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Task Force Urges HHS To Form Committee To Implement Genetic Testing Regulations

A task force to review genetic testing in the U.S. has urged HHS Secretary Donna Shalala to establish an advisory committee that will oversee the implementation of regulations to ensure the safety and efficacy of genetic testing.

The recommendation calls for a non-governmental advisory committee to be established within the HHS Office of the Secretary, which would serve as a coordinating body to oversee the implementation of other task force recommendations throughout HHS.

"The committee would advise the Secretary on implementation of

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In Brief

Huntsman Cancer Institute Joins NCCN; Howard Cancer Center To Honor Mandela

HUNTSMAN CANCER INSTITUTE at the University of Utah joined the National Comprehensive Cancer Network in October. **Raymond White**, HCI executive director, and **Joseph Simone**, senior clinical director and director of the Huntsman Cancer Care Program, will represent the institute on the NCCN board of directors. HCI brings the number of NCCN members to 16. . . . **NELSON MANDELA**, president of the Republic of South Africa, will be given the Lifetime Achievement Award at the Howard University Cancer Center 25th anniversary awards gala Nov. 14. The award will be accepted by Franklin Sonn, ambassador for South Africa. Howard is involved in a collaboration with the Medical University of South Africa. Awards will also be given to Rep. John Porter (R-IL), Howard surgeon LaSalle Leffall, and, posthumously, Jack White, the center's founder. . . . **JOHN MENDELSOHN**, president of M.D. Anderson Cancer Center, was elected to membership in the Institute of Medicine of the National Academy of Sciences. . . . **ROBERT SAMUELS** was elected to a second term as chairman of the National Prostate Cancer Coalition. **Jon Huntsman**, chairman and CEO of Huntsman Corp, and **Michael Milken**, founder and chair of CaP CURE, were elected as honorary co-chairmen of NPCC. . . . **MACE ROTHENBERG** was named director of the phase 1 drug development program at the division of Medical oncology at Vanderbilt University Medical Center. Rothenberg's new program will integrate phase I clinical evaluation with pharmacokinetic and mechanistic studies of experimental

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HHS Should Ensure That Tests Are Valid, Labs Meet Standards

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recommendations made by the task force in this report to ensure that: the introduction of new genetic tests into clinical use is based on evidence of their analytical and clinical validity, and utility to those tested; all stages of the genetic testing process in clinical laboratories meet quality standards; health providers who offer and order genetic tests have sufficient competence in genetics and genetic testing to protect the well-being of their patients; and there be continued and expanded availability of tests for rare genetic diseases," the task force report states.

The task force, established in 1994 by the NIH-Department of Energy Joint Working Group on Ethical, Legal, and Social Implications of Human Genome Research (ELSI), was comprised of representatives from insurance companies, the biotechnology industry, disease advocacy groups, and health care providers.

"For the most part, genetic testing in the United States has developed successfully, providing options for avoiding, preventing, and treating inherited disorders," the report said. "However, problems arise as a result of current practices: sometimes, genetic tests are introduced before they have been demonstrated to be safe, effective, and useful; there is no assurance that every laboratory performing genetic tests for clinical purposes meets high standards; and often, the informational materials distributed by academic and commercial genetic testing laboratories do not provide sufficient information to fill in the gaps in providers' and patients' understanding of genetic tests.

"In the next few years, a greater burden for offering genetic testing will fall on providers who have little formal training or experience in genetics."

The report recommends that the clinical validity and analytical sensitivity of a genetic test be determined through investigative protocols before the test is made available in clinical practice. Data should show the benefits and risks associated with both a positive and negative results, the report states.

Scientific merit of protocols should be reviewed by institutional review boards, assisted by guidelines from the Office of Protection of Human Subjects from Research Risks. Enforcement of IRB requirements could be done through FDA authority, refusal of reimbursement by third-party payers for tests that have not completed a protocol, or through legislation enacted by Congress.

FDA has the authority to regulate genetic testing services, but due to a lack of resources, controls only the test kits marketed to laboratories, said Neil Holtzman, chairman of the task force and professor of pediatrics and director of genetics and public policy studies at Johns Hopkins Medical Institutions. Currently, there is no agency overseeing genetic testing services.

