Early Detection Research Network

Division of Cancer Prevention
National Cancer Institute

Presenter:

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Division of Cancer Prevention
National Cancer Institute

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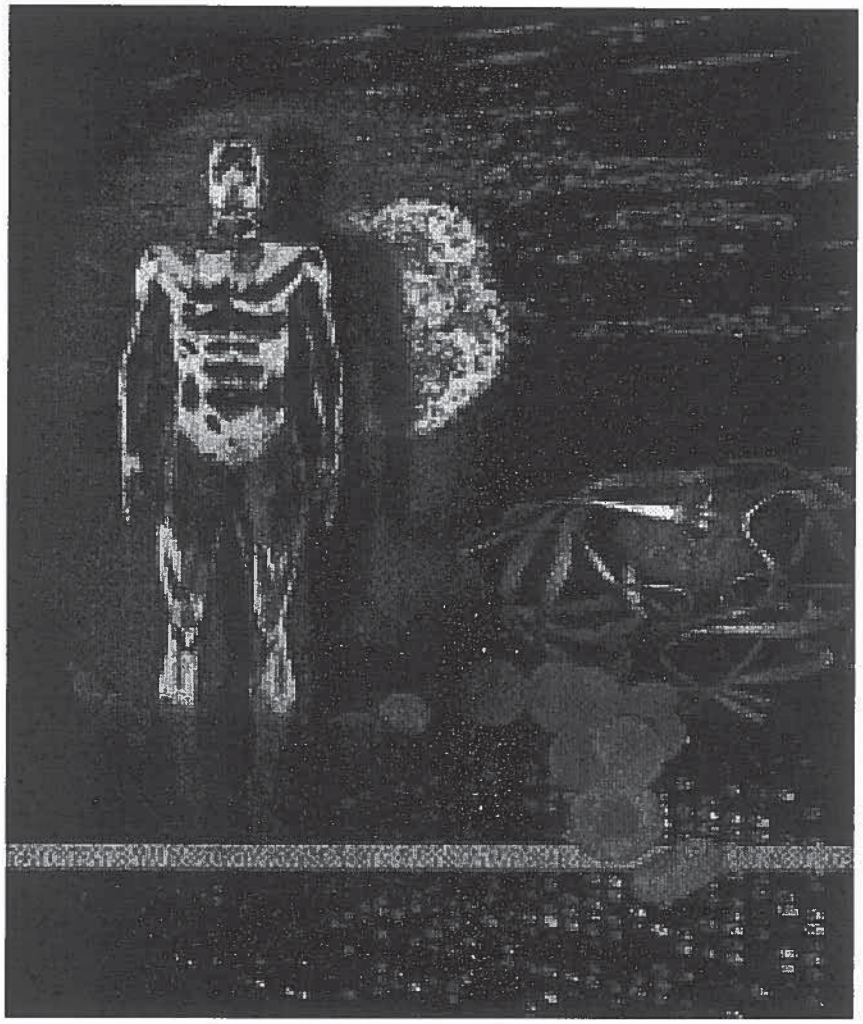
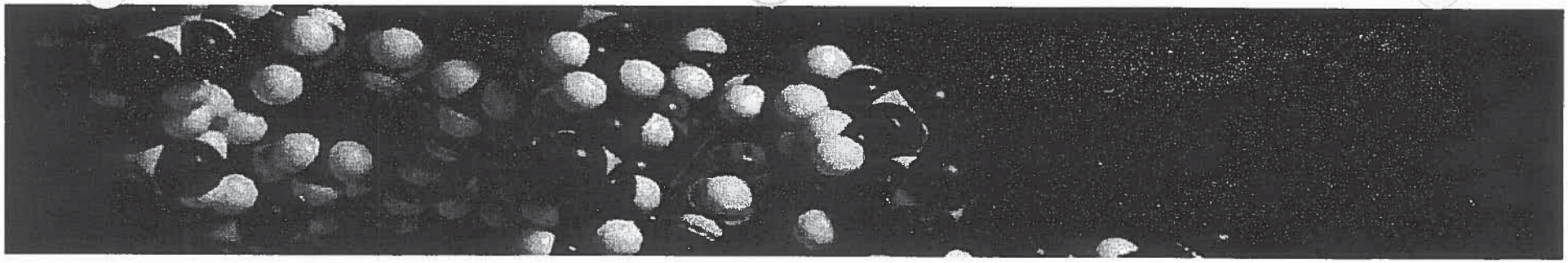
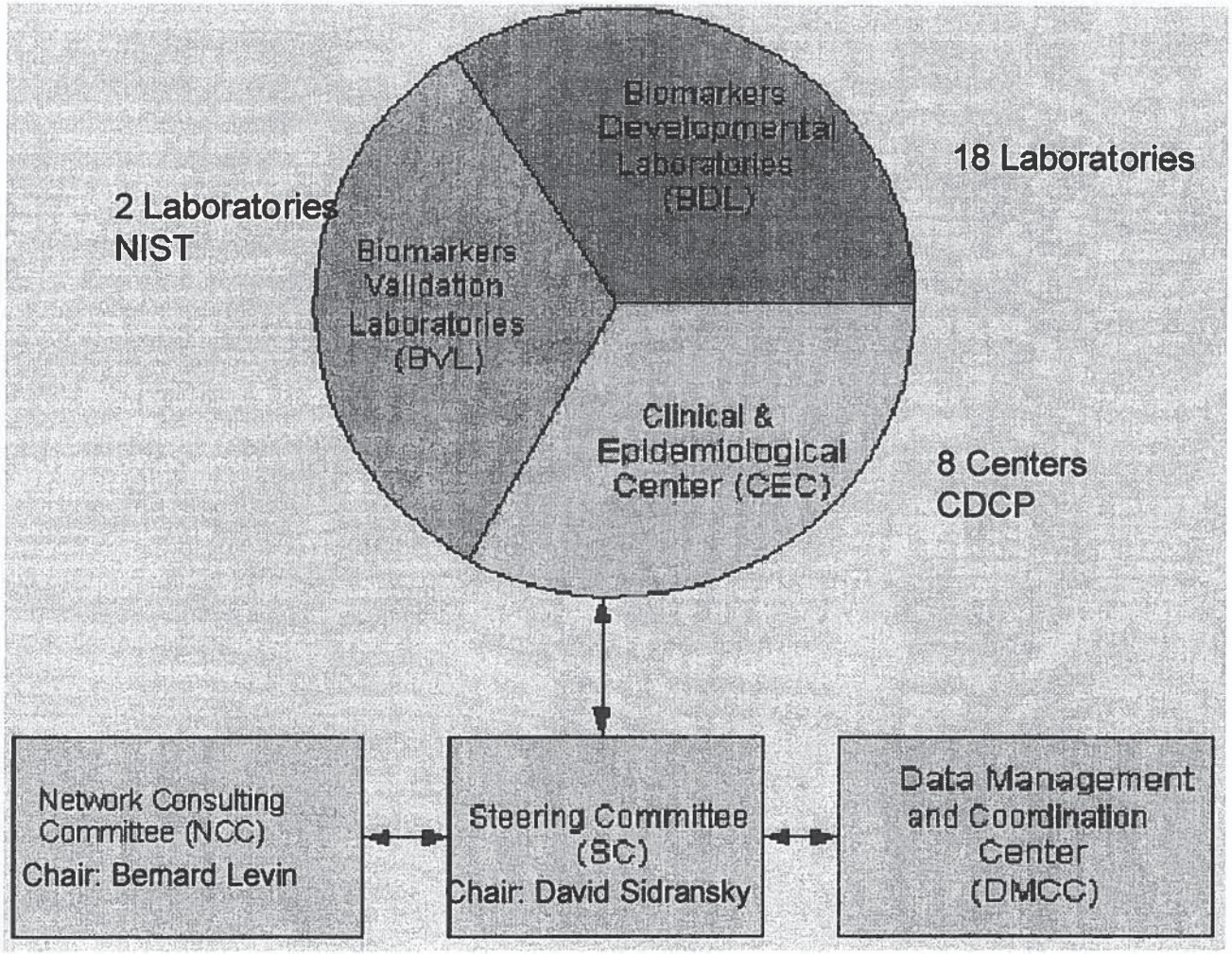


