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Pragmatists vs. Purists: Colon Cancer Screening Guideline Triggers Debate

By Paul Goldberg

The U.S. Preventive Services Task Force earlier this week published a guideline on screening for colorectal cancer.

The guideline is fundamentally different from the consensus guideline put out jointly by the American Cancer Society, the American College of Radiology, and three gastroenterology societies.

The ACS guideline, published in March, discusses the pros and cons of screening methods that have an over-50 percent chance of detecting polyps and colon cancer. In contrast, the Preventative Services guideline, released

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In the Cancer Centers:

NCI Cancer Center Grants Renewed At M.D. Anderson And Indiana University

M.D. ANDERSON CANCER CENTER received renewal of its NCI Cancer Center Support Grant. The five-year renewal totals $52.7 million to support 19 research programs and 24 shared-resource services and technologies used by M. D. Anderson researchers. "The core grant award for 2008-2013 marks a 15 percent increase over the previous five-year renewal," said **Robert Bast Jr**., vice president for translational research and leader of the application process. "M. D. Anderson received the highest numerical score it has ever achieved on a core grant application." . . . **INDIANA UNIVERSITY** Melvin and Bren Simon Cancer Center received the third consecutive renewal of its NCI Cancer Center Support Grant. The five-year renewal will provide $6.5 million. "This recognition by the NCI was made possible by the efforts of scores of our members and associates," said **Stephen Williams**, cancer center director. . . . **EMORY MOLECULAR** and Translational Imaging Center received a five-year, $7.5 million grant from NCI for research on cancer imaging techniques. Four projects covered by the grant will range from clinical studies on the diagnosis of prostate cancer to basic research on cancer-seeking magnetic iron nanoparticles. The principal investigators include: **Carolyn Meltzer**, the William P. Timmie professor and chairman of radiology and associate dean for research; **Mark Goodman**, professor of radiology and hematology and oncology and chairman in imaging sciences; and **Xiaoping Hu**, professor of biomedical engineering and radiology and a Georgia Research Alliance Eminent Scholar. The center was created last year through an NCI planning grant of $1.5 million. It will

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Different Processes Produce Different Screening Guidelines

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Oct. 6, was intended to be a rigorous analysis of impact of several programs of repeated screening.

The differences are profound:

—The USPSTF guideline recommends three modalities: colonoscopy, sigmoidoscopy, or fecal occult blood testing.

—Relying on microsimulation modeling by the NCI Cancer Intervention and Surveillance Network, USPSTF determined that three screening regimens were approximately equally effective in life-years gained: colonoscopy every 10 years, sigmoidoscopy every five years combined with high-sensitivity fecal occult blood testing every three years, and annual fecal occult blood testing.

This is the first USPSTF guideline to incorporate modeling into the writing process. However, because of limitations on the authority of the Agency for Health Care Research and Quality, which runs the task force, the modeling didn't consider cost as a parameter, insiders said.

—Computed tomographic colonography, or virtual colonoscopy, isn't recommended by the USPSTF guideline, largely because the impact of radiation and incidental findings couldn't be definitively evaluated. The ACS guideline includes CT colonography. Also, it includes stool DNA and barium enema, neither of which is recommended by USPSTF.

—The USPSTF guideline recognizes the guiaic Hemoccult II test as an option for accompanying sigmoidoscopy. Hemoccult II and other lower-sensitivity tests are specifically not recommended by the ACS joint guideline, which viewed them as the benchmark other modalities had to improve on. The society's guidelines recommend higher-sensitivity blood stool testing.

—The USPSTF guideline recommends that routine screening of asymptomatic individuals at average risk begin at age 50 and stop after 75. Screening shouldn't be performed routinely after age 76, and should stop altogether at 85, because conditions other than colorectal cancer may be more likely to affect such patients, the USPSTF guideline states. The ACS guideline makes no recommendations for stopping.

In an earlier guideline, USPSTF recommended screening men and women over 50, but noted that no data existed to compare screening modalities.

Debate Over Process

The two competing guidelines raise questions about what a screening guideline should look like.

Should guideline-writing be a pragmatic and, if necessary, political process aimed at increasing screening? Or should it be a pure, intellectual exercise that excludes vested interests, follows a pre-specified plan, considers screening strategies (as opposed to modalities), and rigorously weighs health benefits against potential harm before making a recommendation?

