Smeltzer observes, "has been patented and has intellectual property rights attached."

One of Genset's goals, says Smeltzer, is to enable companies to target drugs to the patients whose genetic profile indicates they are most likely to benefit. At the same time, Genset will use genetic markers to identify and eliminate patients who seem likely to experience bad side effects, says Smeltzer.

A similar collection of SNPs is being put together at the Massachusetts Institute of Technology's (MIT's) Whitehead Institute for Biomedical Research with corporate support. Last April, three companies—the pharmaceutical giant Bristol-Myers Squibb of New York City, the biotech firm Millennium Pharmaceuticals Inc. of Cambridge, Massachusetts, and Affymetrix of Santa Clara, California, the maker of digital genetic analysis "chips"—pledged an investment of $8 million a year for 5 years to develop a set of genetic markers for use in pharmacology. The project will be led by MIT gene mapper Eric Lander.

According to one geneticist who asked not to be identified, Lander and Affymetrix are hoping to announce a proprietary digital diagnostic tool called the "poly2000 chip" that can simultaneously monitor 2000 SNPs in a single DNA sample. Lander could not be reached for comment. Affymetrix Chief Executive Officer Stephen Fodor, a speaker at the 11 September NHGRI meeting, confirms that his company is developing the technology for this project. He adds that he was uncertain about the intellectual-property claims on SNPs that might be used on this chip and had often wondered, "Can we put them on a chip and sell it [with reasonable property-rights agreements]?"

During last week's council meeting, Collins said he was concerned that such private claims might make it hard for researchers to get unconditional access to SNPs or other new types of markers—such as a set of single nucleotide changes that create errors in protein coding, which he dubbed "misSNPs." If these get caught in "a tangled mesh of patents and licenses," Collins warned, "then we are really in a mess."

Council member Jeanne Lawrence of the University of Massachusetts Medical Center in Worcester suggested that NHGRI issue a statement saying that SNPs were so "obvious" scientifically that they shouldn't be patentable. Another suggested that Collins and his staff should conduct a series of seminars to educate the U.S. Patent and Trademark Office (PTO) about the need to avoid SNP patents. An NHGRI staffer replied that PTO officials "have not welcomed" such offers in the past. Indeed, the PTO declined to take part in the 11 September discussion, the staffer said. Cox then urged NHGRI to assemble "a ton" of SNPs and make them public.

Members of the panel asked company executives attending last week's session whether their businesses would be "threatened" by such a move. Williamson indicated that Merck's would not. He said the company had become accustomed to paying royalties on many small patents that went into each pharmaceutical product, but recently Merck "suddenly noticed that royalty claims were stacking up" on each product to an unacceptable degree. Over the past 5 years, Merck has invested tens of millions of dollars in efforts to publish and share basic genetic data—for example, creating a public database of "expressed sequence tags" (ESTs) from human DNA that can be used to identify human genes—to avoid this layer-cake effect. Affymetrix's Fodor said he was chiefly concerned about the continuing uncertainty over who owns SNPs, but he did not oppose a public SNP repository. And Incyte Pharmaceutical's vice president David Bailey said that "we were not threatened at all" by Merck's release of EST data, which simply "added value to our database." The same, he felt, would apply to SNPs.

Collins concluded the discussion by noting that it would be too expensive and possibly controversial for NHGRI to try to go it alone in creating a SNP repository. He noted, however, that some NIH institute chiefs have already expressed interest in helping. For example, Richard Klausner, director of the National Cancer Institute, is ready to contribute. Queried by e-mail, Klausner says: "Francis and I have discussed this for months, and I believe that this is a very important resource for us to begin to assemble." The NHGRI session closed with staffers promising to look into costs and logistics. Soon the institute will decide whether to take the plunge and fund another big genomics project.

–Eliot Marshall

GENETIC ENHANCEMENT

From Science Fiction to Ethics Quandary

Newspaper readers across the United States got a jolt last week. Full-page ads announced: Children made to order. The ad offered a checklist of traits—including musical ability, athletic prowess, and protection against premature baldness—for parents to choose for their offspring. And it provided a toll-free telephone number and a Web site for readers to set up an appointment. Tiny type at the bottom of the page provided the only giveaway: The ad is promoting a science fiction movie called *GATTACA* (a clever play on the letters of the genetic code), set to open in late October. Get ready for a few weeks of hype about using genetic manipulation to enhance individual qualities.

Coincidentally, the day before the ads ran, a group of leading gene-therapy researchers was discussing exactly that issue—and they concluded that the possibilities aren't entirely in the realm of science fiction. At the first Gene Therapy Policy Conference sponsored by the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH), scientists predicted that within 2 years, a researcher will propose a gene-therapy experiment that, although initially aimed at curing disease, could eventually be used to enhance a trait in healthy people. "It's going to happen," pediatrician and gene-therapy researcher W. French Anderson of the University of Southern California in Los Angeles told the conference. "It's going to happen pretty quickly, and it's going to happen in the guise of something else."

Panelists pointed out, for example, that research teams are already working on genetic treatments to restore lost hair and to strengthen muscles. Researchers are likely to propose the first tests of such therapies in chemotherapy patients or those with muscular dystrophy, but if they prove effective, it would

End of the slippery slope? *GATTACA*'s fictional world.

be extremely difficult to prevent doctors from prescribing them widely, says Anderson. He and others urged the RAC, which advises NIH director Harold Varmus, to treat such proposals with caution until ethical concerns such as fair distribution and the potential for eugenics can be addressed.

