

Before looking at the administrative history of HGP, it is important to see where the project stands today. Some call this the post-Genome Project Era. They are not correct. The reality is that HGP is not

quite finished, and the world is just entering the genome era. The climax to the project that helped introduce the era came in February 2001 with the publication in *Nature* and *Science* of the respective findings of HGP and Celera.⁴ At the time, 90 percent of the human genome was completed in terms of sequencing. What happened was that the original HGP scientific goal of a complete genome was retained, but an interim goal added—the 90 percent “rough draft”—which was set forth as the symbolic finish line. The last 10 percent was targeted subsequently, and it is expected that a complete, “polished” draft of the human genome will be ready in 2003. This is the 50th anniversary year of the discovery of the double helix structure of DNA.

Since 2001, HGP (as well as Celera) has moved forward with post-Genome Project activity, even as they finished what they had started. Their projects are in a transition phase. For HGP, the transition marks a sixth phase.⁵ The first phase, extending

from approximately 1980 to 1986, was one of conceptualization. Phase two, from 1986 to 1990, was the period when a national program to sequence the human genome was adopted by the U.S. government. By "national" is meant a program that involved two agencies in coordination, the Department of Energy (DOE) and the National Institutes of Health (NIH).

In the third phase, 1990–1993, the initial implementation took place, and NIH established itself as lead agency. The program was expanded to an international venture and initial scientific and organizational strategies activated. The fourth phase, from 1993 to 1998, was a time of maintaining momentum and of project growth. It included actions to find ways to accelerate the pace of research via pilot projects. It began with an internal crisis in terms of HGP leadership and ended with another crisis due to external threat.

The fifth phase ran from 1998 to 2001. It marked a reorientation of HGP to a crash program style of operation. The period ended with the achievement of the reorientation goal—the draft genome—and acclamations of triumph. As noted, the present sixth period—2001–2003—is one of transition, completing work on the genome sequence, while simultaneously moving to the next research frontier of applications.

That frontier seems limitless. HGP is charting new goals aimed at understanding how the human blueprint functions. In particular, HGP will ask how the genome makes people different, with some more vulnerable to genetically based disorders than others. Answering such a question is a first step to what may be eventual HGP applications: "individualized medicine" and "regenerative medicine."⁶ People will be diagnosed from their genetic makeup to determine what diseases they are likely to get. In some cases, those malfunctions may be headed off through new drugs and other genetic therapy. That future, while not yet here, is arriving fast, and its implications are vast for government and the biotechnology industry.

HGP continues, as does its budget and organizational structure. The budget is rising and the organi-

zation is growing. The present organization of HGP is that of an international consortium. There is a de facto "lead" organization. This is the U.S. National Institutes of Health. NIH has two principal partners in funding: the U.S. Department of Energy and the Wellcome Trust. The Wellcome Trust, reputed to be the wealthiest health-oriented foundation in the world, has made HGP a priority.

While HGP has a significant intramural research program, the great bulk of its funds are spent externally, mainly by universities. Early on, HGP adopted, as a principal management strategy, the establishment of research centers as the way to accomplish its goals. In 2001 there were 16 major centers in the United States and abroad involved in human genome sequencing. Several other centers are concerned with different aspects of genome research and technology. Five of these formed the core of the human sequencing component of HGP: the Whitehead Institute for Biomedical Research; Washington University in St. Louis; Baylor College of Medicine; the Joint Genome Institute (a cluster of three national laboratories under DOE); and the Sanger Centre (now Sanger Institute) in England. Known as the G-5, these centers will have performed 85 percent of the genome sequencing by the time the project ends in 2003.

The remaining centers will have undertaken 15 percent of the sequencing. NIH has only nominal control over its university centers, and none directly over those of DOE or the Wellcome Trust. What ties the consortium together is the informal leadership of NIH and the mutually agreed upon requirement that all performers must place their findings into a common repository—the GenBank—maintained by NIH. They are required to do so within 24 hours of discovery, and what is in GenBank is open to all. It was this particular HGP requirement of total openness that made it difficult for Celera, concerned about its proprietary rights, to cooperate with HGP.⁷

As noted, the present period is one of transition for HGP. The public management challenge today is to hold the consortium together to finish the human genome blueprint, while moving forward to new objectives. The HGP has undertaken projects to sequence the genomes of the mouse, rat, and other

living creatures. It is also probing relations between genes and proteins. Three new research centers beyond the major 16 have been established to work on particular research initiatives relating to human variation.⁸

Comprehending the genetic bases of such differences is critical before taking steps to apply this knowledge. In doing so, HGP is developing novel relationships with pharmaceutical companies and others. It has even found ways it and Celera can work in partnership, although Celera is still a rival, having already produced a draft sequence of the mouse. The likelihood is that rivalry will diminish in the future. A decision by Celera's parent company to move Celera in a different direction caused J. Craig Venter, HGP's competitor, to resign from Celera in early 2002.

HGP has pioneered a frontier not only in science, but also in organization. The Manhattan Project and Project Apollo were concentrated national projects, and industrial relations were those of sponsor-performer. HGP has been a pluralistic transnational project, involving management by two U.S. agencies and a major partner that is a private foundation in a foreign country. It has utilized universities and national labs as performers. While having cordial relationships with a number of companies,⁹ its best known relation with industry, Celera, has been adversarial. Whether this is a model for the future remains to be seen, but it is certainly different from earlier Big Science ventures.

At the same time, like Manhattan and Apollo, there will be long-lasting impacts on policy, for genome knowledge can be used not only to help people, but also for negative purposes. Like every powerful technology, what happens depends on human judgment. HGP has supported research in legal, ethical, and social impacts in recognition that it was creating a dual-edged sword. Finally, HGP may have a transformative impact on NIH. The project's "large-scale approach" is seen by some other institute directors as a potential way to accelerate advances in other spheres of NIH research.¹⁰ Those who have managed HGP have presided over the first steps in what will be a multifaceted revolution.

The Human Genome Project: A Management Case History

On May 10, 1998, J. Craig Venter, a former NIH scientist turned biotech entrepreneur, announced he was setting up a new company, Celera, that would sequence the human genome within three years for \$300 million. This was four years ahead of the target date for the publicly funded, \$3 billion Human Genome Project. The announcement was taken by virtually everyone as a direct challenge to the government effort and the bioscience establishment.¹¹

The media called it a race for the Holy Grail of biology, the complete description of the human genome. James Watson, Nobel Prize-winning biologist, co-discoverer of the double helical structure of DNA, and first director of the Human Genome Project, saw the struggle as one of good versus evil, public versus private interests. He likened Venter’s assault on the genome project to Hitler’s annexation of Poland. He asked his successor as project director, Francis Collins, whether he was up to the challenge. Would he be a Churchill or a Chamberlain?¹²

Two years later, in 2000, at a White House ceremony led by President Clinton, in which British Prime Minister Tony Blair participated by teleconference, a draw was declared. Although the public and private projects were still not finished, they had reached a climactic point where the human genome could be almost fully sequenced in a preliminary way. In 2001, scientific papers were published by HGP and Celera, and biology’s own “Project Apollo” was heralded a resounding success.¹³

How did this huge project—involving thousands of researchers, costing billions, and extending well

over a decade—get started? How did it get organized? What was its scientific strategy and how was it implemented? What were the factors that affected its pace and direction? What lessons can be learned about leadership and management of large-scale technical ventures from this particular experience?

To answer these questions, it is necessary to review HGP’s history. The present period is one of transition, as the HGP finishes and polishes the human genome draft and initiates new research paths. A number of these activities involve partnerships with the private industrial sector, in contrast to earlier experience. HGP is moving from development of a tool to its uses.

In getting to this transition period, HGP has gone through five previous phases. The following study of the project tracks events through these eras, which include:

1. Conceptualization—when HGP was developed, 1980–86.
2. Adoption—when HGP began, first as a DOE project, then as a national effort, involving NIH and DOE, 1986–90.
3. Initial implementation—when James Watson gave shape to the effort, 1990–93.
4. Maintaining momentum and growing—when Francis Collins succeeded Watson and sought to speed the venture, 1993–98.
5. Reorientation—when HGP shifted dramatically to a crash project, 1998–2001—and achieved its reorientation goal.

Francis S. Collins, M.D., Ph.D.
Director, National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland



Francis S. Collins, M.D., Ph.D., is a physician-geneticist and the director of the National Human Genome Research Institute, NIH. In that role he oversees a complex multidisciplinary project aimed at mapping and sequencing all of the human DNA, and determining

aspects of its function. Many consider this the most important scientific undertaking of our time. A working draft of the human genome sequence was announced in June of 2000, an initial analysis was published in February of 2001, and the completed sequence is anticipated in the spring of 2003. From the outset, the project has run ahead of schedule and under budget, and all data has been made immediately available to the scientific community, without restrictions on access or use.

Collins was raised on a small farm in Virginia and home-schooled until the sixth grade. He obtained his undergraduate degree in chemistry at the University of Virginia and went on to obtain a Ph.D. in physical chemistry at Yale University. Recognizing that a revolution was beginning in molecular biology and genetics, he changed fields and enrolled in medical school at the University of North Carolina. After a residency and chief residency in internal

medicine in Chapel Hill, he returned to Yale for a fellowship in human genetics, where he worked on methods of crossing large stretches of DNA to identify disease genes. He continued to develop these ideas after joining the faculty at the University of Michigan in 1984. This approach, for which he later coined the term "positional cloning," has developed into a powerful component of modern molecular genetics, as it allows the identification of disease genes for almost any condition, without knowing ahead of time what the functional abnormality might be. Collins' team, together with collaborators, was successful in applying this approach to genes for cystic fibrosis, neurofibromatosis, Huntington's disease, multiple endocrine neoplasia type 1, and a particular type of adult acute leukemia.

In 1993, Collins accepted an invitation to become the director of the National Center for Human Genome Research, which became an Institute in 1997. In addition to overseeing the International Human Genome Sequencing Consortium and many other aspects of the Human Genome Project, Collins founded a new NIH intramural research program in genome research, which has now grown to become one of the premier research units in human genetics in the country. His own research laboratory continues to be vigorously active, exploring the molecular genetics of breast cancer, prostate cancer, adult-onset diabetes, and other disorders. His accomplishments have been recognized by election to the Institute of Medicine and the National Academy of Sciences.

6. The present transitional phase, 2001–2003, when HGP is being fully completed as the post-genome sequencing projects are begun.

HGP is often called the most significant federal science and technology undertaking since Project Apollo. It certainly has been a historic milestone for biomedical research, not just technically, but managerially. It has been controversial throughout its history.¹⁴

Conceptualization, 1980–86

In 1953, James Watson and Francis Crick discovered the double helical structure of DNA, later winning Nobel prizes for their achievement. In

succeeding years, biologists all over the world continued advances, probing deeper and deeper into the mysteries of life, particularly the basic building blocks of heredity, genes.