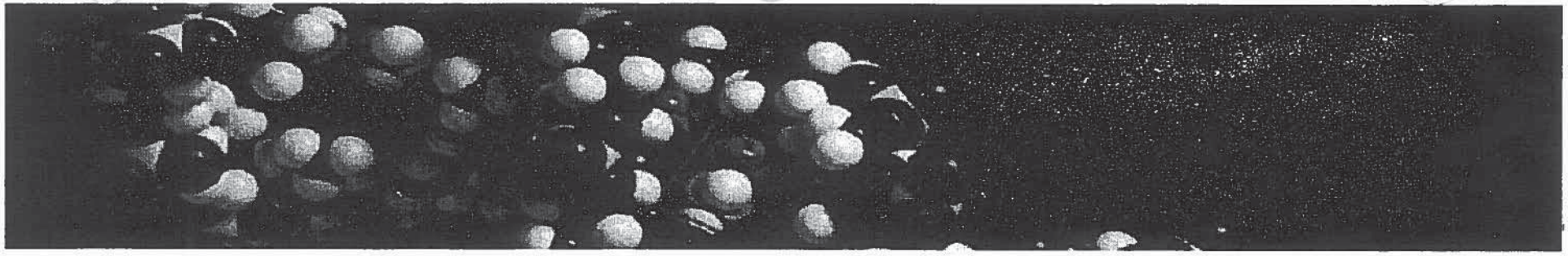
Advancing Translational Research on Cancer Biomarkers

