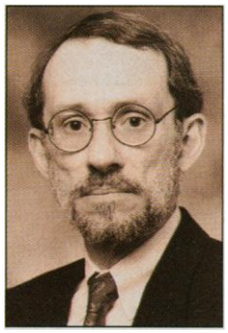
HUMAN GENOME PROJECT

Physicists Urge Technology Push to Reach 2005 Target

In the 1980s, the Department of Energy (DOE) was the first U.S. agency to invest in the Human Genome Project, an attempt to decipher the human genetic code. But DOE's role has been overshadowed in the 1990s by a well-funded latecomer, the National Institutes of Health (NIH). In 1998, for example, NIH will spend roughly $218 million on its National Institute for Human Genome Research. DOE, in comparison, will spend $87 million on genome work. But both agencies have pledged to support the same objective—to determine all 3 billion bases in the human genome by 2005.

This target seemed ambitious when DOE and NIH adopted it 5 years ago. And for DOE, which recently acquired a new management team and is revamping its program, it still looks very difficult. Indeed, this winter, DOE has received a new warning about the difficulty of the task from a group of advisers known as the JASONs—an independent group of physicists and engineers who got together in 1960 to advise the military on weapons design. In a report issued this month, they warn that unless DOE and NIH make a significant improvement in technology used to sequence the genome, they may not reach their goal by 2005.

DOE seems to be taking this warning seriously, although it lacks the budget to make the sizable investment in technology that the JASONs recommend. NIH's genome institute director, Francis Collins, seems less concerned. "We are confident," he says, that with the ramp-up in genetic sequencing being promised by NIH-funded centers, "we will reach a level of output ... that will allow us to cross the finish line in good form." Collins says that if a current snapshot of production is correct, NIH-funded centers will generate 80 million bases of human genomic sequence this year, and will reach an annual production rate of 400 million to 500 million bases in a few years. DOE's program has contributed less than 2 million bases thus far, but hopes to scale up to 20 million in 1998 (see chart).

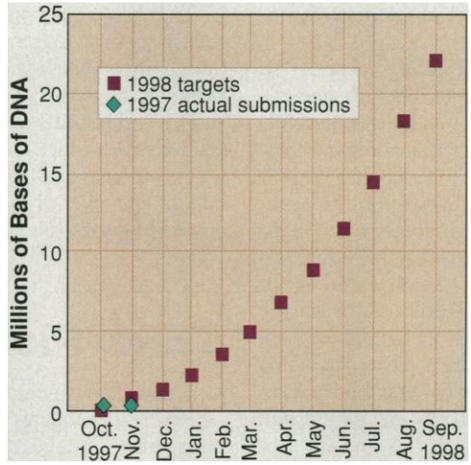


Seeking advice. Patrinos asked JASONs to look at genome project.

The JASONs were invited to take a look at DOE's contribution to the effort by Ari Patrinos, the mechanical engineer who took charge of DOE's human genome portfolio last year. For more than a year, Patrinos has been trying to hitch up three big genome research groups at the Los Alamos, Lawrence Livermore, and Lawrence Berkeley National Laboratories to a common strategic plan, and he looked to the JASONs for help.

Patrinos says he had worked with the JASONs on climate change in the past and thought they might provide a fresh view of the genome project from "outside the community." A group headed by computational physicist Steven Koonin, a provost of the California Institute of Technology in Pasadena, received a briefing from top genome scientists last spring and toured the three major sequencing centers. This month, they released the first of what Patrinos expects will be several advisory reports (see p. 36).

DOE's SEQUENCING GOALS



SOURCE: DOE

Tough targets. DOE has set ambitious goals for this year's sequencing effort.

In their report, the JASONs suggest that DOE's top priority should be to develop "advanced technology" for futuristic genome research, and they urge DOE to increase its budget for such research by 50% (to $20 million a year). The report also makes several suggestions for improving current technology, such as creating a "user group" to improve the performance of gel electrophoresis machines. In addition, it says that DOE should develop a quantitative approach to assessing the quality of genomic data, drawing upon the weapons labs' expertise in computational analysis. DOE should also improve the management of its own genomic databases, the JASONs concluded.

Arguing that sequencers desperately need more efficient machines to read DNA and better software to analyze the output, the JASONs report warns that "if the DOE does not continue to play a leading role in technology development ... it is not clear to us who will." Collins takes issue with this remark, which he considers "not fully informed." He says NIH spends more than $22 million a year on technology development and at least $2.5 million on ideas that have "nothing to do with" current technology.

At DOE, Patrinos must decide how to fit the advice into what he calls "a major reform" of DOE's genome program, which is now under way. Sequencing teams based at three DOE laboratories have been consolidated into a single Joint Genome Initiative, headed by DOE bioinformatics expert Elbert Branscomb, formerly of Livermore in California. Meanwhile, DOE has leased two buildings to create a new "sequencing factory" in Walnut Creek, California. Patrinos has told DOE's genome staff that its first job is to get the factory running and crank out 20 million bases of human genomic DNA within the next year—which he agrees is a "tough" objective. DOE soon will solicit bids to fill its new Walnut Creek factory this summer with $6 million worth of new sequencing equipment.

In some areas, the DOE reform dovetails with the JASONs' advice. The report insists, for example, that "quality issues must be brought to the fore," and it proposes that DOE fund new research on ways to make sure that the published sequences are accurate. Patrinos notes that he is planning a new set of DNA quality-control standards, along with a major overhaul of database management—although not all the details have been disclosed. The report also recommends a "systems approach" to mass-producing biological data and suggests that lab managers create "error budgets" for each stage in the production process. These ideas, which some DOE scientists have called "naïve," are under review.

But Patrinos acknowledges that there is "some tension" between his decision to emphasize a rapid ramp-up in the output of sequence data and the JASONs' recommendation that DOE focus on new technology. He concedes that, without a larger budget, the DOE project cannot invest as much as he would like in new technology projects. For now, he sees no alternative but to emphasize production, noting that he's "a little nervous" about meeting the 2005 target.

–Eliot Marshall