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ODAC Advice Poses Challenge To FDA: Would Iressa Approval Erode Standards?

Approval of the targeted cancer drug Gleevec was a no-brainer for FDA. Efficacy was dramatic, toxicity minimal. Pinpointing patients who stood to benefit from the Novartis drug, describing its target and mechanism of action, was so straightforward that the agency saw no need to seek guidance of the Oncologic Drugs Advisory Committee.

By contrast, AstraZeneca's Iressa (ZD1839), a small-molecule drug the company describes as targeted, presents a challenge for the agency. Iressa's efficacy is dramatic in some patients, but at least for now, they cannot be characterized.

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In Brief:

Mary Simmonds Succeeds Robert Young As ACS President; Wyatt Wins ACS Award

AMERICAN CANCER SOCIETY elected its national officers at a Nov. 2 annual meeting in Dallas. The society also presented its annual awards. **Mary Simmonds**, clinical professor of medicine at Pennsylvania State University College of Medicine, was elected president. She succeeds **Robert Young**, president of Fox Chase Cancer Center. **David Zacks**, a partner for Kilpatrick Stockton, LLP of Atlanta, was elected chairman of the board. Zacks replaces **H. Fred Mickelson**, president of Corral Creek Consultants. **Ralph Vance**, professor of Medicine in the Division of Medical Oncology at the University of Mississippi School of Medicine, was elected president-elect. **Gary Streit**, president of Shuttleworth and Ingersoll, PLC of Cedar Rapids, Iowa, is chairman-elect. **Thomas Burish**, president of Washington and Lee University, was elected vice chairman. **Mark Clanton**, a national health care consultant and former physician executive with Blue Cross Blue Shield of Texas, was elected first vice-president. Second vice-president is **Stephen Sener**, associate director for the Residency Training Program in Surgery at Northwestern University Medical School. Elected lay officers include treasurer **Jean McGill**, president of Noble Investments Inc., of Tulsa, Okla., and secretary **Anna Johnson-Winegar**, deputy assistant to the U.S. Secretary of Defense. ACS presented its 2002 Distinguished Service Award to **Stephen Wyatt**, associate director for cancer control at the Lucille P. Markey Cancer Center at the University of Kentucky in Lexington. The Humanitarian Award was presented to **Lovell Jones**, professor in the departments of Gynecologic Oncology and Biochemistry & Molecular Biology at the

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ODAC Members Say Testimony Of Patients Influenced Decision

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Studies of a combination of Iressa with standard chemotherapy for non-small cell lung cancer showed no benefit, but a single-arm study reported a miniscule response rate of 10.1% in the third-line indication, with the lower bound of the 95% confidence interval dipping to 5%, a level usually defined as statistical noise.

On Sept. 24, ODAC struggled to reconcile the lukewarm data with extraordinary testimonials of patients benefiting dramatically and unexpectedly from the drug (**The Cancer Letter**, Sept. 27). Now everyone with a stake in drug development is waiting to see how FDA will interpret the committee's advice in setting the bar for the entire generation of targeted cancer drugs.

"We took an objective look at the information," said ODAC chairman Donna Przepiorka, reflecting on the committee's 11-3 vote to recommend accelerated approval. "There is no report of a patient with lung cancer that has resolved spontaneously. To see activity at this level means that something is going on."

Under FDA regulations, accelerated approval can be granted when a surrogate endpoint like tumor shrinkage is viewed as "reasonably likely to predict clinical benefit."

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The response data met the minimum standard, said Przepiorka, an oncologist at the University of Tennessee. "I think we gave AstraZeneca a clear indication that we expect a lot more work to determine how this drug is used, but there is no way that we could say that it should stay off the market, when we have seen benefit," she said.

The decision to recommend approval did not come easily to ODAC member Otis Brawley, professor of medicine, oncology and epidemiology at Winship Cancer Institute at Emory University. "I know I changed my mind four times, and it may have been more," Brawley said. "If I were to vote again, I'd still have torn feelings."

As he wavered, Brawley considered the consequences of putting a minimally toxic drug of unclear efficacy on the market.

"I worried that lung cancer patients will get this drug off-label, foregoing proven treatments," Brawley said. "I worried about the added cost to society and the inconvenience to cancer patients who do not benefit. And I worried that the potential approval of Iressa would make it more difficult for a more promising drug to be approved for this indication."

