The NCI/FDA Proteomics Research Program, Its Research, and Diagnostic Tests by Private Industry (e.g., OvaCheck™): Fact Sheet

1. What was the National Cancer Institute/U.S. Food and Drug Administration Clinical Proteomics Program?

A collaboration between the National Cancer Institute (NCI) and the U.S. Food and Drug Administration (FDA) began in 1997 and was led by Lance Liotta, M.D. Ph.D., formerly of NCI's Center for Cancer Research, and Emanuel Petricoin, Ph.D., formerly of FDA's Center for Biologics Evaluation and Research (CBER). Liotta and Petricoin left NCI and FDA in 2005 and are now at George Mason University, Fairfax, Va., where they are heading a newly formed Proteomics Institute. With the departures of Liotta and Petricoin, opportunities and mechanisms for interactions between the agencies are being evaluated.

The NCI/FDA proteomics program was originally conceived with the scientific goal of applying proteomics techniques to cancer in order to understand the flow of information within the cell and the organism. Petricoin and Liotta developed new technologies to analyze the molecular networks of diseased and normal cells. These technologies included the use of tissue specimens to develop tools for protein fingerprinting.

Potential benefits of clinical proteomics include developing individualized therapies using targeted treatments that could be predetermined to be effective for each patient; determining the toxic and beneficial effects of treatments in the lab before using them in patients; diagnosing cancer earlier than is now possible; and improving the understanding of tumors at the protein level, possibly leading to better treatments.

Liotta and Petricoin developed a new type of protein microarray to analyze the molecular network, or the cellular "circuitry", of cancer cells from a biopsy specimen using a large panel of validated antibodies that specifically recognized proteins that are phosphorylated (have a phosphate group attached to them). Using this approach, researchers study how a particular treatment changes the network, or circuitry, of proteins in a cell and how signaling pathways change if a tumor returns after treatment. Additionally, laser capture microdissection (LCM) was invented in Liotta's laboratory in 1996 and allows the

isolation of pure normal cells, pre-cancerous cells, and tumor cells, if present, from the same biopsy for proteomics analysis.

2. What was the association between NCI/FDA research and the OvaCheck™ test for ovarian cancer that was being developed by private industry?

The former NCI/FDA proteomics program was not involved with the development of OvaCheck™. It was **independently** developed by Correlogic Systems in conjunction with Quest Diagnostics and LabCorp, two non-governmental, private companies. Data posted or published by the NCI/FDA program was not used to assess or judge tests developed using different technology. OvaCheck™ was unrelated to previously published work between Correlogic and the NCI/FDA, and utilized different mass spectrometry instrumentation and detection methods, as well as different sample handling and processing methods.

Scientists at FDA and NCI cannot comment on the work done independently by Correlogic (and specifically OvaCheck ™) since they are not involved with, nor are they privy to, proprietary corporate data.

3. Did the NCI/FDA proteomics program develop a test for the detection of ovarian cancer of their own?

Neither the NCI nor the FDA conducted research to develop a "test" for the detection of ovarian cancer. The NCI/FDA Proteomics Program conducted a series of research studies to examine the hypothesis that proteomic patterns are different in cancer versus control samples. The program worked to refine, improve, and optimize its techniques, to validate the test results, and to identify and sequence the diagnostically important molecules which underpin mass spectrometry readings.

The NCI/FDA Proteomics Program did not work on the development of a commercial test to be used in patients to detect ovarian cancer. It was not involved in the marketing of any early detection tests.

4. The NCI/FDA proteomics program looked for biomarkers that are diagnostic for cancer. Doesn't that mean that they want to develop a test for earlier detection of cancer?

The NCI/FDA proteomics program was involved in validating their techniques, analyzing data, repeating experiments, and optimizing methods. These are all research activities that must be done in a deliberate, step-wise progression and must be rigorously validated before a diagnostic tool or treatment could be developed.

A research paper, published in *The Lancet* in February, 2002, reported a feasibility study. It described an approach, whereby mass spectrometry generated fingerprints (unique identifiers) derived from low molecular weight molecules could discriminate between a study set of ovarian cancer tumors and specimens from healthy high risk women. Neither

the paper, nor the molecules described, were the basis of any test; rather they were a description of an approach. Prospective clinical trials to stringently test the hypothesis have been designed and will have to be completed prior to development and marketing of a diagnostic test.

5. What are biomarkers and how are they identified and validated for use in the clinical setting?

Biomarkers are molecules that exist naturally in the body that can help predict or reflect the presence of a disease, the risk of relapse of the disease, and/or response to treatment.

Successfully translating research on biomarkers from the laboratory to patients involves five phases:

- Phase 1 includes exploratory studies to identify potentially useful biomarkers—this is called the discovery phase.
- Phase 2 is where biomarkers are studied to determine their capacity for distinguishing between people with cancer and those without—the validation phase.
- Phase 3 determines the capacity of a biomarker to detect pre-clinical disease by testing the marker against tissues collected longitudinally from research cohorts.
- Phase 4 includes prospective screening studies.
- Phase 5 is when large-scale population studies evaluate not just the role of the biomarker for detection of cancer, but the overall impact of screening on the population and whether this screening impacts survival.

6. Have government researchers made any efforts to standardize research protocols, procedures and technology so that proteomic results obtained at the NCI or FDA would be comparable to those in other labs nationwide?