By the beginning of the 1980s, biologists were deciphering the human genetic code, one gene at a time. Some individuals speculated that it might some day be possible to sequence the entire human genome (i.e., the full complement of DNA in human cells). This was a technological vision that leapfrogged existing knowledge and technical capabilities. It entailed unraveling 3.1 billion base molecules making up DNA, a project whose scale was far beyond the mainstream of human genetics research.¹⁵

Human Genome Project Milestones

1953	●	Watson and Crick discover the helical structure of DNA.
September 1986	●	DOE reallocates \$5.3 million to initiate a human genome initiative.
1987	●	DOE establishes three genome research centers among its national labs.
1988	●	National Research Council of the National Academy of Sciences panel of prominent genetics researchers publishes report endorsing the HGP. Recommends incremental approach: first mapping and then sequencing.
1988	●	NIH Director Wyngaarden establishes new Office of Human Genome Research and appoints James Watson as its director. NIH and DOE sign memorandum of understanding to collaborate on HGP.
1990	●	Watson develops strategic plan for the project of 15 years, endorsing phased approach of mapping and then sequencing. Six centers established in the U.S. to do the HGP work.
April 1992	●	Watson resigns over conflict with Bernadine Healy, NIH's director.
July 1992	●	Venter resigns from NIH to accept offer to proceed with gene sequencing at a new non-profit, The Institute for Genomic Research (TIGR).
January 1, 1993	●	Healy appoints Francis Collins of the University of Michigan to direct HGP, effective in April.
1993	●	The Wellcome Trust opens new sequencing lab, the Sanger Centre, headed by John Sulston, near Cambridge, England.
August 1993	●	Clinton appoints Harold Varmus to be NIH director.
October 1993	●	NIH and DOE agree on revised plan for 1993-98. GenBank shifts to NIH.
1994	●	NIH rejects proposal from Venter's nonprofit, TIGR, to speed up gene sequencing with "shotgun" method.
May 1995	●	Venter announces TIGR has sequenced first entire genome of a living organism, H. Influenzae. Collins makes new grants to pilot projects at HGP centers to test new strategies and techniques aimed at speeding pace of HGP.
February 1996	●	Wellcome Trust organizes first International Strategy Meeting on Human Genome Sequencing in Bermuda. Forty leaders in genome research agree to make available all results within 24 hours.
January 1998	●	Applied Biosystems produces "next generation" sequencing technology, greatly accelerating the process of sequencing. Partners with Venter to form new profit-making company, Celera. Venter leaves TIGR to become president of Celera.
May 9, 1998	●	Venter announces Celera will sequence entire human genome in three years.
May 12, 1998	●	Collins meets with senior HGP staff, center directors, and key advisors and discusses response to Venter's challenge.
1998	●	Collins shifts to crash program with a 2000 interim goal deadline.
Summer 1999	●	Celera announces successful sequencing of Drosophila in just four months.
December 21, 1999	●	Meeting between HGP team and Venter's group.
March 14, 2000	●	Clinton and Blair issue joint statement on human genome issues.
June 26, 2000	●	Clinton and Blair proclaim a "tie" in completion of the first survey of the entire human genome.
February 15 & 16, 2001	●	HGP and Celera publish separately their genomic findings.
January 2002	●	Tony White, head of parent company, reorients Celera to develop new drugs rather than to pursue Venter's interest in research and sales of genetic information. Venter resigns.
2003	●	Projected completion of HGP.

The first major meeting to discuss the feasibility of sequencing the human genome took place in 1985. Robert Sinsheimer, president of the University of California, Santa Cruz, invited a group of leading life scientists to his campus to discuss such a project's feasibility. Sinsheimer was looking for a large initiative he could promote to build his institution into a major center for genomic research. The meeting stimulated discussion, with plenty of views, most of which opposed the HGP idea. Big Science—research costing billions and organized as a project with milestones, expensive equipment, and a managerial hierarchy—was not in the tradition of biology. It had been pioneered in physics, sparked by the Manhattan Project, and in space with the Apollo experience, but had not penetrated biology to a significant extent. Sinsheimer also ran into bureaucratic obstacles within the University of California system and abandoned the idea.¹⁶

However, the notion of a human genome project continued to percolate within the scientific community. In early 1986, Sydney Brenner of the Medical Research Council (MRC) laboratory in Cambridge, England, urged the European Union to undertake a concerted program to map and sequence the human genome. What enhanced the technical feasibility of the project was the rapid advance of a range of relevant technologies. What might otherwise require thousands of scientists doing extremely difficult and dull tasks over decades could be expedited by the first automated sequencing machines, invented in 1986 by Leroy Hood and Lloyd Smith of the California Institute of Technology.¹⁷

There was another issue that made for conflict. Even if feasible, was deciphering the human genome really the best way to spend limited research money? The work was more like developing a technology, or (worse) data gathering, than conducting basic research experiments driven by theory. It was more industrial than academic in style—not what a good academic scientist was supposed to do. The money and talent would detract from smaller, less expensive, “better” science in the view of many researchers. Also, it would take money from many scientists and give it to a relative few willing to prostitute themselves, said critics. The principal agency supporting biomedical research, the National Institutes of Health, was

responsive to the scientific community in setting its agenda. While scientists debated, NIH waited.¹⁸

Adoption, 1986–90

The trigger for moving beyond talk to action for NIH was the decision by the Department of Energy in September 1986 to reallocate \$5.3 million from its budget to initiate a human genome initiative. The principal decision maker was Charles DeLisi, a cancer biologist who headed DOE's Office of Health and Environmental Research.

To DeLisi, a human genome project was a logical outgrowth of DOE's long-term research mission to study the effects of radiation on human health. Also, it was Big Science, the staple of DOE's national laboratories, which faced a diminishing demand for nuclear work. To the extent Big Science had established any foothold in biology, it had been at DOE in connection with radiation experiments. The DOE move caused great chagrin among many academic bioscientists, one of whom denounced the effort as “a scheme for unemployed bomb makers.”¹⁹ It was clearly seen as a threat. Many non-DOE observers held that if there was to be a Human Genome Project, NIH and the academic scientists who performed research under its purview had to be in charge.

Formulating a Plan

In 1987, as DOE established three genome research centers among its national labs, the National Research Council (NRC) of the National Academy of Sciences convened a panel that included many of the most prominent genetics researchers of the day, including both advocates and skeptics of a human genome project.

The NRC report came out in 1988. It endorsed the HGP. The skeptics and optimists united, but in doing so emphasized the need for a comprehensive, scientifically sound effort to generate maximum knowledge and create as perfect a picture as possible of the genetic makeup of any individual. If the Human Genome Project could be likened, metaphorically, to producing a “book of life,” there was a first stage called mapping, which was the stage of defining the chapters. This meant identifying milestones or markers along the enormous length of a DNA molecule.²⁰

Once these chapters were delineated, the second stage of sequencing could commence. Sequencing meant going deeper, decoding the material in chapters and giving order to the letters within chapters, between the markers. This steady, incremental approach was geared to a total understanding, irrespective of whether some chapters might be more potentially valuable in terms of health or economic benefit than others. It aimed at as complete and accurate a product as was possible. Because the human genome was seen as a giant puzzle, decoding and arranging more than 3 billion chemical letters, it was viewed as a task that would necessarily have to be divided among many investigators.

NRC recommended spending \$200 million a year in new money (meaning the funds would not be taken away from other NIH research). It estimated that HGP would take between 10 and 15 years to complete, and cost as much as \$3 billion. This figure included expenses for infrastructure, as well as the sequencing of simpler organisms for purposes of comparison with the much more complex human genome. NRC recognized there could be more than one agency involved in the HGP, but called for a "lead" agency. It did not specifically name which agency should play that role, but its view in favor of NIH was obvious. This was a project with a goal, but a relatively uncertain timetable. It was not a top-down, managed "crash project" like Manhattan or Apollo. The NRC declared:

A large-scale, massive effort to ascertain the sequence of the entire genome cannot be adequately justified at the present time.... the Council wants to state in the clearest possible terms our opposition to any current proposal that envisions the establishment of one or a few large centers that are designed to map and/or sequence the human genome.... it is of the utmost importance that traditions of peer-reviewed research, of the sort currently funded by the National Institutes of Health, not be adversely affected by efforts to map or sequence the human genome.²¹

Not everyone on the NRC went along with the recommended incremental approach. Significantly, one of the members of the panel, Walter Gilbert, a Harvard University Nobel Prize-winning biologist,

**U.S. Human Genome Project Funding*
(\$Millions)**

The Human Genome Project is sometimes reported to have a cost of \$3 billion. However, this figure refers to the total projected funding over a 15-year period (1990-2005) for a wide range of scientific activities related to genomics. These include studies of human diseases, experimental organisms (such as bacteria, yeast, worms, flies, and mice); development of new technologies for biological and medical research; computational methods to analyze genomes; and ethical, legal, and social issues related to genetics. Human genome sequencing represents only a small fraction of the overall 15-year budget.

The DOE and NIH genome programs set aside 3% to 5% of their respective total annual budgets for the study of the project's ethical, legal, and social issues (ELSI). For an in-depth look at the ELSI surrounding the project, see the ELSI website.**

For explanation of the NIH budget, contact the Office of Human Genome Communications, National Human Genome Research Institute, National Institutes of Health.***

FY	Wellcome Trust	DOE	NIH	Total
1992-2000	306			306
1988		10.7	17.2	27.9
1989		18.5	28.2	46.7
1990		27.2	59.5	86.7
1991		47.4	87.4	134.8
1992		59.4	104.8	164.2
1993		63.0	106.1	169.1
1994		63.3	127.0	190.3
1995		68.7	153.8	222.5
1996		73.9	169.3	243.2
1997		77.9	188.9	266.8
1998		85.5	218.3	303.8
1999		89.9	225.7	315.6
2000		88.9	271.7	360.6
2001		86.4	308.4	394.8
2002		87.8	346.7	434.3
Total	306	948.5	2066.3	3320.8

* These numbers do not include construction funds, which are a very small part of the budget.

** www.ornl.gov/hgmis/elsi/elsi.html

*** This information is from: www.ornl.gov/hgmis/project/budget.html

resigned from the NRC committee before it issued its report. He announced plans to start a private company, the Genome Corporation, that would move much more quickly than NRC recommended, employing a different scientific strategy than the one NRC favored. His new company could potentially gain a proprietary advantage and sell genome data for profit.²²

Gilbert's venture never got off the ground because he could not raise venture capital. However, his action raised many alarms among bioscientists who wanted knowledge to flow freely so they could have access to it for research. Also, some scientists saw the human genome in symbolic terms. It was a gift of God. To make a profit from something so intrinsic to humanity was immoral. If many academic scientists and their allies in NIH looked askance at DOE and its national labs, they were even more wary of business.

