Academy Backs Genome Project

The nation should embark on an all-out effort to map and sequence the genome, says a National Academy of Sciences panel, but how the project will be managed remains unclear

In a report published this week, a National Academy of Sciences committee strongly endorses a massive national effort to map and sequence the human genome. Although the committee recommends that up to $3 billion be spent on the project, it ducks the contentious issue of which government agency should lead it. Apparently hesitant to wade too deeply into policy waters, the committee concluded that the project should be run by a single agency—either the National Institutes of Health, Department of Energy, or the National Science Foundation—but stopped short of saying which one.

The early goal of the project should be genetic and physical maps of increasing resolution—with a fully detailed map of the chromosomes completed within a decade. The ultimate goal, the committee says, is the sequence itself. The immediate payoff will be in speeding the search for disease genes, with implications for diagnosis, treatment, and prevention, it says. Eventually, the map and sequence data will help to elucidate fundamental questions of gene control, genome organization, cellular growth and differentiation, and evolutionary biology.

Since it was first proposed over 2 years ago, this project, which has been likened to a "holy grail" of biology, has been mired in controversy over its scientific merit and high cost. Many biologists agree that mapping the genome, a relatively modest part of the endeavor that involves determining the location of the 50,000 or 100,000 genes along the chromosomes, will be of immense value. But consensus quickly breaks down when it comes to sequencing most or all of the genome—that is, working out the exact order of all 3 billion nucleotide bases that make up the human genetic complement.

Few question that having the sequence would be useful, but whether it is worth the estimated $3 billion to get it reasonably quickly, say over the next 10 or 15 years, is another matter. At that level, the project clearly represents Big Science, raising fears that it will divert funds from other areas of biological research and otherwise disrupt the conduct of heretofore Small Biology.

The committee, like much of the biological community, was divided on these issues when it began, but after a year of deliberation, it came out resoundingly in favor of the project. Obtaining the map and sequence is of such immense importance to medicine and biology, the committee says, that it cannot be left to the normal scientific process. Rather, it merits a special effort, and $200 million a year in "new and distinctive" funds, over the next 15 years. Although the committee avoids providing a total bill for the project, it comes in at $3 billion, in keeping with earlier estimates.

The committee cautions against a crash program, however, recommending instead a phased approach that would begin with mapping and technology development, then move on to sequencing regions of interest and other small genomes. Full-scale sequencing would be postponed until technological advances can make it faster and cheaper.

The committee included some of the staunchest advocates of the project, as well as some vocal opponents. Others, like chairman Bruce Alberts of the University of California at San Francisco, had not been intimately involved in the debate and were "neutral to skeptical," as he describes it.

What brought consensus to this diverse group was the realization that the project could be structured in a way that minimizes disruption to other areas of biological research. As Charles Cantor of Columbia University says, it need not involve "a monolithic institute with thousands of people chained to the bench churning out sequence," but could be a phased approach with an emphasis on comparative genetics and parallel efforts to understand the genomes of other organisms, from bacteria to the mouse. "You can't be against getting this information; it is too fundamental."

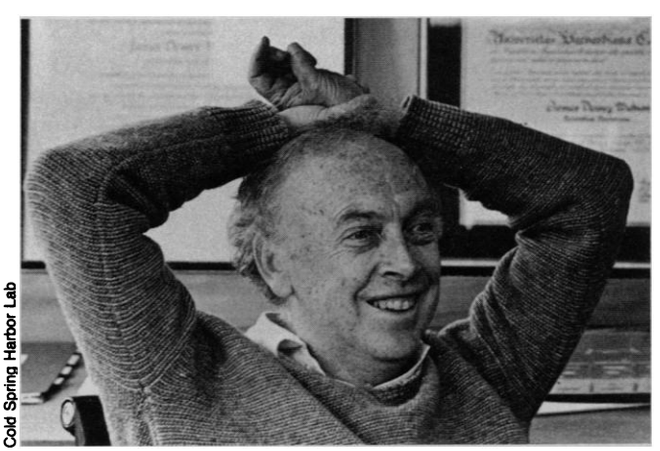
Addressing one of the key concerns of critics, the committee says that no centralized sequencing center is needed, at least not at this stage. Instead, funds should be distributed through a rigorously reviewed competitive grants program to both individual investigators and to about ten multidisciplinary research centers (staffed by 30 to 100 persons) that would focus on both technology development and mapping. A data center and a stock center, for handling and distributing clones and other biological materials, must be established and well funded, the committee says. It also proposes a strong scientific advisory board—with enough teeth to ensure that its advice is heeded—to coordinate the effort and monitor peer review and quality control.

The committee "vigorously encourages" the development of automatic, high-speed sequencing technologies. It also recommends a pilot project, which would begin immediately, with the goal of sequencing 1 million bases of continuous sequence, or approximately five to ten times the amount achieved to date.

At the same time, parallel efforts should be under way to map and sequence the genomes of other organisms, starting with relatively small genomes, like bacteria, yeast,

James Watson

"It has got to go ahead, it is so obvious. The only question now is the rate and under whose auspices."



Cold Spring Harbor Lab

nematode, and fruit fly, and eventually moving up to the mouse. This will avoid the "false emphasis on the uniqueness of human materials for understanding ourselves," the committee says.