"These two guidelines illustrate important differences in how the medical profession makes guidelines in 2008, and the differences have consequences for how clinicians will practice medicine," said David Ransohoff, professor of medicine, cancer epidemiology and cancer prevention and control at the University of North Carolina Lineberger Cancer Center.

"The USPSTF has, over 30 years, developed explicit rules of evidence that are pre-stated and used in every set of guidelines," said Ransohoff, who didn't take part in drafting either of the guidelines. "The process is detailed, thorough, transparent—and expensive. The guiding principle developed by the USPSTF—that is now a critical foundation of the whole field of evidence-based-medicine—is to base choices on outcomes to patients, to weigh the benefits vs. the harms of each possible intervention or choice.

"The ACS process is not pre-stated and does not directly weigh outcomes," Ransohoff said. "One rule it developed for the CRC guidelines—to accept a test that has 50 percent sensitivity at any application—considers

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only one small feature of what a screening test does. This rule doesn't explicitly consider any outcomes, much less weigh them—meaning benefits vs. harms like false positives, serious side effects, and so on."

ACS hasn't employed the same procedure for all of its guidelines, and in the case of the colorectal cancer guideline, the process ultimately became politicized and, according to one participant, resembled "sausage-making."

"It is extremely hard to bring disparate professional groups together, to have them operate totally out of objectivity, not because they are bad people, but because they see the world through different lenses," said Bernard Levin, emeritus professor at M.D. Anderson Cancer Center and lead author of the ACS guideline. "Everyone, in some respects, has their vested interests. Some of it is vested because of financial interests, some of it, because of emotional attachment, and some because of scientific beliefs. With human being flawed as we are, you can't necessarily arrive at the truth with one direct shot. It's something of a tangential approach. That's what I think I learned from this."

After the ACS guideline was published, Levin said the document signaled a "shift in emphasis" for cancer screening. "The important thing about these guidelines is that they stress the prevention rather than detection; prevention by finding polyps that can be removed," Levin said (The Cancer Letter, March 7).

Ransohoff agrees that "at some abstract level, prevention sounds better than early detection."

However, "the choice can't be made in the abstract," Ransohoff said. "You must consider, as the USPSTF does, what are the consequences—on outcomes—of each choice. If our goal is to detect and destroy every adenoma in the U.S. population, that's a big job, because about 50 percent of persons over age 50 have adenomas. We as a profession may decide we want to do that, but we can't make that policy decision until we consider first—explicitly and in detail—the consequences, outcomes, benefits, and harms of that choice.

"The ACS guideline doesn't do that."

Ransohoff said this wording has led physicians to interpret the ASC guideline as a *de facto* endorsement of colonoscopy over other strategies. "Primary care physicians and gastroenterologists immediately started to ask me whether it's ethical to do anything other than colonoscopy," he said.

This is an unfair criticism, says Levin. "This faulty interpretation fails to acknowledge the extensive discussions in the document of the benefits, limitations and possible harms of colonoscopy and the need for quality assurance of all procedures," Levin said. "We didn't imply that we should seek and destroy every adenoma, an approach that would be indefensible.

"While nuanced debate continues, the fact remains that one-half of age-eligible population in the U.S. is undergoing colon cancer screening. That's the main issue here."

Pragmatists vs. Purists

While the debate pits pragmatists against purists, its exquisite nuances may escape the doctors and patients making screening decisions, observers say.

Peter Lance, professor of medicine, molecular biology, and public health at the Arizona Cancer Center, says the impact of the two guidelines would be somewhere between confusion and chaos.

"When you have one august body coming out with one set of recommendations and another august body coming out with different, complicated sets of recommendations, I think it's not going to help us advance the cause of getting more people screened for colorectal cancer," Lance said.

The question is, how much of a purist can you be at a time when technology changes rapidly?

"Both the ACS and USPSTF guidelines have to contend with rapidly changing technology as well as the absence of definitive, randomized controlled trials for some modalities," said Levin. "Colonoscopy—'the gold standard'—has never been the subject of a randomized, controlled trial in a screening population, but both groups endorse it."

Though the USPSTF guideline used a more transparent process, they still have to rely on judgment calls, said Tim Byers, a cancer prevention expert at the University of Colorado Cancer Center, who served on the guideline committee assembled by ACS.