Getting a Director

Armed with the NRC report, James Wyngaarden, NIH director, now made his move. Obtaining a small appropriation from Congress, he established a new Office of Human Genome Research, which reported to him. As director of the office, he appointed, in September 1988, James Watson, who had been one of HGP's strongest proponents in advising him.²³ The appointment of Watson was extraordinarily important. He was the most famous biologist in the world. His appointment brought immediate scientific legitimacy to HGP. Scientific carping diminished quickly. In addition, the Watson appointment to NIH immediately put DOE's program in the shadows. Watson said he had no choice in accepting the appointment: “I would only once have the opportunity to let my scientific life encompass a path from double helix to these billion steps of the human genome.”²⁴

NIH and DOE signed a memorandum of understanding and agreed to collaborate on HGP. HGP thus became a national program. In form, the two agencies might be equal. In reality, NIH was dominant. Watson was not only a great scientist, he was a flamboyant showman. DeLisi soon left DOE, replaced by leaders unknown in comparison to Watson. Also, Congress proved far more generous in funding NIH than DOE. DOE had little choice but to be the junior partner. For better or worse,

HGP became associated primarily with NIH, an agency that had little experience in managing large-scale science and technology projects. Big Science and NIH had to adapt to one another.

In 1989, NIH elevated HGP from an office to the National Center for Human Genome Research (NCHGR). Congress appropriated funds directly to this new entity and gave Watson authority to award grants through an extramural program. He was now in a position to put some of his ideas into action.

Initial Implementation, 1990–93

Keeping his position as director of the Cold Spring Harbor Laboratory on Long Island, New York, Watson commuted regularly to Washington, D.C., and NIH's Bethesda campus. He started with just two employees, with staff gradually expanding. In a move unusual for NIH, Watson developed a strategic plan stretching 15 years. He began with an initial five-year plan. In a move that made it abundantly clear who was in charge of this national program, he declared that the HGP would start “officially” in 1990—thus peremptorily dismissing the four years of effort DOE had expended, as well as NIH's own previous work. Watson said the project would run until 2005, by which time the entire human genome would be sequenced as accurately as possible. He endorsed the phased approach espoused by NRC—mapping, then sequencing. In an unprecedented and bold action, Watson also announced that 3 percent of his budget (later raised to 5 percent) would go to social, legal, and ethical studies of the impacts of the research. He said that there would be societal impacts from HGP, and he wanted them studied so that the technology—and he regarded HGP as developing a new technology or capability—could be used wisely.

Watson was extremely effective with Congress. “My name was good,” he recalled. Leslie Roberts wrote in *Science*:

... members of Congress were spellbound when the eccentric Nobel Laureate swept in to testify. Watson was eloquent in touting the project's goal: “to find out what being human is.” He also had the refreshing quality of saying what he thought, no matter how politically incorrect—an unusual quality in Washington, D.C.²⁵

There were debates within Watson's advisory panel about scientific strategy. Instead of the steady, phased, comprehensive approach of Watson, some advisers favored targeting and understanding disease genes. This was the real payoff, they said. It was what Congress cared about. Watson, however, held his ground. He likened the human genome to a particle accelerator. There was a proper way to build such a machine if it was to work effectively.

Watson pushed the first stage of the project, which was to chart maps of human chromosomes. With chromosome maps in hand, he believed the genes within could be better found and sequenced, and the disease genes would be a byproduct.²⁶

Administrative Strategy

To achieve his purposes, however, Watson could not go along with NIH's traditional single investigator approach. This approach mainly involved grants to individual academic investigators who submitted ideas through peer-reviewed proposals to NIH. It was a basic research model that had served NIH well. However, Watson adopted a "center" strategy, which had been previously used primarily for clinical research, relying on universities. He did not build up an intramural laboratory within NIH. While he allowed university and other research institutions creative freedom to compete for center awards and go through peer review, it was clear that they had to gear their pursuits to HGP goals and fit into a pattern of his design. This was mission-oriented research in a basic science NIH setting. There were six initial centers established to do the work of HGP in the United States, all six at universities. These were the Whitehead Institute for Biomedical Research, affiliated with MIT; the University of Michigan; Baylor College of Medicine; University of Utah; University of California, San Francisco; and Washington University in St. Louis.

In addition to the initial centers, Watson expanded the project to other research institutions in the United States and other countries. He wanted broad involvement, as he insisted the human genome belonged to the world, not just the United States. Soon researchers from England, France, Israel, Germany, Canada, and Japan were involved, usually supported by their own governments. The linkages of U.S. centers with partners abroad placed

NIH at the hub of a consortium of institutions. Watson imposed certain rules through force of his personality. In particular, he was emphatic that researchers in the United States and other countries share information toward a common goal.

While Watson saw HGP in technological terms, he was not really building a machine but aggregating information into a blueprint. The work of HGP was distributed widely, among individuals, institutions, and countries that were in some respects competitors. But, ultimately, information had to be brought together so the blueprint would make sense. What made this "large-scale approach" to science different from other life-science research at NIH was that there was less emphasis on theory and hypothesis as in the traditional model of science. This was a project focused on technical capacity to gather huge data sets of a particular type and assemble them in a meaningful pattern.

This Big Science approach was new to NIH and biology, but had some precursors at DOE. However, the model of organization Watson adopted was one of "distributed" or decentralized Big Science. He built up to perhaps a dozen major academic centers as HGP evolved. Each had its own procedures and quality controls. They coordinated with one another and through Watson's office to divide the labor of HGP. Watson was "directive" and sometimes abrasive, but, as one former center head recalled, he was so able and such a towering figure in biology, "you forgave him."²⁷ Nevertheless, the consortium model was an unwieldy structure for HGP.

Whatever its scientific merit (or limits), this spreading of the project had political dividends in that it meant many institutions (and, in the United States, congressional districts) had stakes in the project. Such support was especially important in the early days of HGP, when it was getting off the ground. This was a period of budget deficit and cost-cutting in government. Other Big Science projects at the time—the Superconducting Supercollider and the Space Station—were under heavy fire. The Space Station barely survived, and the Collider project was terminated by Congress in 1993.

One of the key technical decisions Watson made was to support Robert Waterston of Washington University in St. Louis, and John Sulston, then

with the Medical Research Council laboratory in England, on a pilot project, the sequencing of the roundworm. This partnership ultimately became a backbone of HGP in some ways—a “transatlantic alliance.”²⁸

Conflict at NIH

While Watson coordinated various elements of the international consortium of organizations he had established, he ran into increasing problems with his own NIH organization. Watson did not have an intramural research program, but there was genome work under way at NIH. J. Craig Venter was a scientist who ran a large lab at NIH’s National Institute for Neurological Disorders and Stroke, an entity over which Watson had no control. Venter not only had biomedical ability, but also was attracted to the applications to his science of information technology. He had been among the first scientists at NIH to acquire sequencing machines. Initially, Watson and Venter saw common purpose, but after a while began to contend.²⁹ Venter had developed with a colleague, Mark Adams, “a new technique, called expressed sequence tags, which enabled them to find genes at unprecedented speed.” Venter was an outspoken individual, and he said his approach “was a bargain in comparison to the genome project.” He boasted that his approach would allow him to find 80 percent to 90 percent of the genes within a few years, for a fraction of the HGP cost. Watkins dismissed Venter’s “cream-skimming approach.”³⁰

Venter, however, had the backing of NIH’s new director, Bernadine Healy, an M.D. who had been appointed in 1991 by President George H. W. Bush following her stint at the White House Office of Science and Technology Policy (OSTP). She and Watson had crossed swords earlier when she was at OSTP. Watson had disparaged her ability and suggested she had her job only because she was a woman. Now she was his boss. Moreover, she was actively promoting NIH’s patenting inventions from its employees as part of a technology transfer strategy she espoused.³¹ Venter was her poster child. Watson argued that if NIH patented genes, it would undermine the policy of openness and information sharing he had established for HGP participants.

The dispute became public in the summer of 1991, when both Venter and Watson appeared before a congressional hearing. Venter noted that NIH liked

what he was doing, so much so that it was filing patent applications on the partial genes he was identifying—at the rate of 1,000 a month. Venter’s bravado caused Watson to blow up. He called Venter’s patenting “sheer lunacy,” and declared “virtually any monkey” could do what Venter was doing. Aside from his concern about communication within the project, Watson’s approach was to identify whole genes and determine what they did. He explained that if the patents on sequencing tags held, then anyone could lay claim to a gene without knowing its function. “I am horrified,” Watson told Congress.³²

The Watson-Healy feud worsened. In April 1992, Healy backed an examination by NIH of Watson’s personal shareholdings in biotechnology companies for possible conflict of interest. Outraged, Watson resigned—via a fax from his Cold Spring Harbor lab. He declared that no one could work with that woman.³³ Ironically, Venter, who apparently could work with Healy, resigned in July from NIH to accept an offer of \$70 million from a venture capital company. He intended to demonstrate his gene identification strategy at a new nonprofit, The Institute for Genomic Research (TIGR).³⁴ Venter was utterly determined to proceed with gene sequencing with the approach he chose, and felt the need for an organizational setting that gave him more freedom than NIH. A nonprofit model seemed to make sense, although he felt at the time he was taking a huge personal risk.³⁵

Maintaining Momentum and Growing, 1993–98

A New Leader

The Human Genome Project was in trouble. Unless a new leader of great ability could be found soon, the project would founder. The centrifugal forces operating in the consortium Watson had established were immense. Healy knew she had to find a replacement, fast. While she may not have wanted Watson, she did want NIH to lead HGP. On January 1, 1993, NIH announced that Francis Collins of the University of Michigan had agreed to direct the NIH genome program, effective in April. Collins had achieved renown for co-discovering the genes associated with several dreaded maladies—cystic fibrosis, neurofibromatosis, and Huntington’s disease. He was a medical doctor/scientist and

headed a laboratory that had a secure base of funding from several sources. His laboratory was one of the original genome centers Watson had established. He had to take a cut in pay to become director of HGP. If Watson was a superstar in bioscience, Collins was a very bright star on the rise.

Why did he take the job? One reason was that many other scientists in the program believed he had the right blend of technical and administrative skills, and they pressed him hard. Another was that he wanted it, he said, "because there is only one human genome program. It will happen only once, and this is that moment in history. The chance to stand at the helm of that project and put my own personal stamp on it is more than I could imagine." He also stated, "My whole career has been spent training for this job—this is more important than putting a man on the moon or splitting the atom."³⁶ He recounted that it was Healy who made him realize this was his calling. She asked him to imagine a time in the future when they met as old people in a nursing home. He would say to her: "Damn it, Bernie, you should have made me take the job."³⁷

The Collins appointment was regarded as a major coup for Healy and allowed her to show her own commitment to HGP. With Clinton taking office January 20, she was on the way out, and hiring Collins to bolster HGP might well be seen as her principal NIH legacy. If Watson was universally regarded as the ideal man to get HGP off the ground, Collins was seen by many as the right choice to bring it to fruition.

