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Cancer Genetics Network Approved By NCI Advisors, To Start With 8 Centers

Advisors to NCI approved the formation of a Cancer Genetics Network, a national program for the identification and characterization of genes associated with predisposition to cancer as well as the study of ways to reduce the risk of inherited gene mutations.

The NCI Board of Scientific Advisors voted on Nov. 21 to approve in concept the Institute's plan to award grants of up to $300,000 per year to each of eight centers, a data management center, and a communications center, to begin the network.

The network, which would cost about $17.5 million over the next

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In Brief

FDA Commissioner Kessler To Resign, Says His Goals Were Accomplished

DAVID KESSLER announced his decision to resign as commissioner of the Food and Drug Administration. Kessler said he was stepping down voluntarily after six years as commissioner because he had accomplished his major goals. During his tenure, the agency implemented several historic initiatives: uniform nutrition labeling for packaged food, regulation of tobacco to discourage youth smoking, standards for mammography facilities, and faster approval of new drugs and medical devices. "I have appreciated the opportunity to aid in this public service, but now believe it is time to return to private life," Kessler said in a statement Nov. 25. He said he would leave as soon as a successor is named. Kessler, a pediatrician and a lawyer, was appointed to the post in 1990 by President George Bush. Prior to his appointment, Kessler was medical director of Albert Einstein Hospital in New York. . . . **NANCY MOSS** was appointed deputy director of the Northern California Cancer Center. Moss has been a special expert in demography and population epidemiology at the National Institute on Aging. . . . **EDISON LIU** and **UMBERTO VERONESI** received the 1996 Brinker International Awards for Breast Cancer Research from the Susan G. Komen Breast Cancer Foundation. The Dallas-based foundation presented the Basic Research Award to Liu, director of the NCI Division of Clinical Sciences, for his study of signaling molecules involved in breast cancer and leukemia. The Clinical Research Award was presented to Veronesi, research director, European Institute of Oncology, for his work on conservative surgery in breast cancer.

NCI Advisors Approve Concept For Cancer Genetics Network

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five years, would coordinate the basic and clinical science, training and education programs, and informatics structure that NCI said are necessary to pursue the opportunities presented by advances in genetic medicine.

NCI Director Richard Klausner said the network is an extension of the Institute's traditional role of supporting scientific infrastructures, such as the clinical trials cooperative group program.

"This is phase I," Klausner said to the board. "We will start with a limited number of sites. Those [principal investigators] are going to design the informatics system and come to agreement about sharing data and setting standards.

"In the second year, we could open it up and develop an extended network," Klausner said. "This would be a growing network, hopefully, throughout the nation."

The study of genetic susceptibility to cancer was the first of five "investment opportunities" listed in NCI's 1997-98 Bypass Budget. The document requested $31.5 million in new funds in FY98 for the creation of cancer genetics centers, training programs, clinical trials, and repositories.

NCI staff prepared the concept after receiving recommendations from the Cancer Genetics Working Group (**The Cancer Letter**, Aug. 9).

Board Members' Concerns

Several BSA members expressed concern about the network as described in the concept statement. Questions were raised about specific uses of the grant funds, confidentiality of genetic information, overlap with other registries, and feasibility of the project.

Frederick Appelbaum, director of clinical research, Fred Hutchinson Cancer Research Center, questioned whether the concept should state specifically that funds are to be used for a half-time patient educator and a half-time participant registrar. "It's as if everything is already in place and we know how it's going to work," he said. "The first stage has to be to demonstrate that this is a conceivable project."

"I'm concerned that there are so many specifics that we will get vanilla applications, and it will be difficult to distinguish one center from another, rather than the Baskin-Robbins assortment of flavors," said Eric Fearon, associate professor, internal and molecular medicine and genetics, University of Michigan Medical Center.

"This is basically a huge cohort study we are being asked to launch," said Sharon Murphy, chief of hematology/oncology, Children's Memorial Hospital in Chicago. "These people are not patients, these are asymptomatic individuals. First, we have to stop calling them patients. You can't even followup cancer patients very well, much less healthy people.

"There are issues relating to the feasibility of actually doing this," Murphy said. "Should we get answers to some questions first? Maybe by doing smaller, more targeted demonstration projects."

Caryn Lerman, associate professor of medicine and psychiatry, Georgetown University Medical Center, noted that funding would not support genetic testing of individuals. This could affect the ability of minority populations to participate in testing, she said.