"Granted, in this systematic review they are more systematic and transparent," Byers said. "They lay out their methodology and the quantitation of it. But it's the same kind of process; they just lay it out a little bit more explicitly here.

"But some of the really critical decisions here are still decisions you make without evidence. For instance, when they talk about stopping at age 85 and/or age 75, there is really not a lot of good evidence for those stopping rules. That's still a squint-your-eyes-and-make-your-best-call sort of a guideline," Byers said. "Even though they say this is a systematic review and it's quantitative and it's all very orderly, some of those key aspects are judgment calls.

"I still think there is less to be gained from making it a one-item list than a three- or four-item list," he said.

CT Colonography: Contrasting Views

Both guideline committees reviewed the same data on CT colonography, but came to opposite conclusions.

The results, from a trial by the American College of Radiology Imaging Network, were published in the Sept. 18 issue of the New England Journal of Medicine. The trial enrolled 2,600 subjects, who received both optical and virtual colonoscopy. CT colonography detected polyps 10 mm or larger in 90 percent of participants who were confirmed to have a polyp of this size by colonoscopy.

"ACRIN trial data had been presented at meetings in 2007, but manuscript had not been published, so we could not cite the study per our policy of only using peer-reviewed, published data," Levin said to The Cancer Letter. "We considered the issue of radiation risk carefully, relying on published expert opinion and, in the context of equivalence to optical colonoscopy of sensitivity for detection of large adenomas and cancers, felt that the benefit-to-harm ratio was acceptable."

The same data were reviewed by the USPSTF, and included in a review of literature, but was not part of the modeling.

The review, led by Evelyn Whitlock, of the Kaiser Permanente Center for Health Research, states that the impact of extracolonic findings cannot be assessed reliably based on available data.

"The USPSTF concludes that for CT colonography, evidence to assess the harms related to extracolonic findings is insufficient, and the balance of benefits and harms cannot be determined," the recommendation states.

Byers disagrees. "I think the ACRIN trial is the most definitive evidence to date that in fact CT colonography does have a role to play in screening," Byers said. "Because of the extracolonic findings and because of the cost and because of the poorly quantified radiation hazards, it's not without its problems.

"I suspect that in the long-term, CT colonography might come in to be used in older people, where you are looking only for the larger lesions, where you want to do a less invasive test, and where you might be willing to not pursue aggressive workup of extracolonic findings," Byers said. "I suspect this is something they might want to revisit sooner rather than later."

Mary Barton, scientific director of the USPSTF, said the ACRIN paper doesn't justify reopening the guideline.

"The ACRIN results were incorporated into the evidence report [published with the guideline], and it is the assessment of the Evidence-Based Practice Center and the USPSTF that the recently available data would not change the conclusions of USPSTF regarding the sufficiency of evidence for CT colonography," Barton said to The Cancer Letter.

The Question of Sigmoidoscopy

The USPSTF recommendation of combining sigmoidoscopy with fecal occult testing as an alternative to colonoscopy raises two questions, critics said.

The guideline noted that the guaiac Hemoccult II test was inferior to high-sensitivity fecal occult tests, but didn't specifically recommend against its use. "I believe it is inappropriate to recommend a lower sensitivity guaiac-based FOBT such as Hemoccult II," Levin said.

Exclusion of these tests was one of the pre-specified criteria used by ACS in drafting its guideline, he said.

"We wanted to establish a threshold, and specific target was the guaiac-based fecal occult blood tests, which did not detect more than half of cancers," Levin said. "You could argue that that's too low a threshold."

CT colonography, stool DNA, and barium enema met the bar and were included in the ACS-led guideline even though barium enema is no longer performed and not taught, and even though stool DNA isn't approved by FDA, and is being sold as a "home brew." The test is sold for about $400, compared to high-sensitivity stool blood tests, which cost $10 to $15.

However, "stool DNA technology is changing rapidly," Levin said. "We based our guarded recommendation on published information but with knowledge from meeting abstracts of data that indicated high sensitivity tests are in the offing."

The fact that flexible sigmoidoscopy is included by both ACS and USPSTF indicates that neither entity is being realistic, several observers said.