Collins had a very different leadership style from Watson. Watson was a scientific celebrity and loved the limelight. Collins was relatively unknown, quiet, and did not particularly enjoy the goldfish bowl aspect of heading HGP. Watson was a "big picture" leader, a scientific visionary who would delegate a lot of work. Collins was much more into the nitty-gritty and hands-on details of management. Watson worked hard, but maintained his Cold Spring Harbor lab. Collins was totally absorbed in HGP and left the University of Michigan.³⁸ Watson was a biologist and Collins a doctor and researcher. As a scientist, Watson always spoke of HGP as creating a technology that would advance the scientific frontier. Collins spoke about the health impacts of the technology. Watson assumed he was always "num-

ber one," an attitude that brought his ego into conflict with that of Healy. Collins was more consensual, more comfortable in a team concept of leadership.

In coming to NIH, Collins extracted two promises from Healy. First, he wanted laboratory space at NIH, so he could continue his research even while serving as an administrator and also build an intramural research program staffed by NIH researchers reporting to him. Second, he wanted the organization he headed to have institute status, the major designation at NIH. The Watson office had been established administratively, with minimal congressional authority. With Watson in charge, it had a high status in spite of its bureaucratic base. But without a stronger mandate and position, it was extremely vulnerable to NIH directors and their whims. NIH legislation was thus approved at the beginning of the Clinton administration, and this gave Collins' operation "permanent" status—meaning an NIH director or HHS secretary could not arbitrarily reorganize it out of existence. This action also meant the HGP ultimately would have the same bureaucratic status as the institutes with a research focus on the heart, cancer, and other diseases.³⁹ Eventually, HGP's organizational home was renamed the National Human Genome Research Institute (NHGRI).

Healy set in motion the machinery to provide Collins what he wanted and she left June 30. Ruth Kirschstein, a long-time NIH career administrator, served as interim director. President Clinton announced in August that his appointee as NIH director would be Harold Varmus, a Nobel Laureate cancer researcher from the University of California, San Francisco. As it turned out, Varmus and Collins got along well and formed a cohesive team. Varmus removed an issue by ending his predecessor's drive to patent partial genes.⁴⁰ Moreover, Varmus, unlike Healy, worked easily with Congress, and before too long the NIH budget, HGP included, rose substantially. This internal top-level support aided Collins enormously in managing HGP.

Taking Stock

When Collins took command, he found HGP making progress, but not quickly enough. Most positive was the discovery of disease genes. As Watson had predicted, they were coming as "spinoffs" from the mapping work. These gave Collins ammunition in

testifying before Congress. Every week, it seemed, the discovery of another deadly disease gene could be announced. "The reason the public pays and is excited—well, disease genes are at the top of the list," said Collins.⁴¹ Also, the consortium was growing. Particularly important was an infusion of new funds from Great Britain's Wellcome Trust, possibly the world's largest medical philanthropy, which in 1993 opened a major new sequencing lab, the Sanger Centre, near Cambridge, England. The lab was headed by John Sulston. This meant that the Waterston-Sulston transatlantic connection Watson had funded became potentially more significant in the Collins era.

On the negative side, the mapping was not phasing into sequencing as fast as Collins believed was necessary if the 2005 deadline was to be met. With President Clinton anxious to hold the line on federal expenditures and much of HGP's money still concentrated on mapping, Collins was worried that "we have mortgaged part of our future."⁴²

Nevertheless, he maintained the general approach he inherited. It was an approach he was sure would work, but it was slow, and the various academic laboratories made for a cumbersome structure. Collins' initial change was not in Watson's scientific strategy or organizational approach, but in trying to speed the execution of the project. In October, NIH and DOE agreed on a revised plan for 1993–1998. The plan was to accelerate work toward the goal of completing the human genome by 2005. The database for HGP information, called GenBank, which had been under DOE during the tenure of former Secretary James D. Watkins, now was shifted to NIH, a move that further underlined the NIH leadership role in the project. Moreover, to bolster that role even more and help in project acceleration, Collins continued to add staff and start the building of HGP's intramural research. He achieved a major coup when he enticed a former colleague at Michigan to leave the university to head the intramural laboratory, which Collins wanted to look ahead to applications.⁴³

The Shotgun Alternative

In 1994, NIH received a proposal from Craig Venter's nonprofit institute, TIGR. It involved a dramatic bacterial gene sequencing method called "shotgun." It had been devised by Hamilton Smith,

a Johns Hopkins biochemist, Nobel Prize winner, and member of TIGR's advisory board. Instead of spending months, possibly years, mapping, Smith proposed to Venter a much more brute-force approach. The initial step was to shear DNA into thousands of random pieces. The second step was to sequence the DNA of each fragment. The third step was to use a computer program to align the overlapping fragments to produce a single, contiguous DNA sequence of an entire organism. The boldness of the strategy appealed to Venter virtually from the start. It was compatible with his own methods, going back to his work at NIH. It could help him forward his dream of decoding the human genome.⁴⁴ Venter soon had Smith developing his shotgun strategy under TIGR auspices. Venter deployed eight TIGR personnel and 14 of the most advanced DNA sequencing machines available to the activity. To help pay for this work, TIGR submitted its 1994 proposal to NIH. NIH rejected the proposal, saying the shotgun method would not work effectively.⁴⁵ Venter called Collins to argue his case, to no avail.⁴⁶

In May 1995, after 13 months of effort, Venter and Smith announced their TIGR team had sequenced the first entire genome of a living organism, *H. Influenzae*, at 1.8 million letters of DNA. They published an article describing their work in *Science* two months later. Their announcement sent a shockwave through the HGP community. Even Watson, who had little regard for Venter, said it was "a great moment in science."⁴⁷ What Venter and Smith had shown was that their particular approach, propelled by new computer programs and sequencing machines, could produce results. Nevertheless, most bioscience researchers were skeptical that the technique would work on more complex organisms and certainly not on the most complex of all, the human genome. It was too much akin to relying on a computer to put together a giant jigsaw puzzle. It would force certain pieces together simply because they appeared a fit and would omit others, contended the skeptics.

Collins made clear that HGP would stay on its present course. His goal, he asserted, was to assemble the definitive "book of life." In other words, the HGP approach would yield a complete, high-quality product. The shotgun approach would err and leave gaps. Accuracy was critical where the human genome was concerned, said Collins. He saw two

requirements for achieving the quality product by 2005. The first was "construction of a complete physical map for each chromosome, consisting of a series of purified overlapping fragments of DNA that would provide the raw materials for DNA sequencing. The second was for major improvements in the speed and efficiency of DNA sequencing. Unfortunately, he worried that neither requirement was progressing as he hoped."⁴⁸

Efforts to Speed HGP

Collins was not alone in worrying about HGP's pace. Maynard Olson, who headed the HGP center at the University of Washington, Seattle, wrote a commentary in *Science* entitled "Time to Sequence." While not necessarily subscribing to Venter's approach, he said HGP should get on with the sequencing task, and do so "on time, and under budget."⁴⁹ Also, Waterston and Sulston paid Collins a visit. They were well into their research on *C. elegans*, the roundworm, an organism far more complex than the one Venter and Smith had sequenced. They "were chomping at the bit, urging Collins to let them plunge into all-out sequencing. In the right hands, they argued, the technology was good enough; the only stumbling block was money." "Just do it," Sulston urged. The result might not be as accurate as originally wished, but it would be adequate, they said. It would be a difference between 99.99 percent and 99.9 percent accuracy.⁵⁰

Collins was not ready for such a decision that entailed a major change not favored by many HGP participants. His cautious approach earned him praise in some quarters and criticism in others. What he did do was make several new grants to HGP centers, testing novel techniques and strategies. He said he wanted to see what these pilot projects produced before shifting direction.⁵¹

One strategy that could be employed fairly easily to speed HGP was to get information from HGP out quicker, and seek more communication and cooperation among centers. In February 1996, the Wellcome Trust organized the first International Strategy Meeting on Human Genome Sequencing in Bermuda. In December 1992, NIH and DOE had established guidelines on sharing data and resources, which allowed researchers to keep data private for six months. The question was whether

this policy had to be changed. The answer was yes. A "Bermuda Accord" was struck that stated: "All human genome sequencing information should be freely available and in the public domain in order to encourage research and development and to maximize its benefit to society." HGP participants agreed to release data in 24 hours.⁵²

At the Bermuda meeting, attended by 40 leaders in the genome research community, attention was also given to other aspects of HGP scientific strategy. James Weber, director of the Marshfield Medical Research Foundation in Wisconsin, spoke, touting the shotgun approach. Most of those attending criticized the technique. "They trounced him," a Weber associate stated. "They said [the sequence] would be full of holes, a 'Swiss cheese genome.'" Weber believed the major centers did not want to change from what they were doing to an entirely different strategy. It meant, he said, "overturning their labs." Venter, the foremost advocate of the shotgun approach, was at the meeting, but said nothing.⁵³

Reorientation, 1998–2001

Venter's Challenge

In January 1998, the firm Applied Biosystems, a leading manufacturer of sequencing machines, completed work on its "next generation" technology. The firm believed the advance made was so prodigious that it could assure the 2005 deadline would be met. The new machines sped the process of sequencing enormously. The company knew it could make money selling the machines to HGP and its university centers. It could do even better financially by gaining control of genome data itself and then selling the genomic information. Mike Hunkapiller, president of Applied Biosystems, sought to partner with Venter, who had the scientific expertise Applied Biosystems did not have. Venter seized the opportunity. With his shotgun scientific approach and the bioinformatic technology of Applied Biosystems, he saw his longtime goal, the human genome, now within reach. Soon, Tony White, president of Perkin-Elmer Corporation (PE), parent company of Applied Biosystems, became the third party in the alliance. He provided additional money for the venture. A new profit-making company was formed, called Celera (from the Latin for "swift"). Venter left TIGR to become president of Celera.⁵⁴ Critics noted that the entrepreneurial

Venter had become wealthier with his successive moves: from NIH to TIGR, from TIGR to Celera. Venter, however, recalled he made each move reluctantly, especially the one to Celera. "I didn't want to be in business," he said. "I wanted to do science, but I wanted even more to sequence the human genome."⁵⁵

On May 8, Venter and Hunkapiller met with NIH Director Harold Varmus, and then traveled to Washington Dulles Airport to catch Collins. They informed both men that they had a new technology and the organization to exploit it. Venter said his company would take a limited number of patents and work out license arrangements with pharmaceutical corporations and others interested in the data. He also said he would release sequence data free of charge where appropriate.⁵⁶ Venter remembers the meeting as one in which he stressed a desire for private-public cooperation toward a common goal. He recalls Varmus, at least, as intrigued. Collins, however, has a totally different recollection of what transpired, maintaining that he and Varmus were united, and that Venter's notion of cooperation was on his terms alone.⁵⁷

The next day, the *New York Times* broke the story. HGP now had a private sector rival, it announced. The article declared that the business "venture would outstrip and to some extent make redun-

dant" the \$3 billion public HGP. It suggested that HGP might have troubles with Congress as a consequence. Varmus quickly rebutted these statements in a letter to the *Times*, protesting that the success of Venter's new entity was not a "fait accompli" and that the feasibility of his approach would "not be known for at least 18 months."