Ruthann Giusti, special assistant for cancer genetics in the Division of Cancer Epidemiology and Genetics, and the coordinator of the project, said some provision for indigent individuals would be built in to the award. NCI was concerned that providing funds for testing could be viewed as coercion, she said.

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Louise Strong, professor, University of Texas M.D. Anderson Cancer Center, said she was concerned about how the network would work with other registries of high-risk families. "There is a lot of potential for the same families to be overwhelmed," she said.

"I'd like to know how this Cancer Institute intends to ensure the privacy of the information of women participating in this," asked Amy Langer, executive director of the National Alliance of Breast Cancer Organizations.

"We Don't Have The Answers"

Responding to Langer's question, Klausner said the centers would develop criteria that would have to satisfy NCI. "The idea of the first phase is to get these centers together and to attempt to come up with a plan for creating the type of system we are talking about, that satisfies the issues of confidentiality, encryption, protection," Klausner said.

"The other alternative is for NCI to create an informatics infrastructure," he said. "We don't really feel comfortable, one, with the idea of the government creating an infrastructure for genetic information. Second, you don't want to create a genetics infrastructure and then ask users to somehow fit their use into it.

"We want centers who have the intention of developing standards for genetic testing, genetic counseling, the establishment of genetic information for ascertainment of genotype-phenotype correlations," Klausner said. "Can we design a database that would be useful, would be safe?"

"We don't have the answers to the really important questions," he continued. "We couldn't come to it in all the working groups. How do we actually do it? What are the questions we need? We realized there are probably no answers.

"There is going to have to be a mechanism in place to deal with what questions you would want for breast cancer susceptibility, or prostate cancer susceptibility, and on and on," Klausner said. "There would have to be procedures and protocols. That's the first year, to have these researchers create the infrastructure of the network."

"NCI will play a very strong role at all times in establishing and assuring ourselves of the criteria," Klausner said. "We believe the Number 1 criteria for the issue of research use of genetic information is that it we have to solve to some extent, and document how we are solving it, the issues of privacy and confidentiality."

Executive Committee To Review RFA

BSA chairman David Livingston urged the board to approve the concept with the understanding that the Request for Applications would strike some of the specific wording, and include language assuring confidentiality throughout the network.

Livingston suggested that the NCI Executive Committee review the RFA prior to final approval. He said he would be present at the committee's meeting, as would the co-chairmen of the Board of Scientific Counselors.

However, Paulette Gray, deputy director of the Division of Extramural Activities, said outside individuals who were allowed to read the RFA prior to its publication would be precluded from applying, and would disqualify their institutions from applying.

"I see," Livingston said. "Obviously, I have to strike the idea that the Executive Committee meeting would include the three of us."

The board vote was 27-2 to approve the concept for the network, provided modifications were made to remove wording that board members said was overly specific on use of the grant funds.

The two board members voting against the concept were Murphy and Daniel Von Hoff, CEO and director, Institute for Drug Development, Cancer Therapy and Research Center, San Antonio. Board members abstaining from voting were Joan Brugge, scientific director, Ariad Pharmaceuticals Inc., Cambridge, MA, and Gillies McKenna, chairman of radiation oncology, Hospital of the University of Pennsylvania.

"We are making the revisions now and we hope we will be able to address the BSA's concerns up-front," Giusti said to **The Cancer Letter**. "Our goal still is to compete the RFA on a fairly fast track and fund the grants before the end of the fiscal year."

The excerpted text of the concept statement as presented to the board follows:

Cancer Genetics Network. Background: In 1994, soon after the identification of BRCA1 and the localization of BRCA2, a number of professional groups including the National Advisory Council for Human Genome Research, the American Society of Human Genetics and the National Breast Cancer Coalition cautioned that genetic predisposition

testing should be restricted to the research setting. While recognizing the potential benefit of predictive testing, these organizations raised concerns about the complexity of interpreting and communicating information concerning a positive or negative test result, the uncertain benefit of approaches to risk reduction, and the real risk of insurance and employment discrimination borne by those seeking testing. However, the identification of an increased prevalence of identified cancer susceptibility genes (BRCA1 185delAG and BRCA2 6174delT) among young Ashkenazi Jewish women with breast cancer has made mutation detection potentially clinically relevant and has also made screening for these identified mutations commercially attractive.

