As part of an intensive effort to develop a new generation of machines that will sequence DNA at a vastly reduced cost, scientists are decoding a new human genome — that of James D. Watson, the co-discoverer of the structure of DNA and the first director of the National Institutes of Health’s human genome project.

Decoding a person’s genome is at present far too costly to be a feasible medical procedure. But the goal now being pursued by the N.I.H. and by several manufacturers, including the company decoding Dr. Watson’s DNA, is to drive the costs of decoding a human genome down to as little as $1,000. At that price, it could be worth decoding people’s genomes in certain medical situations and, one day, even routinely at birth.

Low-cost decoding may bring the genomic age to the doctor's office, but it will also raise quandaries about how to safeguard and interpret such a wealth of delicate and far-reaching personal information.

The first human genome decoding, completed by a public consortium of universities in 2003, cost more than $500 million. With the same technology, dependent on DNA sequencing machines made by Applied Biosystems, a human genome could probably now be decoded for $10 million to $15 million, experts say.

Much greater efficiency is expected from the new generation of DNA sequencing machines, based on different, highly miniaturized technologies. One machine, made by 454 Life Sciences, has been on the market since March 2005. Another, made by Solexa, will start shipping this summer. Applied Biosystems will start marketing its own next-generation machine next year.

Last month, at a training course organized by the Cold Spring Harbor Laboratory on Long Island, researchers were learning how to use the DNA decoding machines made by 454 Life Sciences. Looking like a hybrid between a washing machine and a giant iPod, the machines cost $500,000 each, not counting the computer software needed to analyze the results.
At their heart lies a plate of light-sensitive chips, the same as those used in telescopes for detecting faint light from distant stars. On top of the plate sits a glass slide pitted with thousands of tiny wells, each containing a fragment of the DNA to be decoded.

As each unit of DNA is analyzed in a well, a flash of light is generated by luciferase, the enzyme that fireflies use to make themselves glow. The telescope plate records the twinkling lights from each well and, at the end of the run, which lasts four or five hours, the sequence of units in each well’s DNA fragment has been recorded. The fragments are about 100 units in length, and from their overlaps a computer can then be set to piece together the entire genome they come from.

In the training course, the project was to analyze DNA from a Tasmanian devil, a marsupial afflicted with a mysterious malady called devil facial tumor disease. The researchers found that the genome was laden with a virus that had integrated its sequence into the devil’s DNA.

The 454 machine can assemble small genomes like those of bacteria, which perhaps accounted for the presence at the course of three scientists from the Department of Homeland Security. But the human genome is about 600 times larger than a bacterium’s and includes many repetitive sequences that, like identical pieces in a jigsaw puzzle, make the solution much harder.

At the Cold Spring Harbor course, researchers heard Dr. Watson, the laboratory’s chancellor, say that 454 Life Sciences had asked to sequence his genome with their new machine. Only two human genomes have been sequenced to date. The genome sequenced by the public consortium was a mosaic of DNA from several anonymous people. The consortium’s rival, Celera Genomics, prepared a draft sequence, most of it from the genome of its former president, Dr. J. Craig Venter.

Dr. Watson told the students that he had given the company permission to publish the sequence of his genome, “provided they didn’t release to the world that I have some disease I don’t want to know about.”

Genomic information can already reveal a lot and will reveal much more as the roles of new genes are discovered.
“I think that personal genetic information should ordinarily be kept secret,” Dr. Watson said. “But I have said that 454 can put mine out there, even though it’s saying something about my sons.”

So far, however, 454 Life Sciences has not published Dr. Watson’s genome, and it is not clear how much progress the company has made. Christopher K. McLeod, its chief executive, said, “Technically, we’ve done a lot of good work on it.” But, he added, “I don’t think we want to discuss where we are.”

Mr. McLeod expressed reservations about releasing personal genetic information, despite having Dr. Watson’s permission to do so. “Jim feels there are certain things he’d be comfortable releasing,” he said. “I’m not sure we would agree.”