http://cancer.gov/edrn



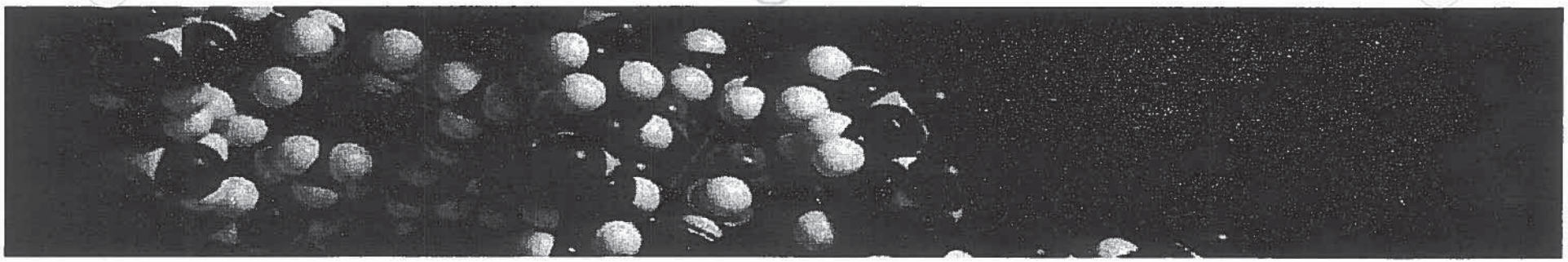


An "infrastructure" for supporting collaborative research on molecular, genetic and other biomarkers in human cancer detection and risk assessment.



Goal: Establish a comprehensive approach to biomarker development

- Foster interaction between academic, clinical and industrial leaders to encourage development of biomarker assays for cancer detection and risk assessment
- Establish scientific criteria to evaluate biomarkers as indicators of early cancer, prognostic factors of preinvasive cancer, markers of risk, or as surrogate endpoints
- Develop and institute a quality assurance program for biomarker testing and evaluation



Created Multi-institutional Partnership

Industry

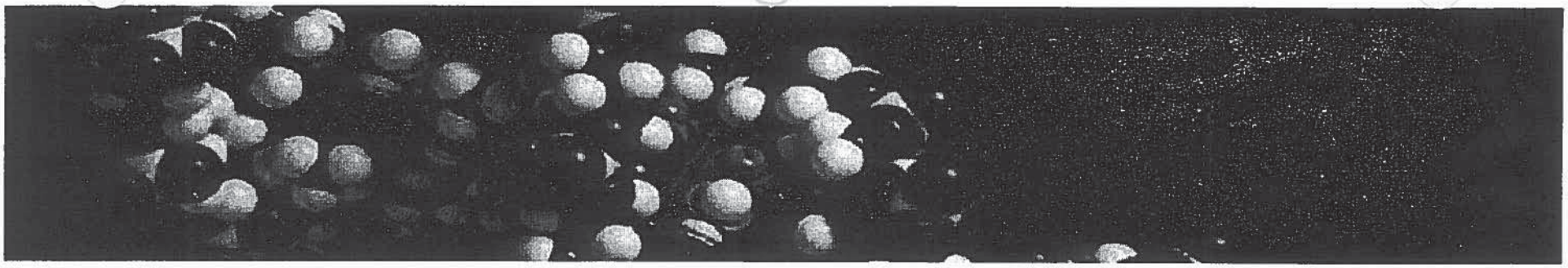
Abbott Pharmaceuticals
Advanced Biosciences Lab, Inc
Atairgin Biotechnologies, Inc.
Bayer Pharmaceuticals
Bristol Myers
Circon Corp.
Ciphergen Biosystems, Inc.
Clenomics
COBE BCT, Inc.
Corixa
Genetica Inc.
ORCA Biosciences, Inc.
Oxford GlycoSciences
Proteome Sciences
Roche
Research Genetics, Inc.
Spectral Imaging
Urosciences Group
Zeneca Diagnostics