Indeed, mutation detection for an increasing number of susceptibility genes including APC (familial adenomatous polyposis), RET (multiple endocrine neoplasia 2a, 2b), MSH2 and MLH1 (hereditary non-polyposis colon cancer), p53 (Li-Fraumeni syndrome) and pl6 (hereditary melanoma and melanoma-associated syndromes) as well as for BRCA1 and BRCA2 is a commercial reality and marketing efforts aimed at providers and consumers can only be expected to increase the demand for and use of these tests. The American Society of Clinical Oncology has, in fact, proposed the integration of testing for genetic predisposition into the standard care of affected families in at least some clinical settings.

As articulated in the 1997/1998 NCI Bypass Budget proposal, recent advances in understanding of the genetic basis of tumor development represent an extraordinary opportunity for new investment in cancer research. There is a critical need to expand and integrate support of basic, clinical, and epidemiologic research. The aim of these efforts is to identify and characterize genes which cause or modify inherited predisposition to cancer and to develop and assess the efficacy of risk reduction strategies. The expedient identification and enrollment of sufficient numbers of individuals with predisposing mutations into appropriate studies will require a coordinated, comprehensive and broad-based effort. Moreover, as genetic testing becomes more widely available through commercial laboratories and becomes integrated into clinical practice, there is a limited window of opportunity to develop an infrastructure that will encourage the linkage between genetic testing and participation in state-of-the-art research projects and intervention trials (screening, prevention and treatment).

NCI has long recognized the importance of organizational infrastructures, such as the clinical trials cooperative groups and the Community Clinical Oncology Program as platforms for research. These infrastructures facilitate the conduct of research, enhance communication of research results, and promote the translation of new approaches into clinical practice. In the spring of 1996, recognizing the complexity of developing and implementing an infrastructure to support genetic research, the NCI Director convened an ad hoc group of experts, the Cancer Genetics Working Group, to provide advice. The deliberations of this working group provided general guidelines for the development of the concept of the Cancer Genetics Network as described below.

Purpose of RFA: The Cancer Genetics Network is proposed as a dynamic informatics and research infrastructure linking centers which counsel and test individuals for hereditary cancer susceptibility. The objectives of the Network are to: (1) develop and disseminate high-quality information about genetic susceptibility and testing; (2) develop and assess approaches to informed decision-making, counseling, and laboratory testing procedures; (3) collect and pool data linking specific mutations with phenotypes; and (4) enhance participation in cancer genetics research. The Network will accomplish these objectives through registry and education/ outreach functions. These functions will be independent but closely integrated and facilitated through the informatics infrastructure of the Network.

The Network will maintain a voluntary and confidential registry of individuals who seek information on genetic testing for cancer susceptibility at participating centers. Demographic, risk factor, cancer incidence and mortality data will be collected and annually updated. Data on cancer treatment and interventions (prophylactic surgery, screening, chemoprevention) will also be obtained. Participation in the Network registry will permit registrants to be informed directly of relevant new advances in cancer genetics and of potential access to cutting edge research programs aimed at understanding and reducing the expression of hereditary cancer predisposition in which they might participate. As such, the Network will provide a

platform for further research conducted through or in collaboration with Network investigators.

The Network will directly support the development and pilot testing of educational resources and programs in cancer genetics both for health care providers and for the general public. Network sites will serve as laboratories for the development of innovative approaches to education and community outreach. It is anticipated that materials developed and pilot tested through the Network will be made available for further development and distribution through the NCI as a national resource. The Network will identify, condense, and disseminate state-of-the-art information on cancer genetics through an accessible, electronically-based system which will be fully integrated with and will provide input and quality control to existing NCI informational resources (CIS, OCC, PDQ, etc.). The Network will promote development of guidelines for informed consent for genetic testing, genetic counseling, and laboratory testing procedures.

Participating sites will: (1) recruit individuals who seek information about genetic testing to participate in the Network registry and collect baseline demographic, risk factor, family history and genetic information on these registrants; (2) annually update registry data on family history, cancer incidence and intervention/prevention measures; (3) develop locally based community outreach programs for cancer genetics and area directories for referral and support services; (4) develop and evaluate educational programs and materials (individually and in collaboration with other Network centers); (5) collaborate in the development of Network policies and procedures through participation in the Network Steering Committee, the Network Education and Outreach Subcommittee, and the Informatics Subcommittee; and (6) collaborate in Network-wide projects and activities.