Another factor may be that the company is developing a more powerful model of its machine that will be able to read DNA fragments that are 200 or even 400 units in length. These longer-read lengths should make it more feasible to decode large genomes, like those of people.

The 454 machine is at present being bought chiefly by researchers and by the large genome sequencing centers established by the public consortium. But it has begun to show promise for the clinic. One new use is in screening tumors for genes known to be mutated in cancer, a task that existing machines do not do well. Spotting which mutation has occurred in a patient’s tumor can help in the choice of chemotherapy.

Although the 454 model is the only next-generation DNA sequencing machine on the market, it will be joined this summer by the machine from Solexa. The Solexa instrument, which will cost $400,000, works on somewhat similar principles but uses fluorescent dyes to visualize the structure of DNA. And next year Applied Biosystems will introduce its next-generation machine, based on a technology developed by George Church of Harvard, said Dennis A. Gilbert, the company’s chief scientific officer.

Each of the manufacturers claims special advantages for its technology, ensuring that researchers will have a rich choice.

David Bentley, Solexa’s chief scientist, said that the company’s DNA sequencing machine had already decoded several bacterial genomes and that he was planning to
sequence a human genome — that of an anonymous man from the Yoruba people of Nigeria. An African genome was chosen because there is greater genetic diversity in African populations, Dr. Bentley said.

The demand for whole genome sequencing is a long way off, in Dr. Bentley’s view, but not so distant that it is too early to think about the consequences of generating such information. He advocates that two people should control access to a person’s genome sequence — the patient and the physician.

Why not the patient alone? Dr. Bentley said genomes would be so difficult to analyze correctly that interpretation should stay within the medical profession. Otherwise, freelance services will spring up, offering to predict whether a person will get heart disease or their age of death. This potential for misinformation “would have a huge adverse impact on the medical use of genetic information,” Dr. Bentley said.

A recent example of genetic misinformation occurred last month when a DNA testing genealogy company, Oxford Ancestors, told Thomas R. Robinson, an accountant at the University of Miami, that he was a descendant of Genghis Khan. Only because Mr. Robinson sought a second opinion did he find that the information was incorrect.

Technology, not medicine, is the immediate force behind the quest for the $1,000 human genome. The new decoding machines are being developed because they are possible, not because hospitals are demanding them. But the makers expect that demand will grow as researchers develop new uses.

“As we drop the price and increase the capability, there are applications that couldn’t be done before,” like a researcher being able to screen a thousand patients for cancer mutations, Dr. Gilbert said.

At present, only a handful of genes are monitored by doctors in clinical practice, and specific tests for these genes make it unnecessary to decode a person’s entire genome. But at some point, the new machines or their successors may make genome decoding a routine medical test.

Already, every newborn baby endures its heel being pricked to draw a few drops of blood, which are tested for a handful of enzymic deficiencies. But when genomes can be
decoded for $1,000, a baby may arrive home like a new computer, with its complete genetic operating instructions on a DVD.

**Genomes Decoded Here**

New generations of DNA sequencing methods, like the one below designed by 454 Life Sciences, may someday make the procedure routine.

1. DNA sample is separated into small sections of 100 base pairs.
2. The double-stranded DNA is split into single-stranded DNA segments.
3. The DNA strips bind to beads, one strand per bead.
4. The beads are placed in an oil and water emulsion, trapping each bead in an oil bubble. The strands are made to multiply.
5. DNA beads are dropped into wells of a fiber-optic plate. The credit-card-sized plate has about 1.6 million wells that can each hold one DNA bead.
6. Nucleotides are flowed across the plate in separate order. When they combine with the appropriate base, light is produced. The strand is reconstructed base by base.
7. Light from reactions is recorded onto a light-sensitive plate. Software analyzes the sequence of units in each well's fragment and reconstructs the whole genome from the overlaps.

*Source: 454 Life Sciences*

*Al Cranberg/The New York Times*