"The fact is that flexible sigmoidoscopy is on a decline," Levin acknowledged. "There are very few people doing it. When it's done in high-volume settings, it's a fine technique, but in most cases it's not happening, and evidence is that it's not done well by most people who do it only intermittently."

Lance, who is a critic of both guidelines, agrees that sigmoidoscopy is not a practical option. "Internists

and family practitioners aren't being trained to do sigmoidoscopy," he said. "Almost as a trade union, the gastroenterologists are against doing sigmoidoscopies, because they can bill more for doing a colonoscopy."

Byers said this isn't exclusively a question of supply. "We are running a program in Colorado, where we offer free endoscopic screening to people without health insurance, and we offer either a sigmoidoscopy or a colonoscopy, and what we find is that fewer than 1 percent of the people choose a sigmoidoscopy," Byers said. "Basically, people are voting strongly for colonoscopy now."

In an editorial published in the September issue of the journal Cancer Epidemiology, Biomarkers and Prevention, Lance suggests a flow chart approach whereby patients would first be offered an optical colonoscopy, and, if declined or inappropriate, CT colonography, and, as a fall-back position, fecal immunochemical testing.

The current guidelines don't strike him as viable. "I think we are living in Cloud-Cuckoo-Land, frankly," said Lance.

An editorial that accompanies the USPSTF guidelines in the Annals of Internal Medicine states that the new guidelines would have been more useful had they included cost comparisons.

"What do these differing processes and recommendations tell us about the current state of the art in making guidelines?" ask Michael Pignone, an assistant professor of cancer prevention and control at UNC, and Harold Sox, the journal's editor.

"First, the consistent application of defined methods for gathering, interpreting, and rating evidence promotes transparency and internal consistency. Second, modeling is useful because it integrates different types of evidence to estimate the net benefit of different screening strategies.

"However, to be most informative, modeling must evaluate all of the relevant strategies and their costs. Third, guideline makers must decide on a process for using modeling results and follow it consistently.

"Finally, recommendations should be specific about starting and stopping ages, testing intervals, and follow-up. In short, we think the public is best served by a relatively structured, comprehensive, transparent approach in which the entire body of evidence drives the recommendations."

The USPSTF recommendation is posted at www.annals.org.

The ACS guideline is posted at www.caonline.amcancersoc.org/cgi/content/abstract/58/3/130.

2008 Nobel Prize Awarded For HIV And HPV Discoveries

By Kirsten Boyd Goldberg

The 2008 Nobel Prize in Physiology or Medicine was awarded to two French scientists for the discovery of HIV and a German scientist for discovering that human papilloma viruses cause cervical cancer.

One-half of the prize was awarded jointly to Françoise Barré-Sinoussi, of Institut Pasteur, and Luc Montagnier, director of the Paris-based World Foundation for AIDS Research and Prevention, for the discovery of HIV in 1983.

The other half of the prize was awarded to Harald zur Hausen, professor emeritus and former chairman and scientific director of the German Cancer Research Centre in Heidelberg, for the discovery of HPV as the cause of cervical cancer.

The award for the HIV discovery re-opened the question of the role of former NCI scientist Robert Gallo, who became embroiled in a bitter fight with Montagnier and his group over who discovered the virus, whose HIV test was patented first, and whether one group had taken samples of the virus from the other.

Only three scientists can share the prize, awarded by the Nobel Assembly at Karolinska Institutet in Stockholm, Sweden.

NCI Director John Niederhuber said Gallo's work should received some recognition.

"As a National Cancer Institute scientist, Dr. Robert Gallo was instrumental in every major aspect of the discovery of the AIDS virus," Niederhuber said in a statement earlier this week. "Dr. Gallo discovered Interleukin-2 (IL-2), an immune system signaling molecule, which was necessary for the discovery of the AIDS virus, serving as a co-culture factor that allowed the virus to grow.

"Numerous scientific journal articles, many co-authored by Dr. Gallo and Dr. Luc Montagnier, cite the two scientists as co-discoverers of the AIDS virus," Niederhuber said. "Additionally, Dr. Gallo discovered the blood test for AIDS.

"While we are pleased that two scientists who contributed so much to AIDS research were recognized today, I am extremely disappointed that the NCI and all of the resources it brought to bear on the discovery of the AIDS virus—along with the technology to make blood banking safe and the drugs that have made AIDS a chronic disease—weren't, in some fashion, recognized," Niederhuber said.