The task force did not recommend FDA as the agency that should be responsible for regulating this area of genetic testing, but did list FDA as one option. The task force would like FDA to work closely with the advisory committee to help implement regulations, Holtzman said.

Recommendations of the task force were presented to Shalala last month. Shalala has requested staff to report back on the document by the end of the year, Holtzman said.

The recommendations are more likely to be implemented than earlier recommendations because they address genetic testing more broadly, and bring together the concerns of individuals involved in every aspect of genetic testing, Holtzman said.

"The task force made a decision early on that it was not going to make recommendations for specific tests, or specific diseases, or specific categories of diseases, but make them broadly for genetic tests," Holtzman said. "The task force is a broader

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Editor & Publisher: Kirsten Boyd Goldberg
Editor: Paul Goldberg
Staff Writer: Catherine Fiore
Circulation: Rena Guseynova

P.O. Box 9905, Washington, DC 20016
Tel. (202) 362-1809 Fax: (202) 362-1681
Editorial e-mail: kirsten@cancerletter.com
Customer service: service@cancerletter.com
World Wide Web URL: http://www.cancerletter.com

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organization where all of the stakeholders were brought to the table. Here consumers, industry, and clinical groups all had a full voice at the table."

The text of the ELSI task force report is posted on the National Human Genome Research Institute website at http://www.nhgri.nig.gov/ELSI/TFGT_final.

In Congress

Time Running Out On Proposal To Double Market Exclusivity

As the Congressional session draws to a close, hope is dimming for a controversial proposal to double the five-year market exclusivity term currently given to companies that develop new drugs.

Under a proposal advanced by Bristol-Myers Squibb Co. and two other drug companies, the government would launch a "demonstration project" to study the impact of extending the innovators' exclusivity in return for a royalty payment of 3% of the drugs' net sales.

The royalty would be paid to NIH for research on cancer, AIDS, diabetes, heart disease, stroke, and other life-threatening diseases, the proposal states. Companies would also be required to invest an equal percentage into research and development for additional uses of the drug receiving exclusivity.

If the proposed amendment to the Waxman-Hatch Act is not approved before Congress adjourns for the year, the BMS drug Taxol would not qualify for the extension under the demonstration project, observers said. Taxol's five-year exclusivity expires in December.

Congress is scheduled to adjourn Nov. 7.

The legislative proposal, "Demonstration Project to Fund Biomedical Research," which currently has no sponsor, was aired during a recent hearing of the Senate Labor, HHS, and Education Appropriations Subcommittee. The hearing was held by Sen. Arlen Specter (R-PA), chairman of the subcommittee.

BMS developed the idea for a proposal in collaboration with SmithKline Beecham and Schering-Plough, sources said. The drug companies sought to establish the demonstration project by amending the Labor, HHS, and Education Appropriations bill, observers said. The bill has been stalled as a result of debate over President Clinton's proposed national reading and math tests.

At the appropriations subcommittee's special hearing Oct. 21, the proposal appeared on the agenda as a "legislative proposal to enhance funding for medical research." However, the cryptic designation did not protect the proposal from an attack by Sen. Dick Durbin (D-IL) and Rep. Henry Waxman (D-CA).

At a press conference earlier that day, Durbin called the demonstration project a "moonlight mackerel" and compared it to the $50 billion tax cut for tobacco companies that was mysteriously inserted into the balanced budget agreement earlier this year.

"Special interest groups will always try to sneak in a backdoor deal and call it a benefit," Durbin said at the press conference. "The odor emanating from this provision can't be masked by a flower for the NIH."

Durbin estimated a five-year extension of market exclusivity would cost consumers $10 billion in higher drug costs, most of which would be absorbed by Medicare. The potential $500 million to $750 million that NIH would receive in royalties would not justify the cost to taxpayers, Durbin said.

"[The proposed legislation] is being sold as a panacea to the difficult choices the Congress has had to make to sustain our country's scientific crusade against diseases like AIDS, cancer, diabetes, and heart disease," Waxman said in a statement to the Senate Appropriations Subcommittee on Labor, HHS, and Education. "In reality, this is a stark special interest deal which only serves the financial interests of a small number of prescription drug companies."