Government

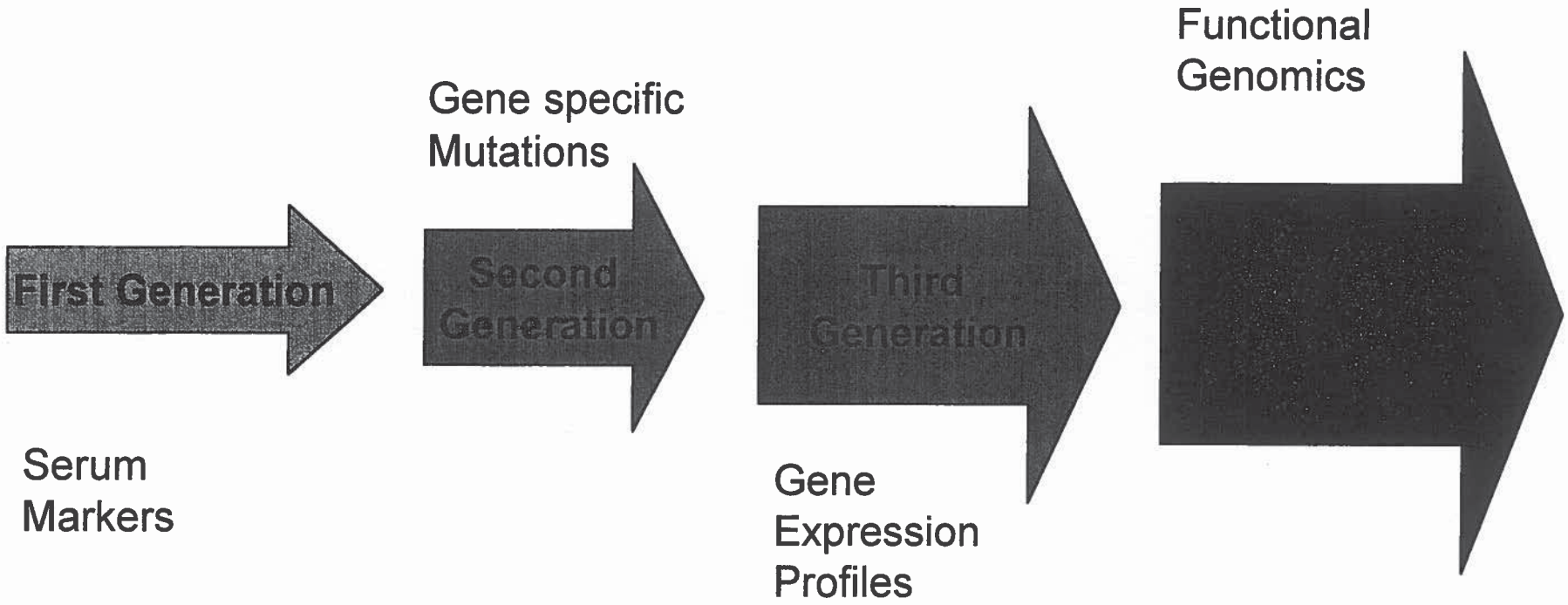
National Cancer Institute
Centers for Disease Control and Prevention
National Institute of Standards and Technology

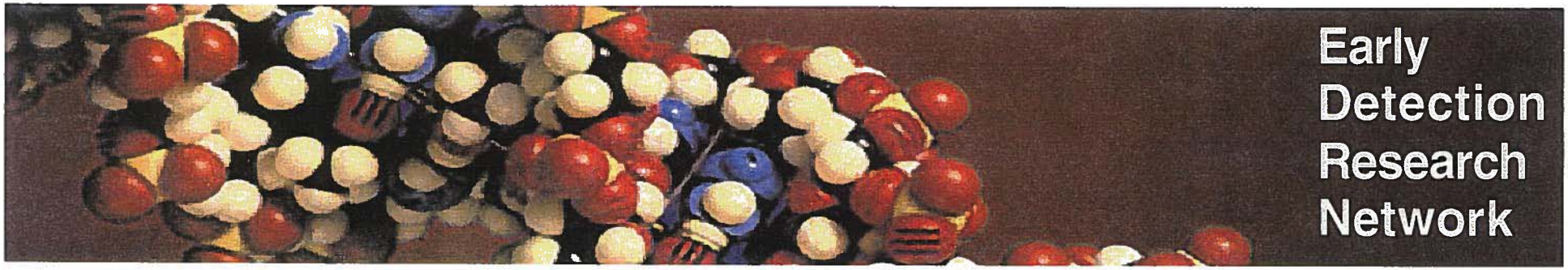
Academia

University of Texas, San Antonio
New York University School of Me
Brigham and Women's Hospital
University of Michigan
Creighton University
M.D. Anderson (3)
Johns Hopkins University (4)
UCLA
University of Alabama
Fred Hutchinson Cancer Center
Eastern Virginia Medical School
Northwestern University
University of Pittsburgh
UT Southwest University Medical
Thomas Jefferson University
University of Washington
Yale University
University of Maryland (2)
University of South Florida
Duke University Medical Canter
University of Colorado