Setting the Bar

Lung cancer is a difficult disease for developing a targeted drug, said Brian Druker, associate professor of medicine at the Oregon Health Sciences University and one of the scientists who developed Gleevec.

"If you look at the preclinical validation, it's hard to argue with the EGF receptor as the target," Druker said of the Iressa studies. "The first question I want to have addressed is, has the EGF receptor been shut down with an inhibitor? If it hasn't been shut down, I don't think we've learned anything from these studies, except that we might need more potent inhibitors.

"But if you have shut down the EGF receptor, then it tells you that expression of EGF receptor in most tumors isn't sufficient to predict responses, but there may be a subset of patients for whom EGF receptor inhibition is a fantastic treatment approach. Defining who those patients are may be quite difficult, but is critical to our understanding of the use of these agents."

In chronic myelogenous leukemia, Gleevec's first indication, measuring whether the molecular target—bcr-abl translocation—was shut down was an easier task than it is with lung cancer, Druker said.

"With Gleevec, we took a disease where we

understand what drives the growth of the tumor," Druker said. "But when we ask ourselves how many other disease are there, where we have this knowledge, the reality is that there are almost none. Where you go from here is you muddle around with questions like this until you have a greater understanding of all these diseases."

Translating the science of molecular targeting into approval criteria is no simple matter. "Somewhere you have to draw a line, and drawing that line is the hard part," Druker said.

Consider a drug that benefits 5% to 10% of patients. "Do you relegate this to something that would require five or 10 more years of study to find who these five or 10 percent of patients are?" Druker said.

It's unknown whether Iressa shut down the EGF receptor in the tumors. AstraZeneca did not attempt to explain why some patients responded to the agent while others did not, why there were more women than men among responders, and why typical responders had slower-growing adenocarcinomas. Similarly, the company did not explain why front-line trials of Iressa in combination with chemotherapy were negative, claiming only that development of the drug for the front-line indication was unrelated to its development for the third-line indication.

ODAC chairman Przepiorka said there is no need for new standards for targeted drugs.

"There is no difference in review of these drugs than for any other drugs," said Przepiorka. "The criteria for approval are not changed. We can't favor one category of drugs over another."

Fleming: Approval Would Erode Standards

Biostatistician Thomas Fleming, a consultant to ODAC at the September meeting, cast one of the nay votes on Iressa. A month later, his view of the agent is unchanged: approval of Iressa would invalidate the criteria for approval of cancer drugs.

At the invitation of **The Cancer Letter**, Fleming, chairman of the Department of Biostatistics at the University of Washington, spelled out his reservations about the data:

"I remain very perplexed by the proceedings at the Sept. 24 ODAC review of Iressa, where the Committee considered a proposal for accelerated approval in the setting of third line treatment for NSCLC patients.

"What are some of the key facts relating to clinical data for Iressa in NSCLC, and the review by ODAC of the application for accelerated approval?

"ODAC recognized that the uncontrolled data regarding effects of Iressa on symptoms did not provide 'substantial evidence' of benefit. Specifically, ODAC agreed with FDA that '*the data supported only a soft claim of symptom management, and that a randomized, controlled trial with a no-drug arm (either placebo or best supportive care) would be required for substantial evidence.*'

"Regarding objective response rate data, the supportive 0016 trial had only 17 third-line patients who were progressors on both first and second line regimens, (even when including the Japanese patients who had a much higher response rate than US patients), with only one of these being a responder. Hence, one is left with a single trial, Study 0039, to assess response rate in 'third line' patients with resistant or refractory NSCLC.

"As noted by FDA, in these patients, this study achieved a response rate of 10%, (i.e., 14 responders in 139 third line patients). Most of the responses were in patients with slow-growing adenocarcinomas, and a large fraction of responders who had measurable disease had only one or two lesions. (It appears these results do not even meet the protocol's statistical criteria to establish adequately favorable effects on response rates).

"In contrast to these relatively unimpressive data on this biological marker from a relatively small uncontrolled trial, one has two excellent randomized trials, involving over 2,000 patients and with follow-up providing almost 1,500 deaths, that yield consistent and compelling evidence that Iressa provides no benefit on survival, response or time to progression, (in fact, with an estimate for a 1 week reduction in survival duration on the 500mg dose of Iressa and a 2 week reduction on the 250 mg dose, with a standard error of only 2.5 weeks), in a very closely related clinical setting. (These conclusively negative results were obtained regarding effects of Iressa in combination with standard chemotherapy even though in vitro and in vivo model work had suggested the agent would have additive or synergistic effects with platins and taxanes).