A sticking point in the debate over the project, for both the committee and the biological community, has been whether the entire genome should be sequenced, with the cost and labor that implies, or whether the effort should be focused on known regions of interest, say the 5% of sequences thought to code for genes. After some debate, the committee came down in favor of sequencing all 3 billion bases.

Although early efforts should focus on regions of particular interest, by the time sequencing begins on a massive scale it will probably be easier and cheaper to sequence whole blocks without trying to discriminate among them. In addition, the committee notes, many of the apparently uninteresting stretches will undoubtedly prove to be otherwise. "The genome sequence will serve as a basic 'dictionary' that will catalyze striking advances in our understanding of cells and organisms."

All of this can be done for about $200 million a year, or about 3% of the federal budget for biological research. And most important, the report concludes, it can be done without threatening the existing biological research community. To ensure that, however, the money must be "new and distinctive," which means it should not be diverted from currently funded research. Making that stick is another matter. NIH officials have expressed concern, for instance, that Congress may appropriate such "new and distinctive" funds, but later, if enthusiasm wanes, the institute will be stuck with the bill.

Second, funds should be distributed through peer review, and divided roughly evenly between individual investigators and multidisciplinary research centers, which would probably be affiliated with major universities. Such an organization, the committee says, "ensures that our extraordinarily successful pattern of doing biology will be preserved."

The committee envisions about ten such research centers, and many smaller research groups—about 1200 people in all, in the first 5 years of the project. And that is roughly how it came up with the figure of $200 million; $120 million for salaries and support, and $55 million for construction and equipment. The remaining $25 million would go to the stock and data centers and to administrative costs.

These figures, admittedly, are rough. "It's big enough to get it done but not so big that it will detract from other areas," says James Watson of Cold Spring Harbor Laboratory. "Two hundred million dollars is not that much money."

As for how the mammoth project should be managed and administered, the committee admits that it has little expertise in this area. It plunges in, nonetheless, at least part of the way. It recommends, though not unanimously, that the project should be run by a single agency, which would receive a direct appropriation from Congress. However, in a move that may leave those in Congress scratching their heads, the committee declines to specify whether it should be NIH or DOE. These two agencies have been engaged in something of a turf battle over that very issue. A third possibility, the NSF, is generally seen as an unlikely one.

"You can't be against getting this information; it is too fundamental."

Even the recommendation of a single lead agency was not decided until the last minute, in a flurry of long distance phone calls just as the report was going to press. What the committee strongly feels is that scientists—not bureaucrats—should have a major role in guiding the project, but translating that into a feasible policy proved tricky. The original recommendation was that the project should be run by a committee of independent scientists, who would make the major decisions and instruct the agencies on how to distribute their funds. It took a reviewer, well versed in Washington ways, to convince them that the idea would not fly in Congress or the agencies.

"In the earlier version we waffled a little on how it should be administered," admits Victor McKusick of Johns Hopkins University, "and we still don't get into specifics in that regard."

Since the committee members could not agree, the report presents three options, with a majority endorsement of the first: a single agency with a scientific advisory board; an interagency committee and a scientific advisory board; and the same interagency committee, but with one agency to handle administration.

Although the lead agency would have ultimate responsibility, the committee pushes for a strong advisory board that would have a prominent role in peer review and scientific coordination of the project. To give the board the necessary teeth, it would have a full-time chairman, who would be a distinguished scientist, a paid staff, and a rotating membership appointed by the lead agency.

The committee maintains publicly that it was not its role to designate a lead agency, but individual members admit that doing so would have been difficult, if not impossible, given their strong views on the topic.

Some committee members think DOE should get the project simply because of its commitment and resources. Moreover, DOE was one of the early advocates of the project, has experience in managing large-scale tasks of this nature, and is keen to do the job. Other members, including Watson, are said to be adamantly opposed to a central role for DOE.

The main problem is peer review. "The argument against DOE is that while they talk about peer review, it is not clear that they do it," says Alberts. " We were unanimously worried about whether the money would be spent in a competitive way or go to the national labs to bolster their programs. We would be happy with DOE if it would change its way of operating. There are hints that it will."

NIH, on the other hand, is perceived to have expressed very little interest in running the project, at least not at the scale the committee believes is necessary. While most of the committee favored NIH, "you can't have a lead agency that doesn't want to do it," says Alberts. "That is part of the reluctance, on the part of the committee, to say who should do it," adds Watson.

Part of NIH's hesitation is a concern that the project will drain funds from other research areas. To Watson, the solution is simple: locate the project within the NIH director's office, thereby minimizing the possibility that it will compete with other institute funds. "We would hate to see it in GMS [the institute for general medical sciences] where it might take money away from the things they do so well."

A decision on a lead agency could be made by the agencies themselves or Congress, which is expected to hold hearings soon. What matters most, committee members say, is that Congress appropriate funds for the project, not who should run it.

The Academy's report is the second to come out in favor of the genome project—the first was by an advisory committee to DOE. The congressional Office of Technology Assessment will weigh in next, with a report due out in April that addresses in greater detail the administrative issues the Academy panel did not.

Watson, for one, expects Congress to be persuaded of the importance of the project. "It has got to go ahead, it is so obvious. The only question now is the rate and under whose auspices." ■ **LESLIE ROBERTS**