Montagnier's team isolated the virus now called

HIV-1 in 1983. A year later, Gallo's team published that it discovered the virus that causes AIDS, and called it HTLV-IIIB.

In 1991, after 10 years of battling the Pasteur Institute over royalties for a blood test, Gallo conceded and an independent study confirmed that the virus came from the Pasteur Institute. Gallo contended that the French virus accidentally contaminated cultures in his laboratory (The Cancer Letter, July 15, 1994).

Then-NIH Director Harold Varmus brought the legal dispute over royalties to a close by officially acknowledging that the French virus infected the U.S. work used in creating the blood test, and agreed on a split of royalties that provided the Pasteur Institute with the largest share.

The Department of Health and Human Services dropped charges of scientific misconduct against Gallo in 1993.

In its announcement of the prizes, the Nobel Foundation stated, "Françoise Barré-Sinoussi and Luc Montagnier discovered human immunodeficiency virus."

The Foundation statement continues:

"Virus production was identified in lymphocytes from patients with enlarged lymph nodes in early stages of acquired immunodeficiency, and in blood from patients with late stage disease. They characterized this retrovirus as the first known human lentivirus based on its morphological, biochemical and immunological properties. HIV impaired the immune system because of massive virus replication and cell damage to lymphocytes. The discovery was one prerequisite for the current understanding of the biology of the disease and its antiretroviral treatment.

"Following medical reports of a novel immunodeficiency syndrome in 1981, the search for a causative agent was on. Françoise Barré-Sinoussi and Luc Montagnier isolated and cultured lymph node cells from patients that had swollen lymph nodes characteristic of the early stage of acquired immune deficiency. They detected activity of the retroviral enzyme reverse transcriptase, a direct sign of retrovirus replication. They also found retroviral particles budding from the infected cells. Isolated virus infected and killed lymphocytes from both diseased and healthy donors, and reacted with antibodies from infected patients. In contrast to previously characterized human oncogenic retroviruses, the novel retrovirus they had discovered, now known as human immunodeficiency virus (HIV), did not induce uncontrolled cell growth. Instead, the virus required cell activation for replication and mediated cell fusion of T lymphocytes. This partly explained how HIV impairs the immune system since the T cells are essential for immune defence. By 1984, Barré-Sinoussi and Montagnier had obtained several isolates of the novel human retrovirus, which they identified as a lentivirus, from sexually infected individuals, haemophiliacs, mother to infant transmissions and transfused patients. The significance of their achievements should be viewed in the context of a global ubiquitous epidemic affecting close to 1% of the population.

"Soon after the discovery of the virus, several groups contributed to the definitive demonstration of HIV as the cause of acquired human immunodeficiency syndrome (AIDS). Barré-Sinoussi and Montagnier's discovery made rapid cloning of the HIV-1 genome possible. This has allowed identification of important details in its replication cycle and how the virus interacts with its host. Furthermore, it led to development of methods to diagnose infected patients and to screen blood products, which has limited the spread of the pandemic. The unprecedented development of several classes of new antiviral drugs is also a result of knowledge of the details of the viral replication cycle. The combination of prevention and treatment has substantially decreased spread of the disease and dramatically increased life expectancy among treated patients. The cloning of HIV enabled studies of its origin and evolution. The virus was probably passed to humans from chimpanzees in West Africa early in the 20th century, but it is still unclear why the epidemic spread so dramatically from 1970 and onwards.

"Identification of virus-host interactions has provided information on how HIV evades the host's immune system by impairing lymphocyte function, by constantly changing and by hiding its genome in the host lymphocyte DNA, making its eradication in the infected host difficult even after long-term antiviral treatment. Extensive knowledge about these unique viral host interactions has, however, generated results that can provide ideas for future vaccine development as well as for therapeutic approaches targeting viral latency.

"HIV has generated a novel pandemic. Never before has science and medicine been so quick to discover, identify the origin and provide treatment for a new disease entity. Successful anti-retroviral therapy results in life expectancies for persons with HIV infection now reaching levels similar to those of uninfected people."

Gallo, now at University of Maryland School of Medicine's Institute of Human Virology, released a statement Oct. 6 congratulating the Nobel Prize winners.