Waxman is co-author of the Drug Price Competition and Patent Term Restoration Act of 1984.

"This proposal would completely overturn the delicate balance of equities in the 1984 Act, without any careful or systematic regard for the implications for all of the commercial interests at stake, as well as the public welfare," Waxman said in the statement, co-authored by Reps. Sherrod Brown (D-OH), Peter Deutsch (D-FL), and Pete Stark (D-CA).

"Any revisions to the 1984 Act must be made in the same spirit and to the same effect as the original statute," Waxman, Brown, Deutsch, and Stark said. "For this reason alone, we would strongly oppose this proposal and seek its defeat in the House of Representatives."

Three members of the Senate subcommittee—Specter, Tom Harkin (D-IA), and Robert Bennett (R-UT)—attended the hearing.

"I'm apprehensive about more money for NIH in exchange for a greater period of exclusivity,"

Specter said at the hearing. "If the period of exclusivity is warranted because of generating more research to provide more products to help more people live longer lives, I think that's a very powerful argument if that can be qualified."

Harkin said amending the Waxman-Hatch Act may be unfair to the sponsors of generic drugs, who have made sizable investments into research and development to enter the market for paclitaxel.

"Taxol is well on its way to becoming a billion dollar drug and certainly needs no additional legislative preference to ensure its success," Scott Hallquist, senior vice president and general counsel of Immunex Corp., said at the hearing. Immunex produces a generic paclitaxel which is currently marketed in Canada for the treatment of metastatic breast and ovarian cancers. The company said it is interested in entering the US market.

"We just want our chance to compete," Hallquist said.

Opponents of the proposal said an extension of exclusivity for drugs like Taxol will translate into higher prices for consumers. Without generic competition, drug companies will have no reason to lower prices.

The proposed language for the demonstration project does not preclude the sponsors from raising prices to cover the 3% royalty payment, nor does it provide assurance that the 3% will be new money for NIH, and not a replacement for appropriated funds, opponents said.

Economic Incentive Cited

According to supporters, the extension would allow companies to lower the prices of branded drugs. Without the constraint of a five-year period to recoup the costs of research and development, companies would not need to raise prices as high as they are currently.

"My experience in this field has led me to conclude that the economic incentive established by an extension of exclusivity is likely to generally produce societal benefits which outweigh the limited cost savings generated by earlier introduction of generic goods," said Kenneth Clarkson, director of the Law and Economics Center at the University of Miami. "The added benefit of off-budget financing for the NIH under this Demonstration Project shifts the balance even further in favor of exclusivity."

The list of supporters of the proposal includes the National Coalition for Cancer Survivorship, the National Alliance of Breast Cancer Organizations, the American Society of Clinical Oncology, Eastern Cooperative Oncology Group, Cancer Care Inc. the Candlelighters Childhood Cancer Foundation, US TOO International, Y-ME National Breast Cancer Organization; the Alliance for Lung Cancer Advocacy, Support & Education; and the Oncology Nursing Society.

"If patients are to receive the benefit of basic biomedical discoveries, there must be more innovative approaches to encourage both the public and private sectors to pursue greater clinical research opportunities," said a letter signed by ASCO, ONS and eight advocacy groups.

"The legislative proposal would provide incentives for companies not only to contribute to NIH funding, but also to conduct their own privately sponsored research in the same therapeutic area as the drug receiving additional exclusivity," said the letter addressed to Specter.

"While this demonstration project would extend patent exclusivity, there would be important benefits to the public from such an effort," Robert Young, president of Fox Chase Cancer Center, wrote in a separate letter to Specter. "First, it would ensure that any new drug is fully studied through clinical trials to establish its potential benefit in other diseases and, second, the increased funds directed toward the NIH would accelerate the pace of biomedical research in this country."

"Both of these effects would directly benefit patients with cancer in our country," Young wrote.