Up to eight participating sites will be funded at $250,000 to $300,000 per site annually. Each Network grant will fund a half-time patient educator or communications specialist to develop and evaluate innovative cancer genetics educational materials and programs. The grants will also support a half-time research nurse/registrar who will obtain informed consent and provide baseline data on registrants to the NCI. Applicants will be required to demonstrate a plan for community outreach including educational outreach to minority/underserved populations concerning cancer genetics. This outreach plan may employ a web-site, "hot-line" or other accessible mechanism and should include the development of a directory of local resources. A half-time position for an outreach coordinator will be included. The costs of genetic testing and counseling will not be covered under this award.

It is anticipated that a recompetition will be issued to add new sites to the Network. These sites may be chosen to expand the range of clinical, behavioral epidemiologic, or basic research efforts within the Network, to provide geographic diversity or to include centers with larger populations of minority/underserved patients. As a term of award, new sites will agree to adopt Network procedures and policies.

An Informatics and Data Management Center (IDMC) will also be funded to develop and maintain an informatics system that facilitates both the registry and educational functions of the Network and safeguards the confidentiality of the Network database The IDMC will coordinate Network data management, analysis and reporting.

Applicants may submit a proposal as a participating site, as the IDMC, or both It is anticipated that the initial focus of the Network will be on identifying adults with genetic susceptibility to breast/ovarian or colorectal cancer Ultimately, however, it is expected that the Network will serve as a means to identify and refer individuals with mutations that predispose to cancers of other sites and/or with family histories suggestive of other cancer susceptibility syndromes. During the first funding year, the Network will: 1) develop policies and procedures; 2) develop and pilot test data collection instruments; 3) develop and pilot test the informatics system; 4) survey existing educational materials and set priorities for the coordinated development and dissemination of new educational programs and materials. By the start of the second funding year, registrants will be recruited to the Network registry.

The activities of the Network will be coordinated with the complementary activities of other NIH-supported initiatives such as the Cooperative Family Registries for Epidemiologic Studies of Breast and Colon Cancers. To maximize the utility of the Network database and to permit collaborative efforts, core data on Network registrants will be compatible

with data in the Cooperative Family Registries and will also include core dataset items to facilitate matching with the National Death Index. Applicants are encouraged to develop geographically based consortia and to make use of population-based cancer registries coordinated through the NCI SEER program or other State-based cancer registries.

Patient Advocacy

NPCC Agenda Doesn't Include NCI Planning, Klausner Says

NCI Director Richard Klausner said the research agenda recently advanced by the National Prostate Cancer Coalition suffered from a "disconnect" from the Institute's planning efforts.

"My sense of looking at it is a little bit of disappointment [about] the disconnect between our planning, our communication, our writing the Bypass budget, and [the NPCC agenda]," Klausner said at a meeting of the National Cancer Advisory Board on Nov. 19.

"There is a real variation of grain size, which I think is very important in planning, between recommending projects and large infrastructures," Klausner said.

The NPCC research agenda, formulated by panels of scientists and patient advocates at a conference at M.D. Anderson Cancer Center, is likely to form the basis for the new coalition's request for a dramatic increase in funding for prostate cancer research (**The Cancer Letter**, Nov. 8).

Sources at NPCC said the coalition is weeks away from completing an estimate of the cost of pursuing the research priorities identified at the conference. The final figure, which is likely to be in hundreds of millions, will form the basis of the coalition's funding request for the fiscal year 1998.

NCI officials, Klausner among them, have said consistently that they oppose earmarks for specific diseases. In the era of tight federal budgets, new funds for prostate cancer research would be likely to be carved out of multiple agencies, which could pose serious obstacles for coordination of research, several observers said.

Robert Samuels, chairman of NPCC said the coalition did not intend to exclude NCI from the planning process. "The NPCC research agenda is only a first step," said Samuels after being informed about Klausner's remarks. "The next step is for us to sit down with the key institutional players to make sure that we can move forward in a collaborative way.

"I'd like to schedule that meeting as soon as possible," Samuels said.

Klausner: "I Would Have Participated"

Critiquing the NPCC research agenda, Klausner said the document appeared to have been developed in a manner that was "completely disassociated" from the NCI planning efforts.

