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## Failed prevention trials leave behind bounty of samples

The Women's Health Initiative (WHI), a massive trial that aimed to pinpoint ways to prevent cancer and heart disease, in February reported almost uniformly disappointing results, confounding doctors and the public alike. But most reports of the trial overlooked one important feature: biologists will now have access to a vast database of health records as well as samples of DNA, urine and blood.

"You have this unbelievable database that gives you the opportunity to do a lot of work in follow up," says Bernadine Healy, who in 1991 launched the WHI as director of the US National Institutes of Health. "The bounty that has yet to be tapped from the WHI is enormous."

In January, the National Heart, Lung, and Blood Institute, which administers the trial, threw open the WHI database to researchers. By applying the power of genomics, proteomics and advanced computing to the data, scientists hope to be able to tease out associations between diet, lifestyle and disease.

The WHI enrolled about 162,000 postmenopausal women, 42% of whom took part in randomized trials on hormone replacement therapy, calcium and vitamin D supplements and the effects of a low-fat diet on cancer and heart disease. The others participated in an observational study that collected data on their mental status, medication use and family histories.

The information these studies left behind may help temper the disappointment that resulted from the study's findings: hormone replacement therapy slightly increases the risk of breast cancer, heart attacks and strokes (*Nat. Med.* 12, 8–9; 2006), calcium supplements don't prevent bone fractures (*N. Engl. J. Med.* 354, 669–683; 2006) and a low-fat diet does not protect against breast cancer, colorectal cancer or heart disease (*JAMA* 295, 629–666; 2006).

The low-fat diet results were a particularly bitter pill for those who had hoped the massive study would confirm long-suspected—but disputed—associations between dietary fat and incidence of the two cancers and heart disease.

But experts say the study lost statistical power because the women who were supposed to be on a low-fat diet had trouble adhering to it. By the sixth year of the study, the women were

consuming 29% of their calories from fat, rather than the target 20%.

That does not mean that a low-fat diet does not have any benefit, says Larry Norton, who supervises breast cancer programs at the Memorial Sloan-Kettering Cancer Center in New York. "The only real conclusion you can draw from that study is that it's very hard to get people to change their diets," Norton says. "You certainly can't draw the conclusion that dietary fat doesn't make any difference."

The findings of the osteoporosis study, which reported that supplements of calcium and vitamin D don't protect against hip fractures or colorectal cancer, were similarly compromised by the fact that women in the control group were also allowed to take supplements.

"You can't really say the [calcium] results are negative because they lean strongly in the positive direction, but any real effect is likely to

be quite small," says Susan Ellenberg, professor of biostatistics and epidemiology at the University of Pennsylvania.

Scientists are more unambiguously excited about the 5 million WHI samples stored in 117 freezers in Rockville, Maryland. Researchers are already poring over the dietary records and blood and urine samples from a subset of 544 women using a marker for caloric intake to try to understand the biases that might have occurred when participants self-reported the food they ate.

The WHI has also engaged Perlegen Sciences, a genetic analysis firm in Mountain View, California, to examine 300,000 genetic variations and try to find ones common to subsets of women who get breast cancer, heart disease and stroke.

The database also contains information on diseases beyond those studied in the trials. For example, WHI investigators tracked the incidence of ovarian cancer in the participants, yielding an invaluable resource to those trying to identify a simple indicator of the stealthy, late-presenting cancer.

Because ovarian cancer is relatively uncommon, it has been difficult to design a prospective study with a sample size large enough to identify markers. "The WHI is one of the rare kinds of places where we can do that kind of research," says Garnet Anderson, a biostatistician and co-principal investigator at the WHI coordinating center at the Fred Hutchinson Cancer Research Center in Seattle.

As other scientists begin using the database, their trolling might also pick up markers in blood that would elucidate how a low-fat diet affects the body, for instance, or a protein that predicts whether a person is at risk for hip fractures from osteoporosis.

In any case, the ambiguity of the WHI results may be only temporary. "The future has a lot of promise," says Anderson. "It's a much more uncertain future because it's open-ended. It's just not clear where the key discoveries are going to come from."

*Meredith Wadman, Washington, DC*

### Women's Health Initiative

161,808  
Number of women enrolled



15 years  
Duration of study



5 million  
Number of samples collected



\$725 million  
Money spent

0  
Resulting number of clear public health policies