From the outset, the media treated the Celera-HGP situation as a race between the private and public sectors. On May 9, Venter certainly acted as if he were in a race. He publicly threw down the gauntlet to HGP, announcing Celera would sequence the entire human genome in three years, at a cost of \$300 million.⁵⁸

Collins' Response

On May 12, Collins held a breakfast meeting with senior HGP staffers, center directors, and key advisers, such as James Watson. The meeting had been planned for several months and just happened to occur at this tumultuous moment.⁵⁹ It was at Watson's Cold Spring Harbor Laboratory and there was an emergency atmosphere. The *New York Times* of that morning carried an article implying the takeover of the Human Genome Project by Venter and suggested that the public enterprise might have to be satisfied with sequencing a mouse instead of a human.⁶⁰



Sequencing Lab at the Whitehead Institute for Biomedical Research.

The individuals at the meeting were upset and angry, outraged by what they had read in the newspapers about Venter's challenge. HGP had spent \$1 billion and completed only 4 percent of the human genome at this point owing to the fact very little of HGP had been focused on human sequencing by then. Most of those present had spent years on the project. How could an upstart like Venter steal their glory? He had the benefit of all the results and technology that came from the public money spent and all the public data HGP had released. But he was holding his own information to himself. What if Congress fell for Venter's claims? Would it kill the public HGP? Of course, the group believed Venter's approach would never work. It was one matter to sequence *H. Influenzae* and entirely another to sequence the 3 billion base of a human being. But Venter was resourceful and could not be underestimated. He was seen as the potential "Bill Gates of Biotech."⁶¹

Venter now had a gigantic bankroll from Perkin Elmer and would be getting 300 \$300,000 sequencing machines that were more sophisticated than those HGP had. He would also be getting one of the world's fastest supercomputers to help him reassemble sequenced fragments. The group worried that he would not really share data, in spite of what he was saying to the media, and would seek commercially to exploit what was rightfully free to all. Watson compared Venter's assault on HGP to Hitler's march on Poland. He asked Collins: Are you going to be a Churchill or a Chamberlain?⁶²

Within three days of Venter's challenge, the Wellcome Trust declared it would double its support for HGP at the Sanger Center, to \$330 million, saying Sanger would take responsibility for one-third of the sequencing. Sulston, the director of Sanger, and Dr. Michael Morgan, the Wellcome Trust's program officer, stated that if NIH pulled out of the race to sequence the genome, they would lead the public effort. Speaking before a packed auditorium at the Sanger facility, Morgan declared the Trust would not only double the Sanger budget, but would challenge any patent applications on DNA sequences it regarded as contrary to the public interest. "To leave this to a private company which has to make money," he declared, "seems to me to be completely and utterly stupid." His audience gave him a standing ovation.⁶³

Soon after the Wellcome Trust action, Collins brought some of the principals in HGP together for a meeting near NIH. This meeting marked the point at which Collins articulated a radical change in policy. He had been building toward this altered course for some time.⁶⁴ In December 1997, Collins had met with some of the key center directors who were engaged in the pilot projects he had funded the year before. He had discussed concerns about the way HGP was organized, the fact that there needed to be greater coordination in order to accelerate the project. From work deriving from the pilots, he had a good idea who his top performers were. The issue for him was whether/when to make a move toward a different organizational strategy. Venter helped push him over the edge of decision in 1998. This was no longer a decision on how to meet the 2005 goal Watson had set. It was now a decision to compete with Venter. That would mean a goal of 2001.

Hence, at the 1998 meeting, Collins proposed a possible reorientation in program strategy. He urged that HGP go for an early "rough draft" of the human genome. He emphasized he was not trying to change the ultimate goal, which was still to produce a near-letter-perfect assembly of all 3 billion bases in the human genome. He argued this rough draft not be seen as "a substitute." His aim was to get 90 percent of the sequence completed and made public by the end of 2001, and then fill in the gaps later. The rough draft would be useful to researchers hunting for disease genes. It would also undercut any patent position Venter or some other company might claim. Collins' new position was greeted with dismay by some HGP participants and with enthusiasm by others. In September, his NIH advisory committee gave him formal approval. Collins declared that "this was not a time to be conservative, cautious, or coast along."⁶⁵

HGP had sequenced 5 percent of the human genome by this time. But both NIH and the Wellcome Trust were about to pump more money into the project, as the public project acquired the same machines as Celera. "The day we announced Celera," said Tony White, "we set off an arms race and we were in the arms business. Everyone, including the government, had to retool, and that meant buying our equipment." Venter got the new sequencing machines first. HGP soon followed.⁶⁶

As HGP acquired state-of-the-art equipment, it reorganized. Up to this time, Collins had presided over a loosely coupled consortium of laboratories across the United States, which were coordinated even more loosely with a number of foreign entities. He had maintained that organizational scheme and enlarged upon it. There were now 16 major genome centers capable of sequencing, known as the G-16. The time had come to centralize, he concluded, with the support of his Advisory Council.⁶⁷

Thus, he soon began funneling additional funds to just three centers—Washington University in St. Louis, Baylor College of Medicine in Houston, and the Whitehead Institute. The Wellcome Trust again increased funding for Sanger. DOE did what it could to strengthen its Joint Genome Institute (as its aggregate of three national labs was now called). What emerged in 1998 was a new management model for HGP that would rely mainly on five genome centers, the ones willing to “sign up” to the demanding requirements he set. This group came to be known as the G-5.⁶⁸ This more centralized approach meant that 85 percent of the work would be performed by the G-5, the rest by the remaining 11 centers, which continued in the program. But money was distributed differently, as was power to make decisions.

Collins offered Celera the chance to join the alliance, but Venter rebuffed the offer and said Collins’ new schedule had little to do with reality. Venter accused Collins “of putting humanity in a Waring blender and coming up with a patchwork quilt.” Collins responded by saying Venter’s program was the “Cliff Notes version of the genome.”⁶⁹

Collins also changed HGP’s scientific strategy. He halted mapping and went fully to sequencing. HGP was converted from an academic-style research effort into an industrial-like crash program, with laboratories operating day and night. As competition heightened, the deadline for HGP was moved up again to spring 2000, 18 months earlier than the previous aim. As the new deadline was again moved closer, the information to be attained became less complete. HGP leaders played down the competition and justified the change in terms of good science. “The best service to the scientific community,” explained Eric Lander, director of the Whitehead Institute, who emerged as one of the

most influential directors of the G-5, “is to deliver the draft sequence rapidly and then to circle back and perform in the course of another year-and-a-half, at most, the finishing of that sequence.”⁷⁰

Collins billed himself as the “operating manager and field marshal” of “team sequence,” as he called the reshaped alliance. About half of the sequence would be produced by Washington University in St. Louis, and Sanger, working in tandem. The team at Houston would concentrate on three particular chromosomes. The Whitehead Institute would focus on one chromosome and “whatever [else] needs to be done.”⁷¹ That turned out to be a great deal, and Lander’s center grew particularly rapidly and took on an assembly-line machine appearance.

Collins told his immediate staff to concentrate solely on managing closely the HGP effort. They drew up charts with milestones and interim deadlines, and monitored performance. Collins had weekly conference calls every Friday at 11:00 a.m. with G-5 directors.⁷² “Signing up” meant the directors agreed to allow others in the team access to their work, virtually as they did it. It was a “checks and balances” scheme to make sure what was done under the accelerated schedule was accurate. Going directly to sequencing put tremendous pressure on the group at Washington University to assemble a usable genome-wide map at unprecedented speed and scale. To Collins’ relief, Waterston and his team “delivered.”⁷³

The center directors involved chafed initially at some of the oversight procedures, and Collins took some of them “to the woodshed,” as he put it, to obviate resistance and gain cooperation. But if HGP was to compete with Celera, which had the efficiency of doing all its work in one facility—where hierarchy prevailed, and money and technology were available and focused—HGP had to change in a big way. Center directors, who normally competed with one another for grants and glory, had to operate like division directors within a “virtual organization.” The G-5 group had to subordinate individual egos to the larger goal of meeting an external challenge. Otherwise, they would fail together. Fortunately for Collins, he was backed strongly by Varmus as he reoriented HGP strategy. The centralization and leadership aspects of this strategy went against the grain of NIH culture,

which was very much "bottom up." The crash project approach was precisely what the NRC had warned against in its 1988 report. But it was now 10 years later, and circumstances had changed. Varmus made sure Collins got the additional money and other support he needed to scale up and redirect his operation.⁷⁴

Keeping Cohesion

Collins' decision to concentrate effort and push for an expedited rough draft sequence initially angered some of those earlier collaborators who felt excluded, but after private meetings with Collins, most parties concerned with HGP coalesced. Not all. Sydney Brenner, of the Medical Research Council in England, didn't like the new policy. "Once the genome initiative got consolidated into this managed project, it became a bit like Stalinist Russia," he complained. "If you're not with us, you must be against us."⁷⁵ The key to getting agreement among various participants was the common fear that if Celera "won," they would have to go through Celera and its patent controls and expensive subscription rates to get access to genomic information. Venter said the fears of academic researchers were groundless. Trust, however, was lacking between the two sides. Whitehead/MIT's Lander had industry connections, but he made it clear that his loyalty in the genome race lay firmly behind the public genome project—what he called "the Forces of Good."⁷⁶

One who left the HGP camp was Gerry Rubin of the University of California at Berkeley. Both HGP and Celera had projects to sequence the fruit fly (*Drosophila melanogaster*). For Venter, sequencing the fruit fly before HGP was a way to show his critics how well his shotgun sequencing technique worked. With "an offer I could not refuse," Rubin was enticed to Venter's fruit fly team.⁷⁷ In the summer of 1999, Celera announced *Drosophila* had been successfully sequenced—in just four months, one-tenth the time it had taken to sequence the previous largest genome, which had been much less complex than the fly. Rubin's defection appalled many associated with HGP, but it showed that Celera had more than a scientific strategy and hardware. It had and could get top technical talent. Ironically, Collins had brought Rubin and Venter together at a scientific conference.⁷⁸