The idea of extending the Waxman-Hatch exclusivity was floated earlier this year by Sen. Ron Wyden (D-OR). Addressing the Generic Pharmaceutical Industry Association Sept. 10, Wyden said extension of exclusivity on Taxol may be in the public interest.

"If and when Bristol formally requests an extension of exclusivity on this drug, it may be in the consumer interest to do so," Wyden said. "But I believe that I and other members will be looking hard at what we'll get in the form of pay-back under those circumstances, whether it's a lower price on the drug and expanded programs for indigent patients, or a direct profit-sharing or royalty enhancement for the NCI," he said.

A spokesman for Wyden said the senator was not involved in drafting the proposed language, and has not formed an opinion on the demonstration project.

Public Health Service

HHS Official Transferred To Office Of Surgeon General

Susan Blumenthal, the controversial former director of the PHS Office on Women's Health was scheduled to begin a new job as senior advisor to the President Nov. 3.

Instead, Blumenthal was transferred to another assignment as acting chief of staff at the Office of the Surgeon General, officials said. Blumenthal did not appear at that job either, instead taking vacation that was expected to last two weeks, officials said.

Damon Thompson, a spokesman for the HHS Office of Public Health and Science, said the department is acting under the assumption that Blumenthal would be going to the White House. "No one has told us otherwise," he said to **The Cancer Letter**.

Thompson said the transfer was necessary to allow the HHS to advertise Blumethal's former job at the Office on Women's Health.

The Chronicle of Higher Education Nov. 7 reported that Blumenthal is under an inquiry by the HHS Office of the Inspector General.

According to the Chronicle, the inquiry centers on a Request for Proposals in which applicants were required to submit "scientific papers" that would be published under Blumenthal's name (**The Cancer Letter**, Oct. 3). Sources said members of Blumenthal's former staff have been interviewed by investigators.

Blumenthal did not return a call from a reporter. The White House did not respond to questions. Officials at OIG declined to comment.

Food and Drug Administration

Breast Implant Policy Stands, But Agency To Push For Data

FDA will let stand a policy restricting the availability of silicone breast implants, saying that data are not sufficient to either lift the restrictions or to further limit the devices.

However, FDA said it will push manufacturers to complete studies on the risks of diseases associated with the implants. For its part, the agency said it would streamline the data collection and paperwork required of physicians taking part in a large clinical trial of the implants for reconstruction after breast cancer surgery.

FDA Lead Deputy Commissioner Michael Friedman outlined the agency's decision in letters to a cancer patient advocacy group that sought expanded availability of the implants and an implant recipient organization that sought an outright ban of the devices.

The letters, dated Oct. 15, were sent to Rosemary Locke of the Y-ME National Breast Cancer Organization and Marlene Keeling of the CanDo Organization.

Y-ME filed a petition in September 1996 asking FDA to lift the restrictions on silicone breast implants the agency imposed in 1992. In February 1997, CanDo, which represents implant recipients who say the devices have made them ill, filed a petition asking the agency to revoke permission for manufacturers to make the implants available.

"Public Interest Is Not Well-Served"

The two petitions brought to light a deficiency in the status quo, Friedman wrote in the letters. "Five years after FDA requested safety and effectiveness data, we are still not in a position to approve or deny premarket approval applications for silicone gel-filled breast implants," he wrote. "The public interest is not well served in our current situation."

FDA asked manufacturers for evidence of the safety and efficacy of silicone implants in 1991. A year later, FDA extended the review period in order to make the implants available to women with special medical needs, including reconstruction after breast cancer surgery.

Although studies failed to prove that silicone implants cause other diseases, women who claimed the implants caused connective tissue disorders and other health problems have won jury awards of millions of dollars from manufacturers.

One manufacturer, Dow Corning, last August filed for Chapter 11 bankruptcy and offered a $2.4 billion settlement for implant claims.

Decision To Be Based On Data

In the letters, Friedman said he met with the remaining manufacturers of silicone breast implants to push them to complete the studies required for premarket approval. "We have no preexisting position or bias regarding these products one way or another," Friedman wrote. "We will base any regulatory decisions we make entirely on the available scientific data."