For the moment, the big safeguard against misuse of gene therapy—and against the world depicted in *GATTACA*, in which choice jobs are reserved for the genetically enhanced—is that the technology doesn't work very well. Seven years after the first gene-therapy trial in humans, the technique has yet to produce a definitive cure for a single patient. Although more than 200 gene-therapy experiments are under way, researchers are having trouble delivering DNA into target cells and getting transplanted genes to work for more than a few months. Genetic therapies for complex traits are even more distant. "We don't yet know the genes involved in any of these characteristics," geneticist Huntington Willard of Case Western Reserve University in Cleveland told the conference.

For now, those uncertainties make it "difficult to contemplate enhancements where we can predict the outcome," says Willard. To Anderson, they make gene therapy for enhancement "medically hazardous, morally precarious, and philosophically debatable."

But all that may change, said panelist Theodore Friedmann of the University of California, San Diego. "Technology will make enhancement therapy feasible," he told the conference, and although there will be serious ethical questions to consider, he predicted that some aspects of the practice will eventually be socially acceptable. Social historian Sheila Rothman of the Columbia University College of Physicians and Surgeons in New York City agreed. Once gene therapy shows its first success, she warned, broader applications will not be far behind. The use of human growth hormones, hormone replacement therapy for menopause, and broad use of psychiatric drugs such as Prozac and Ritalin suggest that there is a very blurry line between treatment and enhancement, she says.

Most panelists recommended that the RAC take an open but cautious stance. Several suggested that any therapy with potential applications in healthy people be held to stricter standards than those designed as a last-chance therapy. Other panelists recommended that the RAC should "flag" such experiments, warning the Food and Drug Administration, which has the power to approve or reject individual proposals, to proceed with caution. "We're going to be on the slippery slope of enhancement without knowing it unless we—the RAC, the FDA, and the public—stay alert," said Anderson. A slope that could eventually bring *GATTACA* closer than your local theater.

–Gretchen Vogel

EPIDEMIOLOGY

A Plan to Register Unpublished Studies

It is considered one of the insidious problems in clinical research: Researchers tend to publish the results of trials that show an intervention works, while not even submitting those that don't. As a result, systematic reviews of the literature to determine the efficacy of a particular treatment or preventive measure are likely to be biased, and doctors may end up prescribing useless or even harmful medications to their patients. Now, the editors of 100 journals around the world have proposed a novel way to deal with this problem.

Editorials in this week's issues of the *British Medical Journal* (*BMJ*) and *The Lancet* call for "an amnesty" for unpublished trials. The idea, explains Richard Smith, editor of the *BMJ*, is to get researchers to register the existence of trials they have completed but never published, and post the registry on the World Wide Web. Then, when other researchers perform a systematic review of the literature, they can track down the unpublished results to see if they should be included in the review.

The amnesty idea was initiated by Ian Roberts, director of the Child Health Monitoring Unit at The Institute of Child Health in England. Roberts has been reviewing the effectiveness of interventions in the treatment of brain and spinal cord injuries for the Cochrane Collaboration (*Science*, 5 April 1996, p. 22), an international network of medical researchers who prepare, maintain, and disseminate systematic reviews of the effectiveness of treatments and preventive measures. He realized that unpublished results could skew his analysis. "It's quite clear from the work we've been doing," says Roberts, "that unpublished trials pose a major threat to the validity of systematic reviews."

Other epidemiologists have come to similar conclusions. Over the past decade, says University of Maryland epidemiologist Kay Dickersin, researchers have done five studies assessing the percentage of clinical trials that are completed but never published. "The final publication rate varies from 50% to 90%," says Dickersin, "and on average it is probably closer to 50." David Naylor, a clinical epidemiologist at Ontario's Institute of Clinical Evaluative Sciences, says the bulk of unpublished studies will simply be inconclusive. But he agrees that researchers are more likely to publish results that suggest a treatment works than that it doesn't, resulting in "an unduly inflated and excessively precise estimate of the treatment effectiveness in meta-analyses."

"Unpublished trials pose a major threat to the validity of systematic reviews."

—Ian Roberts

The amnesty idea will be discussed at the International Conference on Biomedical Peer Review, a gathering of journal editors from around the world being held this week in Prague, Czech Republic. Although the editors of 100 journals have already endorsed the proposal, Smith says he hopes others will sign on and help disseminate the call for unpublished work throughout the world. "We want to make it as easy as possible for people to be able to say 'Well yes, this study did happen.' And anybody can report one of these trials. It doesn't have to be the person who did it. It can be any trial you know about that's unreported. We're quite prepared to have the same trial reported more than once."

The idea has not won universal approval in the biomedical publishing world, however. The editor of one journal that is not involved suggested it would "encourage a vast *gemische* of junk." He questions the logic of inviting studies that have never been peer reviewed to be included in systematic reviews. Even Naylor, who wrote the editorial in the *BMJ* introducing the amnesty, wonders whether there is any real incentive to register unpublished trials, as they won't count toward a researcher's publication record. Moreover, he says, a disproportionate number of unpublished inconclusive or negative trials may have been sponsored by pharmaceutical companies that may not want the results publicized.

Naylor suggests that editors should increase the incentives by offering to review trials as submissions and publishing them annually in an electronic supplement. "The amnesty is a nice altruistic idea," he says, "and it's a sign of increasing activism of medical journals to improve the standards of reportage of clinical research. But some kind of more tangible benefit may be needed for this to have a real impact."

–Gary Taubes