By fall, the radical overhaul of HGP was an accomplished fact. With tens of millions of additional dollars that Varmus helped acquire from the NIH budget, the G-5 centers were being equipped with hundreds of new automated DNA sequencers. They were also adding new personnel to man these machines. Ph.D. students, who had been a large part of the HGP workforce and who found genome sequencing tedious, were increasingly complemented by scores of technicians more suitable for the work. The major university centers changed dramatically in style and appearance. Waterston's lab at Washington University in St. Louis employed 200 people working in shifts and operated 19 hours a day.⁷⁹

However, a serious problem surfaced when DOE signaled a possible agreement with Celera to help it sequence the three human chromosomes for which it was responsible. NIH could not order a sister agency to stay in the fold, but did make its disagreement clear. Moreover, the Wellcome Trust contacted Lord Sainsbury, the British science minister, who held talks with Neal Lane, President Clinton's science advisor. In September 1999, Prime Minister Blair also became involved, presumably asking Clinton to intervene. Whether DOE succumbed to pressure from the White House or from NIH, the fact was that DOE dropped its potential Celera relationship before it was consummated.⁸⁰

The entry of Blair into genome policy reflected the degree to which the issue of control of genome data was escalating to summit-level politics. There were those in both the United States and Great Britain who believed the Bermuda Accord on prompt release of DNA sequence data should become a formal international agreement. That did not happen, but the fact that the move was advocated suggests the degree to which many felt the stakes in the HGP-Celera dispute were exceptionally high. It also shows how different were the political atmospherics surrounding HGP at the end of the 1990s from what they had been at the outset of the decade.

HGP had emerged relatively quietly from the scientific community and bureaucracy. It was Big Science, but took a while to become high-visibility Big Science. Similarly, Walter Gilbert had in the early days tried and failed to get venture capital

for a private genomics company. Now politicians and business executives were hyper-attentive to the implications of genome policy. The media, focusing on "the race," followed developments as an ongoing story. Venter proved highly skilled in using the media to make his case. The discoveries of disease genes along the way had added to the sense that serious issues were involved with this research. Policy makers were increasingly aware that biotechnology could well be the dominant technology of the 21st century, and who controlled that technology mattered not only in health, but also in economic competitiveness. They might not fully understand where the genome project fit in, but they assumed it was at the cutting edge. In short, the genome project was now politicized.

Efforts at Compromise

The obvious political heat and visibility of the contest, the bitter words that appeared frequently in the media, issued by both sides, led some participants to seek compromise. In late 1999, urgent discussions took place. Among those involved were Lander, for the public program, and Rockefeller University President Arnold Levine, a member of Celera's advisory board. There was the view that the approaches were complementary. Also, some Celera supporters worried that if HGP "lost," it might cause Congress to cut NIH's budget for genome research in general, an outcome regarded as negative.⁸¹ There was definitely a threat there, as the debate took on ideological tones of government versus business. The more the debate was framed in that way, the more politicians would take sides, and there could be damage, especially to NIH. Venter seemed to be getting the better of the contest in the media. He came across as David versus Goliath, the outsider versus the establishment. Collins wished to manage science, not a public relations campaign, and he had to learn the political aspects of HGP on the job.

On December 21, 1999, the two sides met. HGP was represented by Collins, Waterston, Varmus, and Martin Bobrow, head of clinical genetics at Addenbrooke's Hospital in Cambridge, England. Venter's group included Tony White, Celera executive Paul Gilman, and Levine. Collins brought to the meeting a draft statement of "shared princi-

ples," which he hoped to release if the meeting went well.⁸²

But the meeting soured. Venter insisted on exclusive commercial distribution rights for joint data for up to five years, whereas Collins considered six to 12 months appropriate (by which time HGP would have essentially completed its sequence and made its data available to everyone). Celera also insisted on rights to various applications of the sequence, including being exclusive distributor over the Internet.⁸³

In February 2000, Collins faxed a "confidential" letter addressed to Venter, White, Levine, and Gilman and signed by Collins, Varmus, Waterston, and Bobrow, reiterating the major disagreements between HGP and Celera. Collins wrote: "While establishing a monopoly on commercial uses of the human genome sequence may be in Celera's business interest, it is not in the best interests of science or the general public." Questioning whether Celera really wanted to budge from its position, Collins gave Venter one week to resume negotiations. Failing that, he stated, "We will conclude that the initial proposal whereby the data from the public HGP and Celera are collaboratively merged is no longer workable." On the eve of Collins' March 6 deadline, the Wellcome Trust released the letter to the media, presumably to pressure Celera. Instead, Celera used the letter to denounce its competitor's "slimy" and "dumb" tactics. The leak provided the media a field day and embarrassed Collins, who denied he had anything to do with the leak.⁸⁴ It also showed that Collins could not control the actions of his British partner.

In addition to many public comments condemning HGP, Celera's formal response to Collins on March 7 was that "... we continue to be interested in pursuing good-faith discussions toward collaboration," provided the company's commercial interests were protected. It saw no problem in releasing data intended "for pure research applications."⁸⁵

The President and Prime Minister Speak Out

On March 14, Clinton and Blair issued a statement on human genome issues, including this paragraph:

We applaud the decision by scientists working on the Human Genome Project to release raw fundamental information about the human DNA sequence and its variants rapidly into the public domain, and we commend other scientists around the world to adopt this policy.

The statement was obviously not only aimed at Celera, but other firms that were interested in taking out patents on genes. Another company, Incyte, was increasingly active. It was not pursuing the human genome as a whole, like Celera; rather, it was targeting a search for specific disease genes it saw as potentially valuable commercially. Clinton and Blair saw a possible problem in the future. However, their remarks caused another problem: a huge dip in stock price for Celera, and the biotech industry generally. That was not what was intended, and it made Venter look even more like a symbol of small private enterprise being pressed by big government.⁸⁶ The *Wall Street Journal* gave him op-ed space to plead his case as a victim.

Success

Having become part of the controversy, Clinton now sought to lead in a solution. He told Lane, his science advisor, to "fix it ... make these guys work together." Unaware of the president's action, Collins spoke to Ari Patrinos, the senior administrator of DOE responsible for that department's part of the genome project. He asked Patrinos if he could do anything to defuse the enlarging conflict.⁸⁷ For years, DOE, which began HGP, had been the junior partner in the government enterprise. Now its leadership was needed as a broker. Patrinos had a series of meetings with Collins and Venter, searching for points of agreement.⁸⁸ It was critical that the one-upsmanship cease, he made clear. The reality was that each side had certain advantages. Venter had the benefit of access to all the genome discoveries, which HGP made public. On the other hand, HGP had started earlier and had much more money. However they started, they were now in a dead heat for the "finish line." Indeed, they were racing for a finish line everyone understood was artificially constructed, in the sense that a rough draft would leave more work to do. At the same time, that finish line was probably good enough to be useful scientifically and politically.

Collins chafed at being in a "race" in which the rules were such that every 24 hours he was giving away data that benefited his competitor. The concepts of "winning" or "losing" did not fit under those circumstances, he felt.⁸⁹ Nevertheless, the politics were such he had little choice but to seek "victory" if a compromise proved impossible. Venter was urged by his business associates to avoid a truce and win the race. The benefits from being first were clear from a business perspective. But Venter saw himself as more a scientist than a business executive, and did not want to hurt NIH. Moreover, while he was confident he was ahead, he knew better than anyone the risks in his approach. Nothing was certain.⁹⁰ Under the terms Patrinos was discussing, Venter and the public project would get equal credit. The first public signs that an accord was within reach came in June when Venter and Collins appeared together without incident at an NIH cancer conference. As the final preparations were hastily laid for a White House ceremony to make the official announcement, Venter and Collins, clothed in ceremonial lab coats, appeared on the cover of *Time* magazine.⁹¹

On June 26, at a White House ceremony, Clinton announced that the rough drafts of the HGP and Celera human genomes were ready. Tony Blair attended via teleconference. James Watson was there in a seat of honor. Collins and Venter made a joint announcement, evincing pleasure with their share of the prize. Neither could claim a complete book of life was attained. That would take more time. According to HGP, it would be 2003 when the ultimate goal was attained. But the basic structure—this was now known, and all that remained was to publish the formal scientific papers.⁹²

Unfortunately, the truce broke down in December over plans to jointly publish. On February 16, 2001, Venter published his paper on the human genome in *Science*, and at essentially the same time Collins' group published its report in *Nature*.⁹³ The debate over who "really" won would go on for years, but was already fading in early 2001. The consensus on the part of most observers at this point in time was that history would say both sides won, with humanity the ultimate winner.

Conclusions

The Human Genome Project is generally viewed as a governmental success. It is also seen as having had frustrations along the way, been intensely controversial, and overcome or resolved the issues that came up. These were hurdles that were technical, organizational, and political. What factors were critical in shaping and influencing the course of the program? There are probably a hundred that could be mentioned. Many are scientific or technological, such as the development of new sequencing machines. The emphasis here is on the managerial factors.

Goals

Large-scale, public, technical projects need clear, unmistakable, specific goals. The larger the projects are, the more important it is that these goals be defined and communicated to all constituencies. What a clear goal provides is a constant point of reference against which to measure, direct, prioritize, and modify actions by various individuals and organizations involved.

The major goal of HGP was clear—to sequence the more than 3 billion letters of the human genetic code. The goal was bold—it represented not an incremental decision but a discontinuous change, a leap forward in science and technology. It was estimated that it would take 15 years and \$3 billion to realize the goal. While there are caveats that might be raised about timing and money, the widespread perception today is that HGP is a federal project that has worked, on time and within budget.⁹⁴

While the ultimate goal did not change, HGP did insert an interim goal, the “rough draft” of 2000.

The interim goal may well have been good science strategy; it was surely good political strategy, needed to compete with Celera. It had the positive impact of accelerating HGP’s movement toward the final goal. The interim goal became as important as the final goal in achieving success, since it established HGP’s credibility at a time HGP was under attack in the media and Congress. Significantly, HGP spent approximately the same amount of money to sequence the interim human genome that Celera did in the 1998-2001 period.⁹⁵ Achieving the interim goal diffused the conflict between the public and private sectors. It was a consensus goal—an arranged finish line. Once met, HGP could continue its work, in a less contested setting, toward the final goal.

Organization

Organization has to do with “who does what,” the formal and informal division of labor. It pertains to the allocation of tasks and whether the parts add up to an organizational machine that helps accomplish the overall mission. Sometimes organizational arrangements stand in the way of mission success. Government bureaucracy is viewed as subject to inefficiency, because it is accountable to many constituencies and embodies values other than pure efficiency.