"I am pleased my long-time friend and colleague Dr. Luc Montagnier, as well as his colleague Francoise Barre-Sinoussi, have received this honor," he said. "I am pleased that the Nobel Committee chose to recognize the importance of AIDS with these awards and I am proud that my colleagues and I continue to search for an AIDS vaccine."

HPV Discovery Recognized

Following is the text of the Nobel Foundation's statement on zur Hausen's discovery of HPV as the cause of cervical cancer:

"Harald zur Hausen went against current dogma and postulated that oncogenic human papilloma virus (HPV) caused cervical cancer, the second most common cancer among women. He realized that HPV-DNA could exist in a non-productive state in the tumours, and should be detectable by specific searches for viral DNA. He found HPV to be a heterogeneous family of viruses. Only some HPV types cause cancer. His discovery has led to characterization of the natural history of HPV infection, an understanding of mechanisms of HPV-induced carcinogenesis and the development of prophylactic vaccines against HPV acquisition.

"Against the prevailing view during the 1970s, Harald zur Hausen postulated a role for human papilloma virus (HPV) in cervical cancer. He assumed that the tumour cells, if they contained an oncogenic virus, should harbour viral DNA integrated into their genomes. The HPV genes promoting cell proliferation should therefore be detectable by specifically searching tumour cells for such viral DNA. Harald zur Hausen pursued this idea for over 10 years by searching for different HPV types, a search made difficult by the fact that only parts of the viral DNA were integrated into the host genome. He found novel HPV-DNA in cervix cancer biopsies, and thus discovered the new, tumourigenic HPV16 type in 1983. In 1984, he cloned HPV16 and 18 from patients with cervical cancer. The HPV types 16 and 18 were consistently found in about 70% of cervical cancer biopsies throughout the world.

"The global public health burden attributable to human papilloma viruses is considerable. More than 5% of all cancers worldwide are caused by persistent infection with this virus. Infection by the human papilloma virus is the most common sexually transmitted agent, afflicting 50-80% of the population. Of the more than 100 HPV types known, about 40 infect the genital tract, and 15 of these put women at high risk for cervical cancer. In addition, HPV is found in some vulval, penile, oral and other cancers. Human papilloma virus can be detected in 99.7% of women with histologically confirmed cervical cancer, affecting some 500,000 women per year.

"Harald zur Hausen demonstrated novel properties of HPV that have led to an understanding of mechanisms for papilloma virus-induced carcinogenesis and the predisposing factors for viral persistence and cellular transformation. He made HPV16 and 18 available to the scientific community. Vaccines were ultimately developed that provide ≥95 % protection from infection by the high risk HPV16 and 18 types. The vaccines may also reduce the need for surgery and the global burden of cervical cancer."

In the Cancer Centers:

Winship Awarded $7.4M Grant

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receive additional support from the Emory Winship Cancer Institute, the Georgia Research Alliance and the Georgia Cancer Coalition. . . . **WINSHIP CANCER INSTITUTE** received a five-year, $7.4 million grant from the National Institute of Environmental Health Sciences to study the links between oxidative stress and colorectal cancer. **Paul Doetsch**, professor of biochemistry, radiation oncology, and hematology and oncology at Emory University School of Medicine and deputy director for basic research at WCI, is principal investigator. Participating Emory faculty include **David Lambeth**, **Gray Crouse**, and **Yoke Wah Kow**. Also participating is **Gerald Shadel**, former Emory faculty member now professor of pathology and genetics at Yale University School of Medicine.

Funding Opportunities:

RFA-CA-09-003: Replication and Fine-Mapping Studies for the Genes Environment and Health Initiative. R01. Letters of Intent Receipt Date: Oct. 24. Application Due Date: Dec. 1. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-09-003.html. Inquiries: Elizabeth Gillanders, 301-594-5868; lgilland@mail.nih.gov.

PA-09-004: Understanding the Effects of Emerging Cellular, Molecular, and Genomic Technologies on Cancer Health Care Delivery. R01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-09-004.html. Inquiries: Andrew Freedman, 301-435-6819; freedmaa@mail.nih.gov.

PAR-09-003: Small Grants for Behavioral Research in Cancer Control. R03. Application Due Date: April 20; Aug. 20; Dec. 21; April 20, 2010; Aug. 20. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-09-003.html. Inquiries: Veronica Chollette, 301-435-2837; vc24a@nih.gov.

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