Panel softens cancer gene test warning

Washington. A top-level advisory panel on women's health issues to the US National Institutes of Health (NIH) last week added its voice to demands that pre-symptomatic genetic testing for breast and ovarian cancers should be carried out only within cautious guidelines.

But the Advisory Committee on Research on Women's Health (ACRWH) substantially softened the wording initially proposed by some of its members. While these had sought a virtual ban on such genetic testing outside research settings, their critics argued that such a ban would be patronizing to women.

The strength of feeling expressed in this original goal reflected deep concern over, for example, the news that the private Genetics & IVF Institute in Fairfax, Virginia, is offering $295 screening tests for a mutation in the *BRCA1* gene, thought to confer an 80–90 per cent lifetime risk of breast cancer and a 40–50 per cent lifetime risk of ovarian cancer in Ashkenazi Jewish women with a strong family history of these cancers (see *Nature* **380**, 376; 1996).

The final ACRWH resolution urges that testing "only be conducted when accompanied by pre- and post-testing counselling which addresses the current status of knowledge", including uncertainties about how to apply genetic test results to the prevention and treatment of breast and ovarian cancers.

The resolution does not call for a ban on testing in non-research, for-profit settings. Nor is it legally binding. But as a public statement by a high-profile NIH advisory panel, it is bound to carry weight in an escalating debate. At issue is the wisdom of making genetic tests widely available in the absence of definitive data about their implications, including a test's predictive significance, and whether — and how — to proceed with medical management when women test positive.

The original resolution demanded that pre-symptomatic genetic testing for these cancers "be conducted only under hypothesis-driven, institutional review board approved research studies" which should address questions such as testing accuracy, the risks of diseases related to various mutations, and the appropriate medical management of those carrying mutations.

The final resolution also endorses research aimed at answering these questions under a new initiative by the National Cancer Institute for a National Cancer Genetics Network to provide and collect information on testing issues, and to develop a national protocol for "hypothesis-driven studies".

The initial resolution was developed by a subcommittee led by David Brown, professor of paediatrics, laboratory medicine and pathology at the University of Minnesota School of Medicine. On the first day of last week's meeting, Brown said that the resolution should bar the "unlimited availability" of testing and put it "within the framework of research". But his argument that it was too soon to allow the general availability of genetic screening for breast and ovarian cancer immediately drew criticism from some female members of the committee. Over the next 24 hours the resolution was modified several times. Its final form contains no reference to limiting testing to research settings.

"The way it was changed was much better," said Linda Burhansstipanov, a committee member and director of the Native American Cancer Research Program at the AMC Cancer Research Center in Denver, Colorado. Burhansstipanov and others say that the improvement resulted from the removal of what she describes as "paternalistic language" that patronized women. Another committee member said it signalled a retreat to "the age of 'doctor knows best'".

But others — most notably, Francis Collins, the director of the National Center for Human Genome Research (NCHGR), who did not attend the meeting — disagree that the final wording is an improvement. "It does seem to open the door to carrying out testing outside of [the research] environment," said Collins.

"It's just slightly disappointing that they

chose to back away from a stronger statement," says Collins, who wrote in the *New England Journal of Medicine* earlier this year that "the technical ability to perform tests for mutations should not be confused with a mandate to offer them".

In contrast to the advisory panel's resolution, Collins says that the Hereditary Susceptibility Working Group — which he co-chairs — of the National Action Plan on Breast Cancer will publish a statement in *Journal of Clinical Oncology* next month concluding that "testing at the present time should only be carried out under the auspices of a research protocol approved by an institutional review board".

Numerous scientific groups have recently concurred, arguing that testing for *BRCA1*, a gene which can carry mutations responsible for inherited breast cancer, should be confined to research settings. These include the American Society of Human Genetics, the National Breast Cancer Coalition and the Advisory Council of the National Center for Human Genome Research.

Furthermore, Neil Holtzman, who chairs a task force on genetic testing of the NIH/Department of Energy Working Group on Ethical, Legal, and Social Implications of Human Genome Research, says that in his opinion the *BRCA1* test does not meet the criteria, contained in a set of 'interim principles' released by the task force last month, for making genetic tests publicly available.

But refusing to endorse the non-research use of breast cancer screening would provoke "lay outrage", warned Marjorie Shultz, a professor at the University of California at Berkeley's Boalt Hall School of Law. "Can you imagine yourself saying to a woman who comes to a centre to do testing 'No you can't, unless you're a research subject?'" she asked Brown. "Yes," he immediately replied, arguing that to allow testing on demand would be like permitting patients "to go to their doctor and say 'I decide that I want dicloxicillin today'".

Others fear that a stampede of women to private genetic testing facilities such as the Virginia laboratory would deprive researchers of the subjects needed to answer critical questions. "If everyone goes to a private company and has testing, we're going to lose that data," said Kathy Hudson, assistant director for policy at the NCHGR.

In the end, the NIH is likely to have little authority to regulate private testing facilities. Instead, some experts say, this will be the responsibility of the Food and Drug Administration (FDA) under the Medical Devices Act. The FDA is expected to acknowledge its authority to regulate laboratories that market genetic test services — as well as its lack of resources to do the job — in an opinion shortly to be submitted to Holtzman's task force.

One member of the ACRWH committee argued that FDA regulation would quickly put an end to commercial genetic testing for *BRCA1* and *BRCA2* genes. "The data out there would be laughed at by most of the people in the FDA," said Edward Brandt, Jr, director of the Center for Health Policy Research and Development at the University of Oklahoma Health Sciences Center.

The resolution finally approved by the ACRWH advisory committee last week calls on the NIH to take a lead in publicizing the current lack of knowledge about how genetic test results might be used to prevent and treat breast and ovarian cancers.

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