this word 'reform.'" The full committee chair, Dan Burton (R–IN), said there were "very serious and ... growing problems" in clinical trials, and that "conflicts of interest among members of IRBs" may explain lax reviews.

These comments provoked strong responses from defenders of the system. Gary Ellis, director of the Office for the Protection From Research Risks, who oversees the national network of IRBs from an office within the National Institutes of Health (NIH), said that the "system is not in jeopardy." He observed that "when you set aside the language of danger and menace," the HHS report offers no evidence that patients have been harmed or are at risk. Noting that every clinical trial goes through many layers of ethical review, Ellis said he considered the likelihood of a "catastrophic failure" to be "slight." And children in the fenfluramine study, according to a psychiatrist who chaired the IRB that approved the research, reported side effects no more serious than a headache or fatigue. He insisted that the study had included no white children because almost all the candidate subjects were black and Hispanic.

Robert Levine, an ethicist at Yale University, head of Yale's IRB, and spokesperson for the Association of American Medical Colleges, also rose to the defense. "I reject the mischaracterization" in the HHS report of the IRB network as "a system in crisis," Levine said. He warned against loading down IRBs with new tasks and limitations, noting that funding is inadequate as things stand and that getting qualified reviewers to serve for IRB duty "is not easy." Levine did not think it made sense to impose demanding new conflict-of-interest rules to prevent institutional employees from reviewing studies done within the institution. Speaking as Yale's IRB chair and a Yale employee, he said, there is "no real conflict" in these roles, as "what we really want [as an institution] is rigorous review."

Ellis and Levine both agreed, however, that the IRB system needs improvement. For example, Ellis suggested that federal protections be expanded to cover all private research, some of which is now exempt. Both Ellis and Levine supported the HHS's recommendation that IRBs' workload be reduced. Both agreed that the IRBs and their federal overseers could do a better job of monitoring research, but they said this could require more money to pay for staff.

Neither Shays nor Burton expressed interest in tightening controls on private research—or in boosting appropriations to the IRB system. Shays did say, however, that he intends to bring leaders of the NIH and Food and Drug Administration in for more questioning.

–Eliot Marshall

BREAST CANCER

Australia Takes Two-Step Approach on Genetic Studies

MELBOURNE—With its modest research budget, remoteness, and sparse population, Australia may seem an unlikely place for a model study of the epidemiology of breast cancer. But in the last few months, Australian researchers have been adding the finishing touches to an integrated national program that has won international plaudits for its design and its ability to answer the most compelling questions about breast cancer. The effort combines a nationwide study of high-risk families to track down genes associated with increased breast cancer risk and a population-based study to determine the prevalence and actual risk that such genes confer. "I have nothing but praise and envy [for the work]," says British geneticist Ian Tomlinson of the Imperial Cancer Research Fund. "They will get the sample sizes needed to study the genetic profile of predisposition and genetic changes in [breast] cancer."

The need for such comprehensive epidemiological information arises from the Pandora's box opened by the cloning in 1994 of the first breast cancer predisposition gene, *BRCA1*, followed 15 months later by *BRCA2*. Those discoveries quickly led to tests for mutations in the genes, but there was insufficient data to tell women who tested positive how great a cancer risk they faced. The goal of the Australian program is to assess the risks associated with breast cancer genes as quickly as possible, as well as other factors that could help carriers lower their risk.

Such combination studies are now seen as the model for the genetic epidemiology of cancer. "Almost all sites in a newly funded colorectal cancer registry have adopted this model, with both a high-risk and a population-based component," says Daniella Seminara, who coordinates an international registry on familial breast cancer maintained by the U.S. National Institutes of Health. The Australian data will make up a large proportion of the registry.

Australia's effort owes much to the work of two men: University of Melbourne epidemiologist John Hopper and molecular biologist Joe Sambrook, director of Melbourne's Peter MacCallum Institute for Cancer Research. Although the joint study now appears seamless, its components were formed separately and continue to have a life apart from one another.

A step ahead. John Hopper and colleagues Margaret McCreadie, director of the New South Wales Cancer Council, and Graham Giles, director of the Anti-Cancer Council of Victoria, began their population-based study of breast cancer in 1992, even before *BRCA1* was identified. They had the good fortune to work in Australia, where every breast cancer case in the country must be listed in registries compiled by each state. Individuals are also relatively easy to track down. With a population of only 19 million, Australia is highly urbanized and its families tend to stay together in one city—and those who do move can be located via electoral rolls made complete by the country's compulsory voting registration laws.

On the team. Leaders of Australia's Consortium for Familial Breast Cancer Study are Joe Sambrook, second row, fourth from left, and John Hopper, seated on right.

At the same time, researchers who want to use the data must comply with stringent international guidelines. Hopper adds that Australians, although demographically similar to the U.S. population, have yet to develop a heightened awareness of medical privacy.

Hopper also guessed that developing a population-based database would be useful for a relatively small player on the world scene: "While others were trying to find cancer genes, we were looking one step ahead at what [that knowledge] might mean for the population." Toward that end, Hopper interviewed and took blood samples not only from a selected sample of women who agreed to participate in the study but also from every

first- and second-degree relative. The data could then be used to construct genetic profiles of all patients and their families and to estimate the prevalence of *BRCA1* and *-2*. In addition, the prevalence of new cancer genes in these families could also be determined by dipping into Hopper's database.