"How could one conclude after consideration of all of these data that one has 'substantial evidence' of benefit?

"After thinking about the ODAC proceedings, I have concluded a source of 'evidence' that appeared to have had a major influence on ODAC was a well orchestrated set of testimonials, lasting well over an

hour, from patients who received Iressa. (There was almost as much time spent in hearing the testimonials as there was in ODAC discussion of the scientific data.) When you have conducted an expanded access program involving over 12,000 patients, as the sponsor for Iressa had done, wouldn't you expect you could run out such a show, even when an intervention has at best very trivial effects? (I remember hearing many such testimonials for laetrile after tens of thousands of US patients had traveled to Mexico to receive this agent in the late 1970's, until scientific trials were conducted that established laetrile provided no benefit).

"It would be unprecedented for a product to receive an accelerated approval based, in essence, on a small uncontrolled trial (039) when one has two excellent randomized trials, involving over 2,000 patients, that yield consistent and compelling evidence that the treatment provides no benefit in a very closely related clinical setting.

"In view of the significant concerns arising from the unfavorable efficacy data for Iressa and from the emerging evidence raising important safety concerns related to interstitial lung disease, including interstitial pneumonia, I urge the FDA to require the sponsor to conduct randomized trials of Iressa against standard of care in second or third line NSCLC patients in order to obtain a much more reliable understanding about the benefit to risk profile of this agent in that clinical setting."

"Iressa Saved My Life"

AstraZeneca spokesman Mary Lynn Carver said the company did not arrange the appearances of the nine patients who spoke at the ODAC meeting.

"The patients at the open mike ranged from patients whom we had never seen before to patients who had contracted the company upwards to two years prior, and wanted to make sure that the company knew that this is working," Carver said.

AstraZeneca did not communicate directly with the patients regarding the meeting, Carver said. "The only communication to patients was via National Organization of Rare Disorders, a group that administered the Iressa expanded access program," she said.

"NORD has communicated with that group of patients," Carver said. "I believe they sent the letter out, giving them the basic information: who-what-when-where, and telling patients that if they needed more information, then to contact them. No patient was encouraged to attend by the company or by NORD. These patients came, because they had a story to tell. To quote one of them, 'wild horses couldn't have kept me away.'"

Carver said some of the patients received a travel subsidy from NORD. "NORD offered travel assistance to patients who would not have otherwise have been able to attend who wanted to," she said.

One patient, Charles Riley, 46, literally embroidered the gist of his testimony on the back of his shirt: "Cancer was killing me. Iressa saved my life."

"I have come here on my own, at my own expense," Riley said at the ODAC meeting. "I am not being compensated in any way by AstraZeneca, not have I ever met or spoken to anyone from AstraZeneca. If they wish to compensate me for this trip, I would be delighted."

Subsets and Anecdotes

It's unlikely in the extreme that the key players in the Iressa story need a refresher course on biostatistics. Yet, pondering the agent appears to require interpreting anecdotes and subsets.

"As dangerous as it is to look at subset analysis, there are some issues with the subset analysis that seem to stand out, and we need to start looking," said Alan Sandler, associate professor of oncology at Vanderbilt Ingram Cancer Center.

Performance of individual patients also may offer some clues. "When you see somebody who was doing very poorly, and then is out scuba-diving, it's hard to imagine in lung cancer that it's a placebo effect," said Sandler, an investigator on one of the Iressa studies, who presented the toxicity data to ODAC.

Relying on pathology to assess EGFR expression in lung cancer no simple task, Sandler said. "The problem is, apparently, if you put 10 pathologists in a room together and ask them to grade EGFR expression, you are going to get about a half-dozen different answers," he said. "Establishing what is true EGFR-positivity is step one. Mandating that that is required for entrance into a study would be step two."

ODAC member Silvana Martino said the patients' testimony was helpful to her. "I don't know that they swayed me in any way, but I do feel that they framed the meeting for me in a way that made my decision more personal and more important," said Martino, head of the breast section at John Wayne Cancer Institute.

Martino voted to recommend approval, but was among the nine committee members who shot down the AstraZeneca quality of life data, agreeing with FDA that such data are meaningless in a single arm-trial.

"The thing that I found striking is that this is a drug that, when you look at it overall, has a fairly low response rate," said Martino. "However, from the company data and from the patients, there is the impression that when this drug works—which is not often—it works nicely. Not only does it show you something on an x-ray, but it does appear to reduce symptoms. And it appears to give you the clue that it's going to do that fairly promptly and quickly, and those observations were appearing from the data, but also in the manner in which patients related their own life's events."