In its petition, Y-ME said the clinical trial

established to test the devices and make them available to women with medical needs was not achieving the goal of open access, because of the requirements that trial participation places on physicians.

Friedman said FDA would try to increase access by streamlining data collection and paperwork to ease physician participation. He also promised to write a letter to the American Society of Plastic and Reconstructive Surgeons requesting their assistance to increase physician participation. FDA also will work with the Department of Defense to facilitate access to silicone implants for reconstruction patients under the DOD healthcare system, Friedman wrote.

The CanDo petition also asked FDA to issue a recall of silicone gel implants and polyurethane-coated implants eight years or older. In a 1991 study, FDA found that the risk of cancer with the polyurethane implants was extremely small and did not justify the risk of removing the devices, Friedman wrote to CanDo.

"With regard to silicone gel-filled implants in general, the agency still feels that these products serve a public health need for those patients needing breast reconstruction and those with related conditions," Friedman wrote. "Therefore, FDA does not believe issuance of a recall in this case would be appropriate."

A woman who has concerns about her implants or is experiencing symptoms should contact her physician, Friedman wrote.

For information about the clinical trials of both silicone and saline breast implants, contact Mentor Corp., tel: 800/815-1086, or McGhan Medical Inc., tel: 800/862-4426.

FDA Issues Final Regulations For Mammography Facilities

FDA has issued final regulations to implement the Mammography Quality Standards Act passed by Congress in 1992.

The new regulations expand and strengthen interim regulations in effect since 1994, the agency said.

MQSA requires that all mammography facilities in the US meet certain stringent quality standards, be accredited by an FDA-approved accreditation body, and be inspected annually.

The regulations require that personnel who perform mammography be adequately trained and qualified to conduct mammography examinations and interpret results; that mammography equipment have appropriate design and performance characteristics; and that doctors and patients be quickly and fully informed of results so that any follow-up testing or treatment can begin immediately.

The final regulations toughen the standards for personnel, equipment, quality assurance and quality control, patient notification of results, and accreditation body performance.

Physicians who interpret mammograms must now have 60 hours training in mammography, technologists must keep their skills current by doing an average of 200 mammograms every two years, and medical physicists who survey mammography equipment and facilities must meet initial and ongoing training requirements.

The regulations spell out requirements for mammography equipment, including for motion of the tube-image receptor assembly, image receptor sizes, beam limitation and light fields, magnification, focal spot selection, compression, technical factor selection and display, automatic exposure control, x-ray film, lightening, and film masking devices.

The final regulations also require more quality control of mobile mammography units and set new standards for imaging breast implants. They also require that each facility have a consumer complaint mechanism. In addition, the rules make it clear that original mammograms must be made available to other medical facilities at the patient's request.

All accredited facilities receive a certificate from FDA which must be prominently displayed.

The final regulations were published in the Oct. 28 Federal Register.

National Toxicology Program

Smokeless Tobacco, UV Light, Tamoxifen, Listed Carcinogens In Advisory Panel Report

Advisors to the National Toxicology Program last week recommended listing smokeless tobacco, ultraviolet radiation, the anticancer drug tamoxifen, and the chemicals dioxin and benzidine as "known" to cause cancer in humans.

The review panel of the NTP Board of Scientific Counselors also recommended the continued listing of the sweetener saccharin as an "anticipated" human carcinogen in the federal Report on Carcinogens.

Congress requires the Department of Health and Human Services to issue a Report on Carcinogens every two years. The NTP review panel is charged with examining the data on substances and making recommendations to the National Institute of Environmental Health Sciences, in Research Triangle Park, NC.

Operating under new rules that permit mixes, as well as single chemicals, to be listed in the report, the panel recommended Oct. 31 that smokeless tobacco and inhaled tobacco smoke be officially listed as "known" to cause cancer in humans.

Chemicals in tobacco smoke and in tobacco are already listed in the report, but the new listing would make clear that tobacco products as a whole, whether chewed or smoked, cause cancer in humans.

The review panel recommended that ultraviolet radiation, whether from sunlight or an artificial source such as tanning booths and tanning beds, be listed as "known to be a human carcinogen."