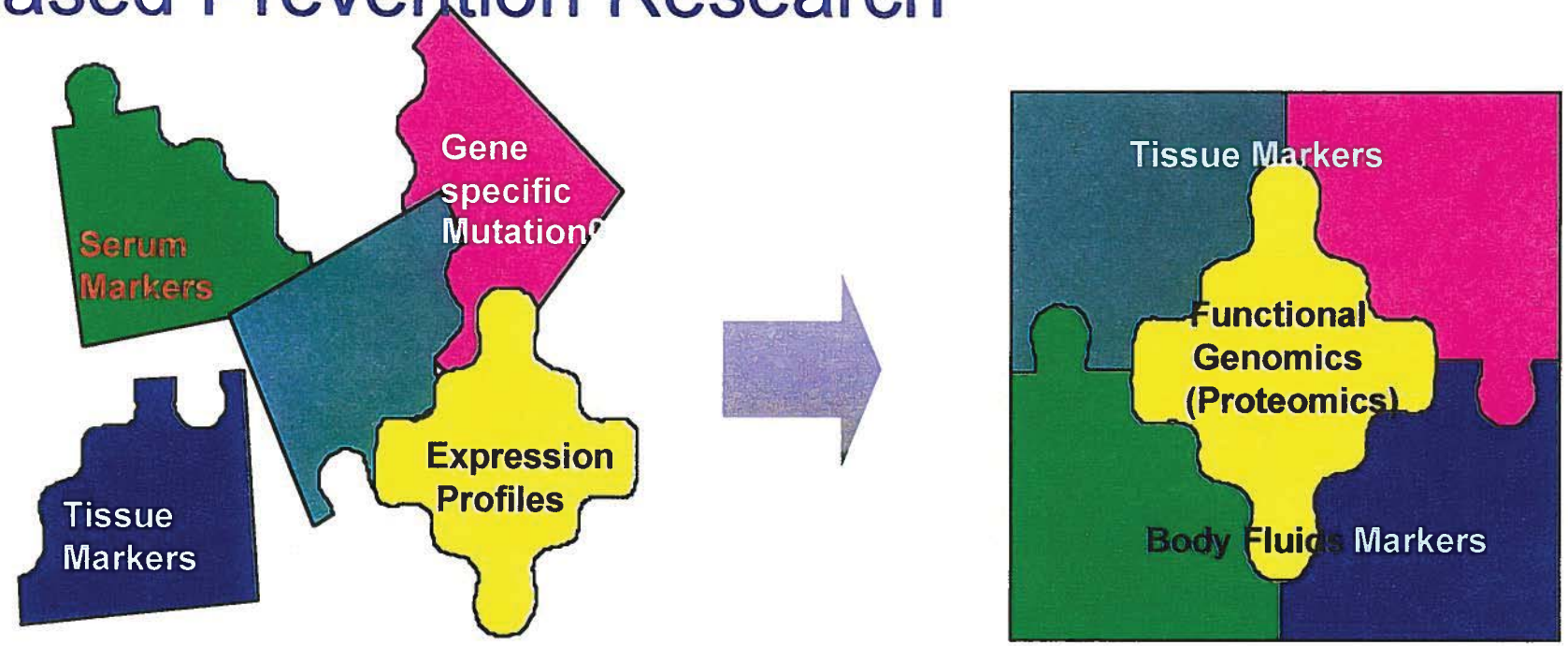


Goal: Support Systematic Approach to Biomarker Development

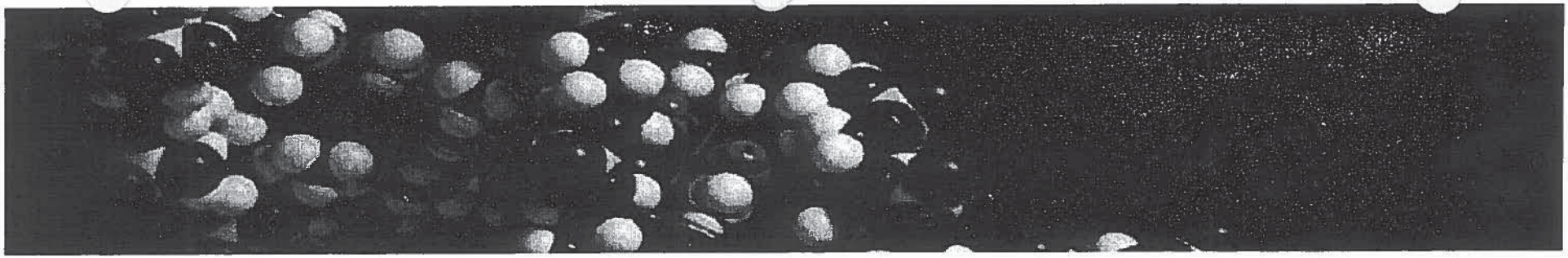




Comprehensive Approach to Molecular-based Prevention Research



Molecular Signatures → **Cancer Prevention**



Milestones Accomplished, FY 2000-2001

April 2000: EDRN fully funded;1st EDRN Steering Committee meeting

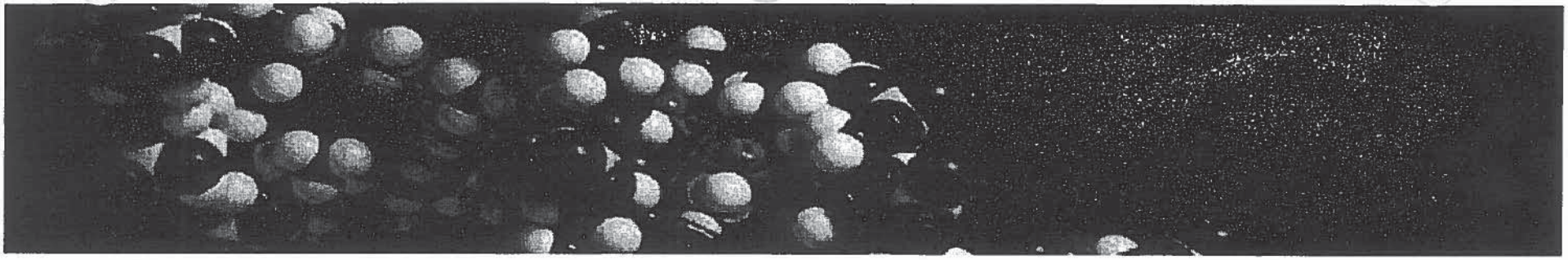
May 2000: EDRN Collaborative Opportunity published

June 2000: Task Force for Molecular Taxonomy of Preneoplasia convened; EDRN brochure published