Martino said Iressa poses a new set of questions for FDA. "There is a whole new ballgame here, and how to play the ball game best is not an answer that I can give you today," she said. "I think this is an evolving event rather than an already figured-out game plan. In essence, that is one of the major questions of the medical field in this country. Do we deal with individuals, or are we making policy decisions for a nation?

"It's tough to separate those," Martino said.

Toxicity Data Emerged After ODAC

In mid-October, the Japanese Ministry of Health Labor and Welfare said that several patients taking Iressa in Japan contracted interstitial lung disease. These adverse events led the company to update the drug's label.

Carver said the Japanese authorities reported the findings after the ODAC meeting.

Iressa was approved for marketing in Japan last July, and according to data AstraZeneca presented to clinical investigators conducting its trials, 14,500 Japanese patients were taking the drug. The company reported 123 cases of ILD (0.84%), and 28 deaths (0.19%).

The company said it has since examined its database, finding that as of Oct. 30, 190 of the 42,802 patients who had been treated with the drug worldwide contracted ILD, and 50 of them died. This translates into the incidence rate of 0.44% and 0.12% death rate.

Sandler said he did not encounter any clear-cut cases of ILD among 139 patients on the study presented to ODAC. "There was one death on the Iressa study in a patient who actually died of hemoptysis, and that was not necessarily related to ILD," Sandler said. "The issue is that all of these folks had end-stage non-small cell lung cancer. Most of them are smokers. Most of them had underlying lung disease."

Of course, an analysis of both safety and efficacy would have been more informative in a randomized trial, Sandler said.

"Having treated a number of patients, and having gone over the data, I am quite comfortable, but I do wish there would have been randomized studies to more definitively prove this point, without questions that always linger from a non-controlled phase II setting," Sandler said.

FDA is expected to reach a decision on approval of Iressa in February.

Capitol Hill:

Lame-Duck Session Unlikely To Approve Funding Bills

With 11 government funding bills yet to be passed by Congress, NCI, like many other agencies, is operating under a continuing resolution.

As it has in the previous years in which continuing resolutions have been necessary, NCI can still award grants and contracts, but its ability to begin new programs is likely to be harmed the longer it takes for a budget to be passed.

Although Republicans will control both the House and Senate next year as a result of the Nov. 5 elections, it is unlikely that the funding bills will be passed quickly, Capitol Hill observers said.

Lawmakers planned to begin a lame-duck session of Congress on Nov. 12. Republicans may assume control of the Senate in the lame duck session if Sen. Dean Barkley (I-Minn.), appointed by Minnesota Gov. Jesse Ventura to fill the seat left vacant by the death of Sen. Paul Wellstone (D-Minn.), caucuses with Republicans, and if Jim Talent (R-Mo.), who defeated Sen. Jean Carnahan (D-Mo.) is seated quickly after certification of election results.

Senate Minority Leader Trent Lott (R-Miss.), the likely candidate for Senate majority leader, said he hopes to wrap up the lame-duck session in a few days and delay major legislation, including the funding bills, until next year.

President Bush has asked the Republicans to address several health-care proposals, including patients' rights legislation, a ban on human cloning,

and an increase in funds for community health centers.

Rep. Richard Gephardt (D-Mo.) said on Nov. 7 that he will not seek a fifth term as minority leader in the House. Rep. Nancy Pelosi (D-Calif.) emerged as the front-runner to replace him, in an effort by Democrats to challege Bush more aggressively. Rep. Martin Frost (D-Texas), who also will run for the minority leader position, is positioning himself as a more moderate candidate than Pelosi.

Sen. Tom Daschle (D-S.D.) is likely to keep his position as Democratic leader in the Senate, according to news reports.

Institute of Medicine:

Feds Should Lead Quality Improvement For Beneficiaries

The federal government should take the lead in improving the safety and quality of treatment provided to nearly 100 million beneficiaries of six government health care programs, according to a report from the Institute of Medicine of the National Academies.

The government should give financial rewards to hospitals and doctors who improve care, and should collect and make available to the public data comparing the quality of care among providers. Enhancing the quality of care in the government programs is likely to improve the rest of the health care system, said the committee that wrote the report, released Oct. 30.