In June 2005, NCI's Board of Scientific Advisors (BSA) approved a Clinical Proteomics Technologies Initiative, a $104 million program aimed at optimizing current proteomics technologies and developing new technologies, reagents, and systems to significantly advance the field of cancer proteomics research. This Initiative is not specific to the National Institutes of Health Bethesda campus, which housed the program in which Petricoin and Liotta worked and Elise Kohn, M.D., currently works. Rather, it is open to the broad cancer research community. The initiative builds on a two year process that sought feedback from the research community through workshops and meetings.

The initiative encompasses a three-pronged strategy:

- Establishment of Clinical Proteomic Technology Assessment Consortia, which will focus on evaluating tools, such as proteomic technologies and reference reagents; develop protocols and perform cross-laboratory studies of common sample sets; and also provide consultative services and training to the community.

- Support of research into overcoming barriers to protein/peptide feature detection, identification, and quantification; and development of mathematical, computational, and predictive approaches for analysis of large scale data.

- Creation of an online, centralized clinical proteomics reagents resource, which will include resources such as antibodies, peptides, and proteins.

NCI is also involved in another major initiative—the National Biospecimen Network. NCI's Biospecimen Coordinating Committee is preparing a report on the development of standards for the collection of biospecimens. These standards will assure that the highest-quality material is going toward high-end and sensitive advanced technologies thus making cross-comparisons possible because high-quality starting material is used for endpoint assays.

7. What additional proteomics research contributed to the current proteomics tools and what is planned next?

Besides ovarian cancer, similar techniques are being applied to other cancers. Researchers are looking for protein patterns and identified carrier protein-bound molecules in the blood that are diagnostic for early-stage aggressive prostate, lung, and breast cancers, as well as patterns that can predict risk for prostate, colon, skin, and pancreatic cancers.

The general strategy of proteomics research is to analyze proteins from the blood or tissue with mass spectrometry and protein microarrays to identify important changes that occur in the progression from normal to disease. The ultimate goal is to use this information for earlier detection of cancer, patient-tailored therapy, and more effective therapeutic monitoring.

8. What is the clinical trial that NCI is sponsoring in the area of ovarian cancer diagnosis?

A NCI-sponsored ovarian cancer clinical trial, involving ten sites, is scheduled to start in Fall 2005. Because over 80 percent of advanced stage epithelial ovarian cancer patients see their cancer return after being treated with standard chemotherapy, biomarkers are needed for predictors of persistent disease and relapse. CA-125, the only FDA-approved ovarian cancer relapse marker, will become elevated in some, but not all, of the approximately 80 percent of advanced stage patients for whom it was increased at initial diagnosis. Elevation in CA-125 may precede clinical evidence of relapse by as much as

six to 10 months or lag behind clinical relapse by the same time intervals, making it a less than satisfactory clinical tool.

Researchers have identified a pattern of proteins that sensitively and specifically recognizes the presence of ovarian cancer (stages I-IV) in blood from affected women. Furthermore, the pattern can distinguish between affected women and unaffected women and those with the presence of non-malignant disease. Investigators hypothesize that significant changes in proteomic signature patterns can be defined and that these will be reliably predictive of relapse. Further, they hypothesize that the protein signature pattern changes will be as good as, or better than, CA125 as a single marker alone or in combination with CA125 monitoring. A serum repository of samples from women with ovarian cancer will be created in order to develop and validate the multiple biomarkers and proteomics tests being created for ovarian cancer recurrence and screening.

The purpose of this protocol is to determine sensitivity and specificity for detection of cancer in patients who are in remission for their disease. This study is an expansion of the trial opened to patient participation in 2000 by Dr. Kohn and called the "Pilot Study of Proteomic Evaluation of Epithelial Ovarian Cancer Patients In First Clinical Remission: Development of a Protein Fingerprint Profile Associated With Relapse," NCI 00–C–0018. The earlier study, conducted solely at NIH in Bethesda, Md., has enrolled 25 or more patients towards a ceiling of 40. Patients are followed up to every three months. At each visit they undergo an evaluation and examination by the medical team, have routine laboratory and CA125 tests done, have a CT scan to see if there is evidence of recurrent cancer, and have a vial of blood taken to be stored for use in development of a pilot proteomics pattern. This trial will close when the new multi-institutional, multi-state study opens shortly. The multi-institutional trial will also follow patients every 3 months with exam, laboratory test, and CA125 and every other visit, a CT scan.

9. What are the mortality and survival rates associated with ovarian cancer?

Ovarian cancer is the fifth most common cancer in women and the leading cause of death in the U.S. from gynecologic malignancies. Approximately 25 percent of patients are diagnosed when ovarian cancer is localized to the ovary. Up to 90 percent of these very early cancers can be successfully treated, while only 30 percent of the patients with more advanced cancers will survive five years.

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Related NCI materials and Web pages:

- National Cancer Institute Fact Sheet 5.18, *Tumor Markers: Questions and Answers* (http://www.cancer.gov/cancertopics/factsheet/Detection/tumor-markers)
- Ovarian Cancer Home Page (http://www.cancer.gov/cancertopics/types/ovarian)

For more help, contact:

NCI's Cancer Information Service
Telephone (toll-free): 1–800–4–CANCER (1–800–422–6237)
TTY (toll-free): 1–800–332–8615
LiveHelp® online chat: https://cissecure.nci.nih.gov/livehelp/welcome.asp

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