July 2000: Secure EDRN web site organized

August 2000: Manual of Operations completed; Metrics for EDRN evaluation developed and approved

September 2000: 1st EDRN scientific workshop; 2nd Steering Committee meeting



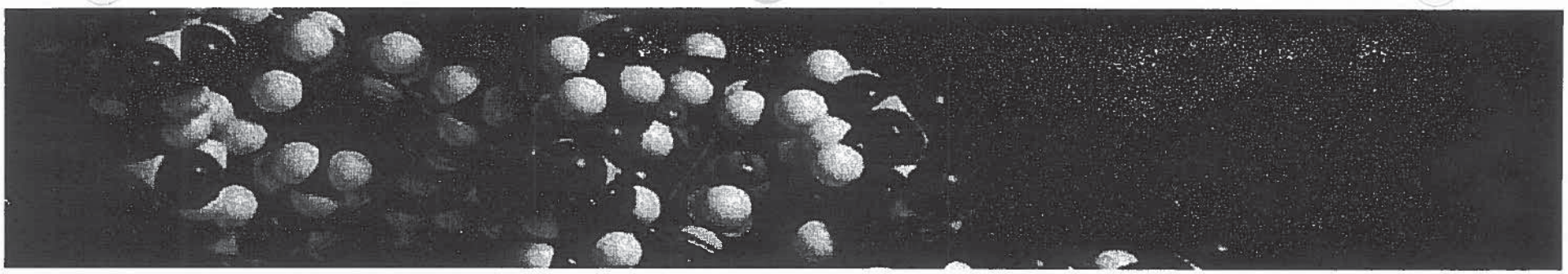
Milestones Accomplished, FY 2000-2001

October 2000: The EDRN initial report published

December 2000: EDRN Knowledge System Working Group: Informatics Pilot Project meeting held in Seattle

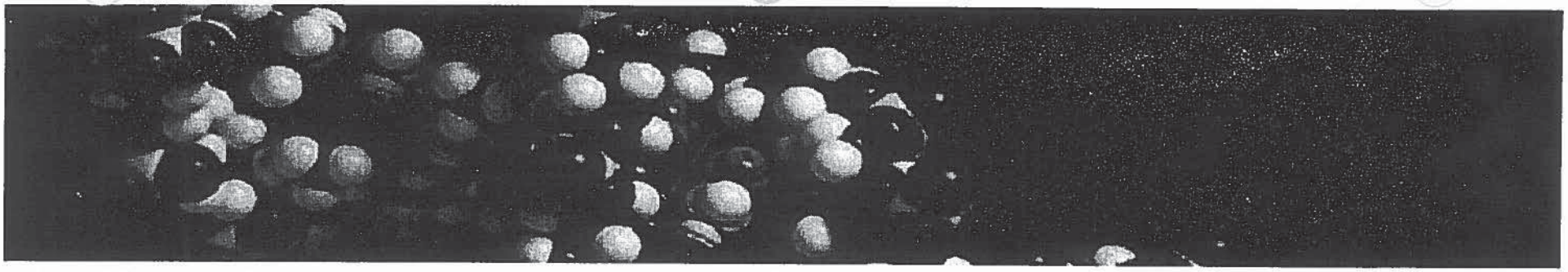
January 2001: 3rd Steering Committee meeting. Collaborative Groups established as "Think Tanks"