Venter felt that he had to leave NIH to accomplish the human genome mission. He moved from NIH to a nonprofit organization (TIGR), and then to a profit-making entity, Celera, to find the best possible base from which to accomplish the sequencing of the human genome. His own success in this

respect shows that there are alternatives to government under certain conditions.

One of those conditions is timing. An earlier scientist-turned-entrepreneur, Walter Gilbert, could not attract business venture capital when he tried to set up a company to sequence the human genome in the late 1980s. When a goal is very distant, its attainment problematic, and its costs enormous, government may be the only instrument able and willing to make the huge front-end research investment necessary. When the multiple, initial technical and financial hurdles of a new field are surmounted, the private sector may enter, as it did in the human genome case.

The way government was organized to pursue HGP was not a result of careful strategic planning. Governmental involvement started through DOE; then came NIH, which quickly asserted itself as "lead agency." While NIH was in charge, DOE retained its autonomy, and at one point almost made an arrangement to work with Celera. Keeping what became an interagency international consortium cohesive and pointing in the same direction was critical to HGP success. There were limits to what NIH, as the lead agency, could do, however, as indicated not only by the DOE possible defection, but also by the independent actions of the Wellcome Trust in England in leaking the Collins letter/ultimatum.

The organizational model of HGP for most of its project life was that of a loosely coupled international consortium. Located in six countries, this consortium had multiple sponsors and performers. There were various players engaged and they often moved in accord with individual rather than project-wide goals. However, in the early days of HGP, the mapping and sequencing tasks were viewed as so vast and technically complex as to require a large number of performers, primarily in the academic community. These performers were structured as centers—groups of researchers and technicians working with sophisticated equipment. Moreover, the first director of HGP wanted to maximize geographical spread and participation as values in themselves. He also involved social scientists, ethicists, and legal scholars, asking them to look beyond the science to its impacts.

However, the downside of HGP's structure was sensed by Collins as early as 1995 and became abundantly clear when Celera came into the picture. Venter's scientific approach and brash style made him controversial to HGP leadership and the scientific establishment generally. But his record showed that a single organization, backed by requisite money and technology, could move fast if led by the right person. Confronted by Celera, the second HGP director, Collins, concluded that HGP's organization was too loose and too uncoupled, a barrier to competing with Celera. He went from the pluralistic model he inherited and on which he built, to a more centralized model, relying on the G-5 centers. Efficiency and speed took precedence over participation. The original organizational strategy might well have made sense in the early years of HGP, when it was getting established. However, later, when much of the scientific groundwork was laid and it was confronted by an external competitor, HGP needed a very different organizational approach.

Political Support

HGP has had political support throughout its history. Had the interim goal not been set and achieved, that support might well have eroded. Goals, organization, and political support go together in government programs, one influencing the other. Politicians may understand little about the technical details of HGP, but they do think they know something about schedules and money. They react negatively to what they perceive as mismanagement, as seen in schedule slippage and cost overruns. Hence, what HGP had to do was to show results to keep the confidence of elected officials.

Luckily, HGP drew on a vast reservoir of political support that is virtually unique to NIH. Had DOE been lead agency, HGP might not have fared as well in getting needed resources. But NIH is among the most favored of government agencies, because Congress and the White House see health research as a priority. NIH, like the Department of Defense, wages war—in its case on disease, and politicians tend to worry about their own infirmities as well as those of their families. If national security helps Defense budgets, so personal security helps get money for NIH.

HGP benefited from this situation. Moreover, NIH Director Varmus proved exceptionally adept in working with the White House and, especially, Congress. Since Varmus also favored HGP within NIH priorities, he helped to shore up HGP's political support.

It should be emphasized that while NIH—and HGP particularly—had considerable goodwill in Congress and the White House, it still had to perform. The HGP spinoffs of disease gene discoveries over the years helped in this respect. The attainment of the interim goal helped even more.

Competition

Competition was a critical factor in HGP's success, but could have been its undoing. It was bureaucratic competition with DOE that induced NIH to get started with HGP. Subsequently, HGP faced internal and external competition.

The internal competition reflected the NIH bureaucratic strategy up to 1998. As noted earlier, when the goal of the HGP was announced and NIH became lead agency, NIH decided to use university-based centers as the prime mechanism by which to accomplish the sequencing goal. Universities are notoriously hard to manage, given their emphasis on freedom of inquiry. On the other hand, NIH believed the top researchers it needed were in the universities. The question was how to enlist them in mission-oriented research of this kind and get their maximum output. One answer was organization (centers) and the other was competition. The centers competed for the money in the HGP budget. The competition was important in getting the universities to maximize their effort and deliver on their promises.

NIH used peer review in managing the competition. That is, those centers that participated had to prove to reviewers, as well as NIH, that they were better than others, or would perform a specific task others could not. This enabled HGP to get academic talent working on the project that was top flight, or at least perceived as such by the scientific community. Center directors, particularly, were members of the academic elite, individuals who had established credentials and were competitive for themselves and their institutions. HGP used

such competitive drives to get the most from extramural research. Non-performing centers could be dropped from the project. This system emphasizing many university centers is probably sound for a project at a scientific frontier, when technical uncertainties are limiting factors, and there is a need to explore more than one route to success. Yet internal competition can also slow down a project that has severe deadlines. There comes a point where what is a valuable form of competition early in a project can be a barrier to achievement later in its life. This is especially so where external competition becomes a dominating factor in decision making.

The external competition came from Celera. It was formidable scientifically and politically. Venter was a strong and determined rival, and the evidence suggests HGP—and the biomedical research establishment—erred for a long time in not taking him seriously. He was tenacious, skilled, and outspoken in his challenge to HGP. His shotgun approach was not valued by NIH and its peer reviewers, but one has to wonder whether it was his approach or Venter himself who was at issue prior to his sequencing *H. Influenzae* in 1995. After that event, he had to be taken seriously. Moreover, in 1998, when he got an edge through new advanced sequencing machines, he forced HGP to realize how capable a rival he was. From 1998 to 2001, HGP moved into a crash project mode and Venter became the enemy. He became the measure against which HGP performance was to be judged, for better or worse. Whether or not HGP wished to be in a race, it was in one.

Leadership

Circumstances affecting large-scale technical projects change over time. The ultimate goal may be a constant, an overall destiny. Getting there entails shifting strategies that are scientific, organizational, and political. Leadership is utterly critical—probably the single most critical factor in success. It took a certain leadership to launch HGP, and another kind to make the changes that are bringing it to a successful conclusion.

HGP had had two very different leaders. Watson was a charismatic leader, a man who will go down in the history of science for co-discovery of the

double helical structure of DNA in 1953. He was the best possible person to launch HGP at a time when it was highly controversial among scientists. Few others could, by sheer personal force, have made HGP not only legitimate, but also "where the action was" in bioscience. Great projects that promise breakthroughs require recruitment of extremely able people. It is almost impossible to quantify this human dimension of projects, but there are certain projects that draw the very top people in a field to them. Having Watson at the helm made a difference in this respect. Watson was also an exceptional "scientific salesman" for HGP before Congress. The spreading of centers around the country was no doubt good science in Watson's mind, but it was also good politics, building a legislative base for HGP at the outset, when it needed it. Internationalizing HGP may have also made sense scientifically, but it additionally served Watson's purpose to make HGP a project for the world, not just the United States. Moreover, it supplemented funding of HGP. Early support of the U.S.-British Waterston-Sulston team turned out to be especially significant.

But it is not at all clear that the volatile, often abrasive Watson was the right man to implement HGP over the long haul. There are charismatic and institutional leaders, the latter following the former. Collins appears to have fulfilled the role of institutional leader well. Less flashy, much more consensual in style, Collins was able to strike an alliance with Varmus, his superior at NIH, nurture congressional relations, and develop a team approach to management that became increasingly critical as time went on.

Collins might have initially operated primarily as a "maintainer" and "augmenter" of the Watson approach during his tenure. But circumstances were such that his greatest contribution to HGP's success was his later decision to reorient the project. The process that led to this decision started before Venter's 1998 challenge, perhaps as early as 1995, when Waterston and Sulston paid him a visit and argued for a rough draft strategy that moved more rapidly from mapping to sequencing. His thinking evolved in 1996 with pilot projects to find ways to speed the project. Then came a meeting in 1997 with HGP principals in which he discussed the need to restructure HGP to meet the 2005

deadline Watson had set. Within months, Collins shifted to a crash program with a 2000 deadline for an interim goal. Perhaps he should have moved sooner toward the crash project mode, but would such a move have been possible in the NIH culture without the sense of crisis that Venter posed? What Celera did was present an external threat that empowered Collins to make big changes. Collins moved from the role of a project manager to a project leader. The bold changes he made affected science, organization, and politics.

Forces internal and external to HGP converged, and Collins acted. He did so in the nick of time and in such a way as to save HGP's credibility. It is ironic that Venter helped Collins reorient HGP. Venter created a crisis that affected not only NIH but also the bioscience establishment generally, putting into sharp question the basic government-university strategy for getting the research done. Collins transformed the loose consortium into a tight alliance with a small circle of performers and decision makers. Had Collins and others not responded, the public HGP might well have "lost"—or appeared to have done so. Appearances can be as important as reality in government, and public ridicule could have been HGP's fate.

Instead, HGP is today acknowledged a success, even as it completes the full decoding of the human genome. If Collins was empowered by external competition, Venter received vindication for his effort when he stood together with Collins at the White House victory ceremony. A negotiated finish line made both sides winners and allowed science to move ahead toward the ultimate goal, a complete genome in 2003.

Ironically, the continuing progress of HGP, and its policy of early release of data, may have contributed to the decision by Celera's parent company to change Celera's course from selling new genomic information to developing drugs. This decision forced Venter to resign as Celera's president and scientific leader in early 2002.

In conclusion, the Human Genome Project shows that relationships among government, national laboratories, industry, universities, and foreign partners are changing dramatically at the frontier of science. The Human Genome Project may well be a harbinger

ger of the future in more ways than one. It is likely a model for large-scale technical projects in the 21st century. The implications of this case for science, policy, and administration are therefore profound.

HGP is both like and unlike the Manhattan and Apollo projects. It is alike in being a mega project that is also a breakthrough project. It is different in being transnational and involving the private industry sector as an autonomous (possibly adversarial) actor, rather than strictly as a contractor. HGP, in the present transition phase, is now consciously partnering with the private sector in looking to genomic applications in health. In some cases, joint funding is involved. There is evidence that other institutes at NIH are looking at HGP as an example of an approach they might emulate.⁹⁶ The next phase in the human genome revolution has already begun.

Implications for the Future

Most observers of the Human Genome Project's history concentrate on the contest between HGP and Celera. This makes sense in view of competition's role in the events. As we have noted, it was a critical factor in accelerating HGP's schedule. However, the record of HGP also shows the importance of partnership as instrumental in bringing about a capability to unravel the human genomic blueprint.