"In the absence of strong federal leadership to address safety and quality concerns, progress will be slow," said committee chair Gilbert Omenn, professor of internal medicine, human genetics, and public health, University of Michigan Health System, Ann Arbor. "We strived to view the health system from the perspective of patients, especially those with chronic conditions, where a premium is placed on care that is coordinated over time, across settings, and across multiple payers. Such a coordinated focus requires government programs and health care providers to unify and standardize their quality-improvement efforts. Our report encourages the federal government to take full advantage of its influential position to set the quality standard for the entire health care sector."

The report, which was requested by Congress, follows two major IOM studies on the quality of health care—the first documenting the extent of medical errors, and the second calling for a national effort to improve safety and quality. Congress specifically asked the committee to review quality-enhancement processes in six government programs: Medicare, Medicaid, the State Children's Health Insurance Program, the Department of Defense TRICARE programs, the Veterans Health Administration, and the Indian Health Service. These programs provide health insurance or medical services to about one-third of the U.S. population.

Quality-enhancement processes in the government programs are being redesigned and are moving in the right direction, but these efforts are insufficient to close the "quality gap," the committee said. Congress should direct the secretaries of the U.S. Department of Health and Human Services, Department of Defense, and the Department of Veterans Affairs to establish standardized performance measures across all six programs, the report said.

Also, the government must provide strong support for development of computerized clinical records, the report said. Congress should consider using tax credits, subsidized loans, and grants to develop a national health information infrastructure. The government should adopt market-based options to encourage investment by providers in information technology, the report said.

The report also recommended:

—The federal government should employ purchasing strategies, such as higher payments and public recognition, to encourage health care providers to adopt "best practices."

—Standardized performance measures should be issued by the Quality Interagency Coordination Task Force. The task force should promulgate standardized performance measures next year for five common health conditions and for another 10 in 2004. By 2007, providers should be required to submit data on the safety and quality of care as a condition of participating in any of the six government programs. Beginning in fiscal year 2008, the collected data should be used to create reports comparing the quality of care among providers.

—The quality reports should be made publicly available. The raw data should be pooled by the Agency for Healthcare Research and Quality.

—In establishing performance measures, the task force should collaborate with standard-setting bodies in the private sector.

The report, "Leadership By Example: Coordinating Government Roles In Improving Health Care Quality," is available at www.nap.edu.

In Brief:

Six New York Institutes Form Cancer Vaccine Collaborative

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University of Texas M.D. Anderson Cancer Center, and **Armin Weinberg**, director of the Chronic Disease Prevention and Control Research Center at Baylor College of Medicine. The Volunteer Leadership Award was presented to **Irwin Belk**, president of The Belk Group Inc., and **Raymond Weisberg**, a former University of California at San Francisco clinical professor of medicine and former contract physician for the U.S. Penitentiary at Alcatraz. . . . **CANCER RESEARCH INSTITUTE** and the **Ludwig Institute for Cancer Research** have begun a cancer vaccine collaborative, consisting of six New York medical centers that plan to conduct early-stage clinical trials. Participating centers include Columbia Presbyterian Medical Center, Memorial Sloan-Kettering Cancer Center, Mount Sinai School of Medicine, New York University Cancer Institute, New York Weill Cornell Medical Center, and the Roswell Park Cancer Institute. The CVC will test vaccines for several different cancer types including melanoma, sarcoma, non-small cell lung, ovarian, prostate, and bladder cancers, which all have the NYC cancer/testis antigen NY-ESO-1 in common, said **Jill O'Donnell-Tormey**, executive director of the Cancer Research Institute. The marker, which will be the target of the vaccine research, was discovered at the Ludwig Branch in New York and Weill Cornell Medical Center. "Testing different vaccine strategies at one time will allow us to more quickly identify the most promising anticancer therapies," said **Eric Hoffman**, director of clinical trials at LICR.. . . . **UNIVERSITY OF MIAMI** Sylvester Comprehensive Cancer Center has created the Braman Breast Cancer Institute for breast cancer. The institute, which combines basic science with clinical trials for breast cancer research and treatment, is made possible by a gift from the Norman and Irma Braman Family Foundation. "The institute will also conduct cutting-edge research to advance international knowledge of the causes of breast cancer and to develop new means of prevention, diagnosis, and treatment," said **Joseph Rosenblatt**, scientific director of the UM/Sylvester Comprehensive Cancer Center. Braman has recruited **Joyce Slingerland**, of the University of Toronto, to lead the institute. Slingerland will hire physicians and research scientists to develop and test new approaches to breast cancer. The center will coordinate the efforts of experts in molecular biology, imaging, surgical care, epidemiology, genetics, radiation oncology and medical oncology. . . . **AMERICAN SOCIETY OF CLINICAL ONCOLOGY** will self-publish its semi-monthly Journal of Clinical Oncology beginning with the Jan. 1 issue. "This is a tremendous leap for ASCO on many levels," said **Charles Balch**, executive vice president and CEO of ASCO. "Self-publishing will allow us to maximize the quality and timeliness of the publication, and to provide readers and researchers with additional features and resources such as direct links to special articles. The move to self-publishing will provide greater, more timely accessibility to the most important and most current clinical oncology research information available." The JCO was first published in 1983 and now has more than 24,000 subscribers worldwide. From 1999 to 2002, Lippincott Williams & Wilkins published the JCO. Prior to LWW, the JCO was published by W.B. Saunders, from 1987-1998, and Grune and Stratton, from 1983-1987. . . . **CHARLES SCOTT** has been named senior director of statistics for the American College of Radiology and group statistician for the RTOG. As head of the ACR Statistical Unit, Scott will direct grants from NCI, the Radiation Therapy Oncology Group and the Patterns of Care Study. Scott was associate director, Quality of Life Research at ACR. He will continue as the senior statistician for the RTOG Community Clinical Oncology Program grant and as co-principal investigator for a grant to evaluate sildenafil for erectile dysfunction after prostate cancer therapy. "Scott's work in developing recursive partitioning analysis classifications of prognostic factors for patients with malignant glioma, non-small cell lung cancer and other malignancies has been instrumental in the design of new clinical trials," said **Walter Curran Jr.**, group chairman of the RTOG and clinical director of the Kimmel Cancer Center at Thomas Jefferson University. Scott replaces **Thomas Pajak**. who held the position since 1981. Pajak will remain with the unit as a senior statistician and continue his work with head and neck cancer research, the evaluation of tumor makers, and the identification of surrogate endpoints for survival in prostate cancer trials, said **Thomas Caldwell**, assistant executive director of ACR. . . . **MICHAEL HAWKINS**, associate director of the Washington Cancer Institute, formerly chief of the NCI Investigational Drug

Branch and director of the Developmental Therapeutics Program at the Lombardi Cancer Center, has accepted a position as medical director of American Bioscience Inc., in Santa Monica, Calif. The ABI lead compound, ABI-007, which is in a phase III trial for metastatic breast cancer, is a cremophor-free, albumin-stabilized, nanoparticle formulation of paclitaxel.. . . . **JAMES HUFF**, a National Institute of Environmental Health Sciences investigator who helped launch federal programs that categorize the hazards of chemicals, will receive the American Public Health Association third annual David P. Rall Award for Advocacy in Public Health in Philadelphia on Nov. 10. Huff was chief of the Monographs Program evaluating cancer risks at the International Agency for Research on Cancer in Lyon, France. . . . **MARY MCCABE** stepped down as acting director of the NCI Office of Communications last week. McCabe had agreed to direct the office for a year. She will return to her previous work on clinical trials issues, out of the NCI director's office, and will work with the Center for Bioethics at the NIH Clinical Center. . . . **INTERNATIONAL** HapMap Project, a $100 million public-private partnership, has begun to create the next generation map of the human genome. Expected to take three years to complete, the HapMap will chart genetic variation within the human genome. DNA will be taken from blood samples collected by researchers in Nigeria, Japan, China, and the U.S. The samples will be processed and stored at the Coriell Institute for Medical Research in Camden, NJ. Researchers from academic centers, non-profit biomedical research groups and private companies in Japan, the United Kingdom, Canada, China, and the U.S. will analyze the samples to create the HapMap. Public funding is provided by the Japanese Ministry of Education, Culture, Sports, Science and Technology; Genome Canada and Genome Quebec; the Chinese Academy of Sciences, the Chinese Ministry of Science and Technology, and the Natural Science Foundation of China; and NIH. The SNP Consortium in Deerfield, Ill., will coordinate private funding, while The Wellcome Trust in London will provide charitable funding for the UK portion of the project. . . . **FINAL REPORT** of the NIH State-of-the-Science Conference on Symptom Management in Cancer: Pain, Depression, and Fatigue, held July 15-17, may be viewed or downloaded at http://consensus.nih.gov/ta/022/022_intro.htm.

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