"I would hope that there would be a way to do such research planning, since in the end, NCI will continue to have a big piece of cancer research funding," he said.

Klausner said the NPCC's proposal for development of genetic markers for prostate cancer illustrates the lack of coordination between the research agendas advanced by NCI and the coalition.

"There is no reference whatsoever to an enormous amount of planning and articulation that we have done about the fact that we are moving to create a complete infrastructure for the genetic analysis of tumors, for discovery of markers, and that's through the Genome Anatomy Project," Klausner said.

Klausner said he would have come to the NPCC conference, had he been invited.

"I was not asked to participate, nor asked to recommend people," he said. "I would have loved to have participated. Because I think it's important that we, as a community, not learn to follow NCI, but learn to speak with consonance. I very much want to hear their recommendations, about what we're doing, what we're not doing, what we should be doing."

Told about Klausner's remarks, Andrew von Eschenbach, a scientist at M.D. Anderson who was the chairman of the research agenda meeting, agreed that coordination is needed.

"I think it's appropriate for the National Prostate Cancer Coalition to call a meeting where NCI, the Department of Defense, the American Cancer Society, CaPCURE and other major players could decide how we are going to work toward the same ends," von Eschenbach, director of the M.D. Anderson Multidisciplinary Prostate Program, said to **The Cancer Letter**.

"This was not intended to undermine anything," von Eschenbach said. "The NPCC research agenda is not in conflict with NCI. It is complementary."

As he compiled the research agenda, von Eschenbach was guided by the NCI Bypass Budget, he said. "The idea was to say—as the Bypass Budget did—that these are the exciting areas; if money is available, that's where we should go," von Eschenbach said.

Altogether, four NCI scientists were invited to the research agenda conference to present the NCI perspective. Two NCI staff members attended. Klausner was not invited because the scientific issues involved were relatively straightforward, and therefore did not require the participation of the Institute's top executive, von Eschenbach said.

"As this process moves forward, I am looking forward to continuing discussions with Dr. Klausner," von Eschenbach said. "This is a collaborative effort."

IOM Seeks Nominations For Cancer Policy Board

The National Research Council's Commission on Life Sciences and the Institute of Medicine are seeking nominations for membership on the new National Cancer Policy Board.

The board has been established under a contract with NIH to study issues in the prevention, control, diagnosis and treatment of cancer. NCI Director Richard Klausner asked the council to form the board earlier this year (**The Cancer Letter**, Aug. 16).

Peter Howley, chairman of the Department of Pathology, Harvard Medical School, was appointed chairman of the board. Howley headed the Laboratory of Tumor Virus Biology at NCI until 1993, when he moved the lab to Harvard. Joseph Simone, executive director of Cancer Care Programs at the Huntsman Cancer Institute, was named vice-chairman of the board (**The Cancer Letter**, Nov. 22).

The board will include no more than 20 members, and will meet at least three times a year, the IOM said in a statement Nov. 20.

The role of the board will be to "examine ongoing research, new technologies, issues arising in delivery of care, and problems faced in the Nation's battle against cancer," the IOM said. "It will also be a common meeting ground for the many federal agencies that sponsor or directly conduct relevant work as well as state and local health authorities.

"The board's most distinctive contribution, however, will be to render advice and make recommendations to advance the Nation's effort against cancer," IOM said. "We anticipate that the board will issue a major report each year."

IOM said it is seeking nominations for the board of "individuals with diverse expertise who have distinguished themselves, earning the respect and trust of one or more cancer constituencies."

Members will include:

—Those who have cancer, have survived cancer, or have cared for a loved one with cancer.

—Clinicians and other health professionals (oncologists, oncology nurses, state and local health officials, health educators, etc.).

—Scientists (molecular biologists, clinical investigators, health services researchers, systems and financing experts).

—Providers of health goods and services (hospitals, pharmaceutical manufacturers, clinics, medical device manufacturers, hospices, etc.).

—Health service payers (managed care organizations, insurers, public programs at the state and local level).

IOM also is seeking suggestions for topics for the board to address.

For nominations, include the nominee's name and address, a cover letter of no more than one page, along with a curriculum vitae.