February 2001: Molecular Taxonomy of Incipient Neoplasia meeting held



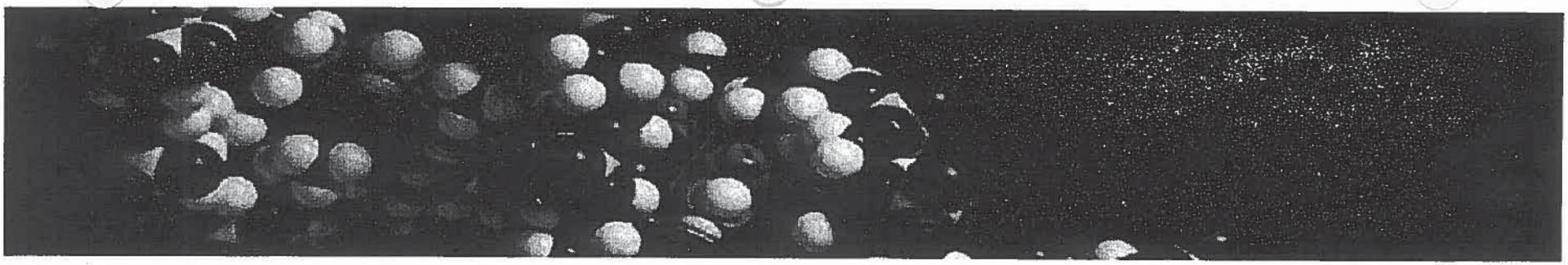
EDRN Progress and Updates

- Infrastructure
- Biomarkers Development and Validation
- Informatics and Information Flow
- Statistical and Computational Tools
- Collaborations