According to the panel's draft report, "Human studies have shown that exposure to solar radiation is causally related to skin cancer, and that use of sunlamps or sunbeds is associated with skin and eye cancer."

In its recommendation to list the drug tamoxifen as a known human carcinogen, the panel emphasized that the benefits of tamoxifen therapy to prevent breast cancer recurrence far outweigh the risks.

"Tamoxifen is known to be a human carcinogen based on studies in humans that indicate a causal relationship between exposure to tamoxifen and cancers of uterine endometrium," the panel said in its report. "However, there is also conclusive evidence that tamoxifen therapy reduces the risk of contralateral breast cancer in women with a previous diagnosis of breast cancer."

The panel made no comment on the use of tamoxifen to prevent breast cancer in healthy women who are at high risk of the disease, as is currently being tested in the Breast Cancer Prevention Trial, funded by NCI.

Saccharin has been listed as an "anticipated" human carcinogen since 1981. At its Oct. 31 meeting, the panel looked at reports by the NIEHS Review Committee and the Interagency Committee Working Group for the Report on Carcinogens. Both of those committees voted in favor of taking saccharin off the list entirely.

The NTP review panel, however, voted 4-3 to continue listing the sweetener. Several panel members said the doses of saccharin given to rats were not so large as they supposed, particularly when compared to possible consumption by children.

The review aimed at removing saccharin, which was sought by the Calorie Control Council, an industry group, was carried out under revised criteria and review procedures announced by HHS last year. The criteria were broadened to allow consideration of such factors as mechanisms of action as well as the standard two-year rodent tests, and also set up a mechanism for petitioning to have a substance removed.

A Canadian study in rats led the Food and Drug Administration to take steps to partially ban the sweetener in 1977, but Congress stepped in to permit saccharin's continued sale as long as it carries a warning label.

In the toxicological studies that led to FDA's proposed ban, saccharin fed to rats at levels of 5 to 7.5 percent of their diet had a greater incidence of bladder cancer. Studies of human saccharin users showed no link to human bladder cancer.

The advisors also recommended that:

—2,3,7,8-Tetrachlorodibenzo-P-Dioxin (TCDD), formed as an impurity in herbicide manufacture, be upgraded from "anticipated" human carcinogen to "known" human carcinogen.

—Benzidine dyes be listed as known human carcinogens.

—Trichloroethylene, an industrial solvent, be listed as reasonably anticipated to be a human carcinogen.

—Tetrafluoroethylene, a chemical used in producing Teflon and other polymers, be listed as reasonably anticipated to be a human carcinogen.

—Cadmium and cadmium compounds, used in batteries, plating, and synthetic products, be upgraded from "reasonably anticipated" to "known" human carcinogen.

—Chloroprene, used as a monomer for neoprene elastomers, be listed as reasonably anticipated to be a human carcinogen.

—1,3-Butadiene, used in making synthetic rubber, be upgraded to "known" human carcinogen.

—Strong inorganic acid mists containing sulfuric acid, used to make fertilizers, rayon and other fibers, pigments, explosives, plastics, and other products, be listed as known human carcinogen.

—Phenolphthalein, an ingredient in some nonprescription laxatives, as an "anticipated" human carcinogen.

In Brief

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drugs. Rothenberg, the executive officer at the Southwest Oncology Group and associate professor of medicine at the University of Texas Health Science Center in San Antonio, will begin the new job March 15. . . . **ANNE KESSINGER** was named president of the American Association for Cancer Education. Kessinger is professor of medicine and chief of the section of Oncology and Hematology at the University of Nebraska Medical Center. . . . **STEVE JENNING** was named health policy analyst with the law offices of Deborah Steelman in Washington. Jenning is the former policy director for Sen. Ron Wyden (D-OR).

Funding Opportunities:

NCI RFA Available

RFA CA-98-001

Title: **Pivotal Clinical Trials For Chemoprevention Agent Development**

Letter of Intent Receipt Date: Dec. 2

Application Receipt Date: Jan. 13

The NCI Division of Cancer Prevention invites applications for intermediate-sized Phase II/III efficacy trials of promising chemopreventive agents in major cancer target organs, particularly prostate, breast, lung, colon, and bladder. The RFA will use the cooperative agreement (U01) mechanism. Total project period may not exceed five years. Anticipated award date is July 1998. Approximately $3 million in total costs for the first year will be committed. Three to four awards will be made.