Nominations should be sent by Dec. 1, to: National Cancer Policy Board, Institute of Medicine and Commission on Life Sciences, 2101 Constitution Ave. NW, Washington, DC 20418, tel: 202/334-1382, fax: 202/334-1317; email: cancerbd@nas.edu.

Klausner Sees Board As Neutral Forum

NCI Director Klausner, speaking to an American Cancer Society press conference Nov. 14, said the Policy Board could act as a neutral forum to bring together constituents of the cancer program to develop standards for evidence-based medicine.

In remarks to NCI's National Cancer Advisory Board last week, Klausner said, "I continue to be optimistic about the value and the need of such a [policy] board.

"This is a good time for the National Cancer Advisory Board to think about prioritizing requests and issues of policy concerns that this board would like to see the National Cancer Policy Board address," he said.

Grants Funding

NCI Projects R01 Payline Will Tighten To 22nd Percentile

Due primarily to the increase in grants funded last year, NCI has begun fiscal year 1997 with less money to fund new investigator-initiated grants than in fiscal 1996.

NCI has about $251 million available to fund new grants and grants due for recompetition, about $10 million less than last year, NCI Director Richard Klausner said to the National Cancer Advisory Board at its meeting Nov. 19.

"We take the increased number of grants coming in as extremely positive, as a measure of a signal we said last year we wanted to give," Klausner said. "That is, we would attempt to make as much money available as possible to communicate that there is an opportunity for our extramural investigators to be funded."

The amount available for new and competing grants could improve as the year goes on, as NCI makes various funding decisions, Klausner said. "The overarching principal we will continue to use to allocate the 1997 budget will be to fund absolutely the best science without regard to the mechanism of funding," he said. "That means we need to apply very rigorous criteria for excellence across all mechanisms.

"We are attempting and intending to maintain the investigator-initiated [research project grants] pool as our highest priority in terms of percentile and the number of grants funded," Klausner said.

The Institute received a $128 million increase in appropriations for fiscal year 1997. Up to 80 percent of the new funds, or $85 million, will support extramural grants, Klausner said.

Projected R01 Payline: 22nd Percentile

Currently, the Institute projects that the "payline" for R01 grants will be drawn at the 22nd percentile in FY97. That means grants that fall within the top 22nd percentile of priority scores as determined by peer review would be within the funding range.

Between 1995 and 1996, NCI increased the payline for R01 grants from the 15th percentile to the 23rd percentile by increasing the amount available for R01s from $120 million to $167 million. Part of the increase came from Congress, and part came from NCI reductions in contracts and the intramural research program.

NCI intended to maintain the 23rd percentile in FY97, but now finds it must back down from that level, Klausner said.

To continue funding for the new grants awarded last year, NCI had to increase its budget for noncompeting grants by $65 million, or 9 percent. That amount includes a cost-of-living increase of 4 percent, mandated by NIH.

Klausner said he opposed the 4 percent increase in discussions with NIH management. "I argued that it should be 3 percent, which is more in line with actual inflation, as far as we can tell," he said. Next year, the increase will be 3 percent, he said.

Another reason NCI is unable to meet the 23rd percentile target is the legal requirement for support of Small Business Innovation Research grants, which increase in proportion to the increase in the Institute's extramural research budget. This results in a $12 million increase in funding for the SBIR grants program this year.

The third change in funding patterns that impacts NCI grants funding is a decision by NIH to fully fund a certain number of grants in their first year.

NCI will use $25 million to "forward fund" R29, or FIRST awards. NCI will save about $5 million a year for the next three years, Klausner said.

Funding for program project grants (P01s) is likely to come from the money NCI sets aside for funding "exceptions" to the recommendations of study sections, Klausner said. "We intend to be able to fund as many [P01s] as we did last year, if not more," he said. "Last year, there was a 28 percent increase in the number of new P01s funded, the majority of which were patient-oriented research."

NCI will continue the Accelerated Executive Review, which funds some grants that fall below the payline. Last year, NCI spent $6.7 million to fund these grants. About 40 percent of R01 grants that qualified for AER involved patient-oriented research, and about 40 percent of these were funded.

This year, NCI divisions will receive a budget to support grants awarded as exceptions, Klausner said. These funds would some R29, R21 and R03 grants that do not receive priority scores within the payline. In addition, divisions will be able to fund R01 grants as exceptions provided the grants do not exceed $350,000 total direct costs for the first year, and are within 10 percentile points of the payline, Klausner said.