HGP, particularly in respect to partnership, may be a harbinger for the future in the way large-scale R&D projects are run. As noted in the previous section, HGP is both like and unlike the Manhattan and Apollo projects with which it is often compared. It is alike in being a megaproject that is also a breakthrough project. It is different in being interagency, transnational, and involving a private foundation as a co-financer. In the present transition phase, industry is becoming involved as a financial partner in supporting research for practical cures in disease. Industry, in working with HGP, accords with "the rules," meaning companies must release findings from the HGP research in which they participate every 24 hours. Other institutes at NIH are emulating HGP's large-scale approach to management, which is a partnership model.

What HGP's approach suggests is that where very challenging objectives are involved, and talent is distributed widely, it may be necessary and desirable to link institutions into vast research consortia. More than one-third of HGP's budget came from sponsors other than NIH. Performers included national laboratories, universities, and researchers in six countries.

Such partnerships have advantages and disadvantages. The negatives are obvious—the partners have wills of their own and may defeat or slow down the achievement of system-wide goals. There has to be a leadership structure of some kind to provide coherence, direction, and pace. The HGP model entailed a "lead agency" approach with NIH fulfilling that role by virtue of dominant funding, political support, and technical competence. While an agency may seek to lead, others may not necessarily follow. Partnerships require leadership of one kind or another, and sometimes a form that works at one point in a project's history may not at another. A mix of stability and change are essential in keeping partners together. Hence, the HGP model is one about which observers who prefer neat organizational lines, strong hierarchical management, and predictable strategy may find fault. There can be inefficiencies in partnership arrangements as consensus takes time to be forged. Nor are performers of R&D in universities or other entities always willing to go along with central decisions. Leadership often comes down to the power to persuade.⁹⁷

Still, for better or worse, HGP does seem to be a forerunner for what is to come. It reveals a type of large-scale "network" or "system" in which the leader (an organization or person) has power that is limited, but can be enhanced. It is not "power over," but "power with."⁹⁸ Bargaining, negotiation, prodding, cheering, complaining, charming, coercing—all are techniques of management in partnership relations. These large-scale systems can include partners who are sovereign nations. That is the case

with the largest science and technology project currently under way in the civil sector, the International Space Station (ISS). NASA is “lead agency” for a project involving at least 16 nations. One of the partners is Russia, which openly defied NASA in selling room on its portion of the Space Station to a wealthy “tourist,” Dennis Tito. HGP thus seems more like its contemporary project, ISS, than predecessors like Manhattan and Apollo. These were both models of centrally controlled national projects. One took place in a war setting and the other was a technological front of the Cold War.

If one looks hard at what is “new” in the way current science and technology programs are being run, the observer sees, increasingly, large-scale R&D efforts that cross agency lines, involve government-private alliances, and stretch beyond the United States. The last-mentioned characteristic is, of course, a reflection of globalization in R&D.

Looking forward, what great projects lie in the 21st century for which HGP is a possible model? One can imagine projects such as: the search for a new disease cure; a way to mitigate global warming, while still having energy to develop economically; a mission to Mars or one to divert oncoming asteroids; a technological front against terrorism; and others. Whatever lies ahead—and the unexpected is to be expected—HGP’s lessons show that diverse institutions can be brought together in pursuit of bold goals that stretch beyond a decade. Partnership takes scientific vision and political will. But it also requires administrative leadership to get multiple, independent partners to adhere. It also helps if there is an urgency born of external competition and threat.

If interagency, intersectoral, and transnational partnerships are going to be the wave of the future in science and technology (and other spheres of policy), what does that say for the skills needed of individual leaders? It certainly suggests they will have to be able to grapple with increasing complexity and greater bureaucratic, political, and cultural diversity. Does current education for the leaders of tomorrow prepare them adequately? If HGP is a guide, the answer matters greatly, for the future is arriving fast!

Endnotes

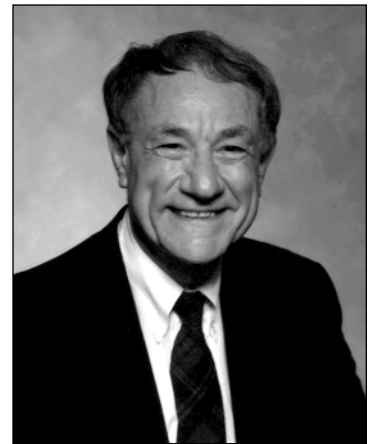
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2. Wade, 7.
3. Most of this money was spent on technology development, genome maps, and model organisms. The sequencing stage—the culmination—was a relatively small part of the overall expenditure. Correspondence to author from Francis Collins, Jan. 29, 2002.
4. J. Craig Venter et. al., "The Sequence of the Human Genome, *Science* (February 6, 2001), 1304-1351. International Human Genome Sequencing Consortium, "Initial Sequencing and Analysis of the Human Genome," *Nature* (February 15, 2001), 860-921.
5. The phases are not precise but do represent significant shifts in emphasis. For example, in preparing for the transition phase HGP funded various technology development projects. Correspondence to author from Francis Collins, Jan. 29, 2002.
6. Wade, 9-10.
7. Other factors, including personality conflicts, exacerbated the situation.
8. Interview with Francis Collins, December 4, 2001.
9. Correspondence to author from Francis Collins, Jan. 29, 2002.
10. Interview with Elke Jordan, deputy director, National Human Genome Research Institute, National Institutes of Health, July 19, 2001.
11. Francis Collins holds that HGP had many goals and the widely reported comparison raised an "apples and oranges" issue that made the public project appear less cost-effective than the private effort. Correspondence to author from Francis Collins, Jan. 29, 2002.
12. Kevin Davies, *Cracking the Genome: Inside the Race to Unlock Human DNA* (New York: The Free Press, 2001), 150.
13. Wade, Chapter 1.
14. Leslie Roberts, "Controversial from the Start," *Science* (February 16, 2001), 1182-1188.
15. Robert Cook-Deegan, *The Gene Wars: Science, Politics, and the Human Genome* (New York: W.W. Norton & Co., 1994), 10-11.
16. Roberts, 1183. Cook-Deegan, Chapter 5.
17. "A History of the Human Genome Project," *Science* (February 16, 2001), 1196.
18. Roberts, 1183-1184.
19. Roberts, 1184.
20. Wade, 30.
21. Cook-Deegan, 131-132.
22. Roberts, 1184-1185.
23. Interview with Elke Jordan, July 19, 2001.
24. Cook-Deegan, 161.
25. Roberts, 1185.
26. Roberts, 1185.
27. Interview with Francis Collins, November 30, 2001.
28. Wade, 15, 32.
29. Interview with J. Craig Venter, November 25, 2001.
30. Roberts, 1185.
31. Cook-Deegan, 328.
32. Cook-Deegan, 332-333.
33. Roberts, 1186.
34. Roberts, 1186.
35. Venter interview.
36. Cook-Deegan, 341; Davies, 69.
37. Collins interview, November 30, 2001.
38. Officially, Collins is on leave, and has been on leave since 1993. Collins interview, November 30, 2001.
39. Cook-Deegan, 343.
40. Davies, 64.
41. Roberts, 1186.

42. Roberts, 1186.
43. Collins interviews.
44. Venter interview.
45. Davies, 106.
46. Collins does not recall this phone call, which Venter remembers. Venter interview. Collins correspondence to author, Jan. 29, 2002.
47. Davies, 107.
48. Roberts, 1187; Davies, 86.
49. Davies, 86-87.
50. Roberts, 1187.
51. Roberts, 1187.
52. Davies, 87, 148.
53. Davies, 142.
54. Davies, 146-147.
55. Venter interview.
56. Davies, 147.
57. Venter and Collins (November 30, 2001) interviews. See Wade's description of the meeting, Wade, 45-46.
58. Davies, 148; Roberts, 1187.
59. Collins correspondence to author, Jan. 29, 2002.
60. Davies, 150.
61. Davies, 5; Roberts, 1187.
62. Davies, 150.
63. Davies, 151.
64. Collins interviews.
65. Davies, 162; Roberts, 1188.
66. Davies, 167.
67. Collins interviews.
68. Davies, 163.
69. Davies, 163.
70. Davies, 163.
71. Davies, 164.
72. "The Public Genome Team Races..." *Newsweek* (April 10, 2000), 52.
73. Collins correspondence to author, Jan. 29, 2002
74. The importance of Varmus cannot be underestimated. Elke Jordan, who served under both Watson and Collins as deputy director, notes that Varmus was an unusually capable NIH director, both internally and in relation to Congress. He made a positive difference in the life of HGP and gave it priority in his budget decisions. Interview with Elke Jordan, July 19, 2001.
75. Davies, 152.
76. The MIT center grew to 200 researchers and technicians and produced one-third of the human sequence. It became the flagship of the U.S. effort according to Davies, 165.
77. Davies, 159.
78. Collins interview, November 30, 2001.
79. Wade, 49-50.
80. Davies, 206.
81. Davies, 198-199.
82. Davies, 199.
83. Davies, 200.
84. Davies, 204. Collins interview, November 30, 2001.
85. Davies, 204.
86. Davies, 205-206.
87. Collins correspondence to author, Jan. 29, 2002.
88. Davies, 238.
89. Collins correspondence to author, Jan. 29, 2002.
90. Venter interview.
91. Davies, 238.
92. Davies, 236-237.
93. J. C. Venter et. al., "The Sequence of the Human Genome," *Science* (February 16, 2001), 1304-1351. International Human Genome Sequencing Consortium, "Initial Sequencing and Analysis of the Human Genome," *Nature* (February 15, 2001), 860-921.
94. While the United States (the National Institutes of Health and the Department of Energy) has spent approximately \$3 billion, the Wellcome Trust has spent hundreds of millions in addition to accomplish the purpose. Other governments have also spent funds. There is also some ambiguity about timing. HGP began in 1986 as a DOE project, became a national project with the entry of NIH in 1988, but HGP Director Watson declared 1990 as the start date for the 15-year time clock. Hence, if one accepts the Watson timetable, HGP will be complete ahead of its 15-year schedule, in 2003. These ambiguities have relevance to the perception of success. Similarly, there were two finish lines—the interim one in 2000 and the final one in 2003.
95. According to Collins, the figure was approximately \$300 million. Collins correspondence to author, Jan. 29, 2002.
96. William Schulz, "Determining Structure: 'Big Science' Protein Structure Initiative Touches Off Lively Debate," *Chemical and Engineering News* (October 15, 2001), 23-26.
97. Richard Neustadt, *Presidential Power: The Politics of Leadership* (New York: John Wiley and Sons, 1976).
98. W. Henry Lambright, *Powering Apollo: James E. Webb of NASA* (Baltimore, Md.: Johns Hopkins University Press, 1995).

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