The RFA will support Phase II/III randomized, placebo-controlled clinical trials to evaluate the chemopreventive efficacy of selected agents or regimens in target populations consistent with the Clinical Development Plans of the DCP Agent Development Committee (see Journal of Cellular Biochemistry Supplement 20, 1994 and Supplement 26, 1996). Investigators may propose any cohort, intervention, or drug for which justification and developmental support can be provided. The following list is provided as an example for which preclinical, early clinical, drug supply, and regulatory support may be available:

1. Prevention of colorectal adenomas in patients having a history of colorectal adenomas or early stage colon carcinoma using selected nonsteroidal antiinflammatory drugs (NSAIDs, including less toxic derivatives), 2-difluoromethylornithine (DFMO), Oltipraz, or the combinations of calcium with vitamin D or an NSAID and of DFMO with an NSAID;

2. Prevention of prostatic intraepithelial neoplasia (PIN), its progression, and cancer incidence by antiandrogens (e.g., flutamide or bicalutamide), vitamin E, selenium, the combination of vitamin E with selenium, fluasterone (DHEA analog 8354), selected retinoids [e.g., all-trans-N-(4-hydroxyphenylretinamide) (4-HPR) or 9-cis-retinoic acid], or 5'-reductase inhibitors (e.g., finasteride);

3. Prevention of bronchial dysplasia, its progression, or second primary upper aerodigestive cancer in patients with a history of resected early stage non-small cell lung cancer (NSCLC) or laryngeal cancer by retinoids (e.g., 4-HPR, 9-cis-retinoic acid or all-trans retinoic acid, possibly in aerosolized formulations), Oltipraz, N-acetyl-l-cysteine (NAC), or the combinations of Oltipraz with NAC or 4-HPR;

4. Modulation of biomarkers in the breast (including mammographic patterns) and new proliferative or precancerous lesions in patients with atypical ductal or lobular hyperplasia or lobular carcinoma in situ by anti-estrogens, retinoids (e.g., 4-HPR or 9-cis-retinoic acid), fluasterone or low-dose DHEA, DFMO, or the combination of vitamin E with selenium;

5. Prevention of dysplastic oral leukoplakia, its progression, and oral cancer by Oltipraz (in chronic smokers), 4-HPR, DFMO or curcumin;

6. Prevention of cervical intraepithelial neoplasia (CIN II/III), its progression, and cervical cancers by 4-HPR, DFMO, Oltipraz, or selected NSAIDs;

7. Prevention of recurrence or new lesions in patients with Ta/T1 bladder carcinoma with or without tissue in situ (TIS) (post-BCG) by 4-HPR, DFMO, or selected NSAIDs;

8. Prevention of precancerous lesions in Barrett's esophagus, their progression, and esophageal cancers by DFMO, retinoids, or Oltipraz.

9. Progression of precancerous lesions of the skin, their progression, and skin cancer by DFMO, retinoids or curcumin.

Study endpoints should include changes in the most promising SEBs (such as those in preinvasive disease or proliferative disease), the development of new premalignant lesions, and, as appropriate, the occurrence of new invasive cancers. This emphasis on SEBs requires that the research team include strong collaborative support from the areas of pathology, biochemistry and molecular biology, and cancer biology and carcinogenesis.

The clinical trial design should include an adequate number of participants and should be of sufficient duration to assure statistical power to address the study questions of chemopreventive efficacy, long-term safety and acceptability, and SEB validation. To this end, biostatistics and clinical trial design expertise should be included from the first efforts in study planning and design.

Inquiries: Gary Kelloff, DCP, NCI, 6130 Executive Blvd Suite 201, Bethesda, MD 20892, or Rockville, MD 20852 (for express/courier service), tel: 301/496-8563, fax: 301/594-2943, email: kelloffg@dcpcepn.nih.nci.gov