The investment is beginning to pay off. "We've had various [U.S.] meetings to establish common protocols [for population-based studies]," says Robert Haile, director of the genetic epidemiology program at the University of Southern California in Los Angeles. "But Australia is about 2 years ahead of us." Adds epidemiologist Beth Newman of the University of North Carolina, Chapel Hill: "Hopper uses a very rigorous sampling design that allows him to estimate penetrance [estimate of risk] in an unbiased fashion. His may be the only group in the world that is going about this in the right way."

Hopper has studied 460 case families to determine how often *BRCA* mutations trigger cancer. He estimates the risk of breast cancer in women carrying a protein-truncating *BRCA1* mutation to be less than 40% by age 70, half the previous estimate. "The striking feature is that the majority of mutation carriers had no family history going back to a first- or second-degree relative. The simple idea that family history and *BRCA1* mutations go together [in predicting cancer] is breaking down," says Hopper, who presented his findings last November at the American Society for Human Genetics meeting. Newman agrees, saying that "the assumptions we made may have been wrong. ... The more we can find out about environmental factors and other causes, the more we can help determine risk factors for each individual."

A national approach. Hopper is also lending his epidemiological expertise to the second arm of the Australian program, a national effort to identify other genes and environmental factors that cause the bulk of inherited breast cancer by studying high-risk families. Until now, Australian researchers have lagged behind their U.S. and European counterparts in such efforts. "A lot of people frenetically put in grants, but no one had [access to] enough families to get a good analysis," says geneticist Nick Hayward of the Queensland Institute for Medical Research (QIMR) in Brisbane, about the community's past efforts to win funding. "We needed a national approach [targeting very high risk families]."

Enter Sambrook, who left as director of the University of Texas Southwestern Medical Center at Dallas in 1995 to come to Peter MacCallum, a cancer clinic with a high-powered basic and clinical research program. Although he hadn't worked in Australia since his student days in the 1970s, Sambrook was no stranger to megaresearch, having managed a multimillion-dollar national consortium exploring the molecular factors underlying cardiovascular disease. "I loved getting people to work together, while staying in the background," he says about his work in Dallas and, previously, at Long Island's Cold Spring Harbor Laboratory.

Sambrook first raised the idea of a national consortium to tackle breast cancer genetics at a Sydney meeting of clinicians, epidemiologists, and molecular biologists in early 1995. Although the researchers already recognized the need for a broader approach, Sambrook set things in motion. "Here was an internationally respected figure, able to command the attention of Australia's researchers and funding bodies," says Hayward. And everyone wanted to be on Sambrook's team. "It was because of Joe that a single consortium was formed," notes QIMR's Georgia Chenevix-Trench, one of its founders. "Nobody was silly enough to want to compete with [him]."

Star status. Actress Olivia Newton-John *(right)* has lent her fame to the cause, meeting with Hopper and family interviewers.

Sambrook's timing was also fortuitous. Pressure from breast cancer activists led the then-Labour government in 1994 to create a $1.25 million fund for cancer research. The fund, called the Kathleen Cunningham Foundation, gives grants that are matched by anticancer councils in each state. Last year the foundation gave Sambrook a 3-year, $266,000-per-year award, which he used to launch the consortium. Such an arrangement would have been beyond the scope of the major funding body, the National Health and Medical Research Council, which typically supports institutions and individuals.

The consortium, known as KConFab, hopes to answer how genetic predisposition and environmental factors work together to determine a woman's risk of breast cancer. "The interaction between genes and the environment is the next big area," says Sambrook. "Even with *BRCA1* and *-2* carriers, we don't know the consequences of these mutations, whether to advise mastectomy, or what preventive measures might help. The only way to answer these questions is with statistical power." KConFab also hopes to serve scientists working in related areas by establishing tissue banks and an epidemiological database. Researchers send in a proposal for material much as they would for a grant, explains Trench.

Playing the percentages. KConFab's rapid move off the drawing board to reality owes much to existing groundwork. The Hopper study had already established guidelines for epidemiological questionnaires and blood collection protocols, while the cloning of *BRCA1* in 1994 and the reality of mutation testing had aroused panic among women with a relative diagnosed with breast cancer, says Judy Kirk, an oncologist at Sydney's Westmead Hospital and chair of KConFab's ethics committee. "They felt genetic testing would be appropriate," she notes. State-supported Family Cancer Clinics were set up to provide high-risk families with counseling, testing, and treatment, and these clinics serve as a funnel for collecting KConFab families.

With KConFab now running at full steam at 27 institutions across Australia and New Zealand, data are already appearing. One surprising finding is that the frequency of *BRCA1* and *-2* mutations in very high risk families is significantly lower—at about 15%—than the 40% to 50% found in earlier overseas work. Although it's technically possible that researchers are missing cryptic mutations in the *BRCA1* and *-2* genes, says Ted Edkins, who runs a testing laboratory at Princess Margaret Hospital for Children in Perth, overseas researchers have found that the majority of *BRCA1* and *-2* mutations produce a truncated protein easily identified in current tests.

The consortium has also created new research opportunities. For example, University of New South Wales psychiatrist Ian Hickie is planning a psychoimmunological study of women from high-risk breast cancer families that would have been unthinkable a year ago. He's piggybacked a modest grant onto KConFab's ongoing program and will employ a nurse to coordinate skin immunology patch tests and psychological measures in with the regular KConFab protocols. "This is an incredible value-added resource," says Trench.

These factors have made KConFab into a global model for doing cancer epidemiology. Sambrook calls it "a turning point for the way research is done in Australia," and many researchers can hardly wait to take the next step. "Melanoma genetics could be the next ConFab off the line," says Hayward.

–Elizabeth Finkel

Elizabeth Finkel is a science writer in Melbourne.