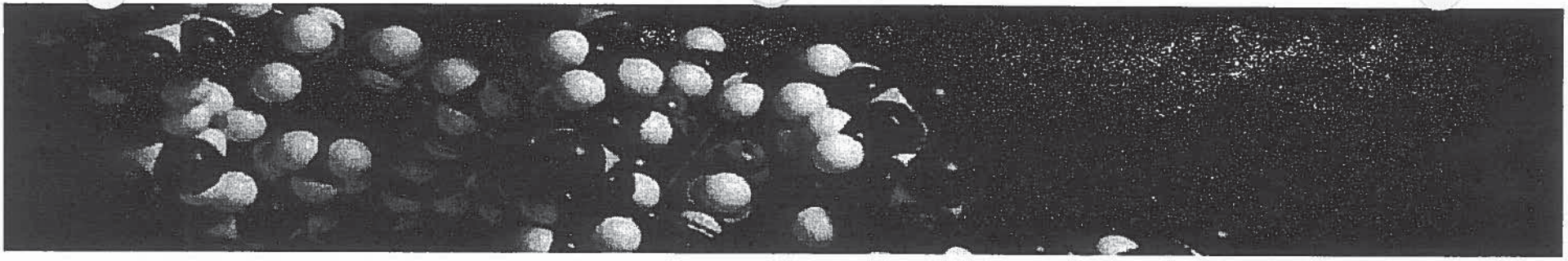
Goal

Develop investigator-driven management structure

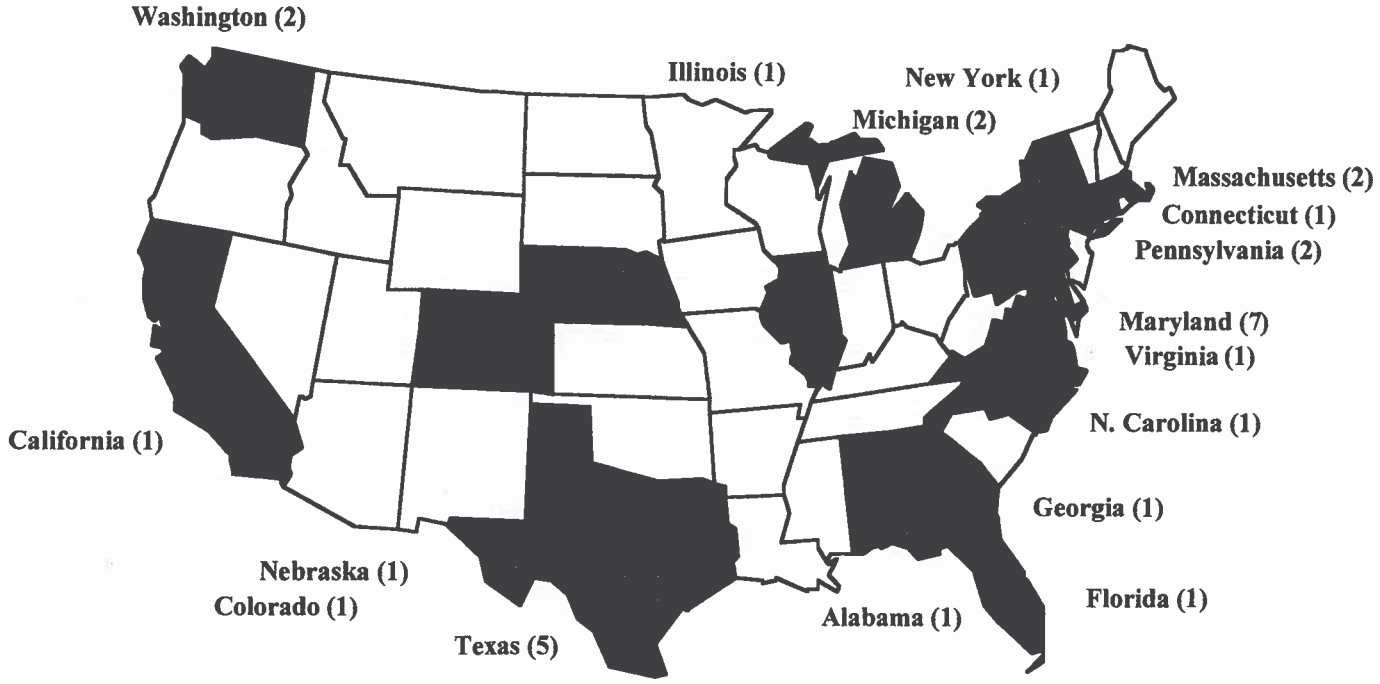


EDRN Profile

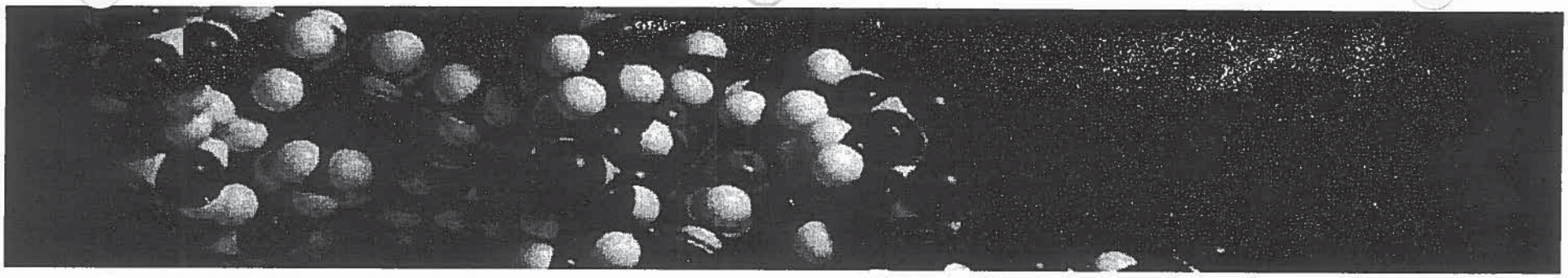
- 31 funded laboratories and centers
- Approximately 120 participating institutions; 300 investigators



Supporting Laboratories/Centers across the Country

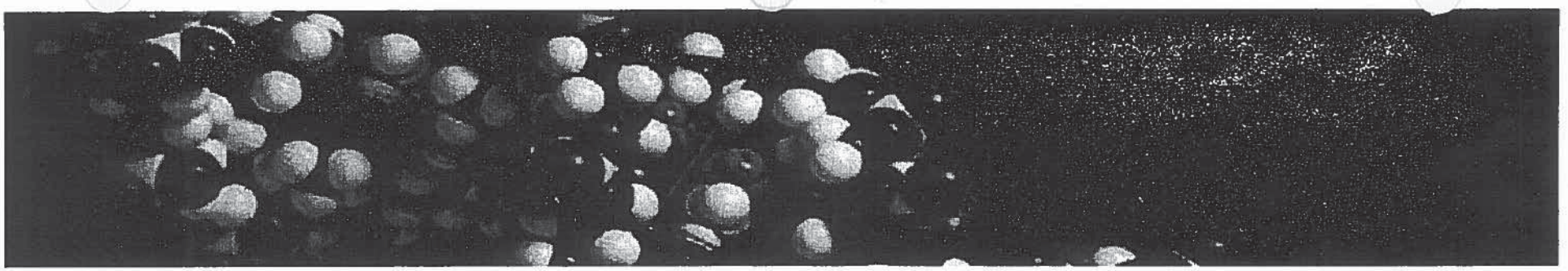


Note: Number in parenthesis indicates the number of awardees

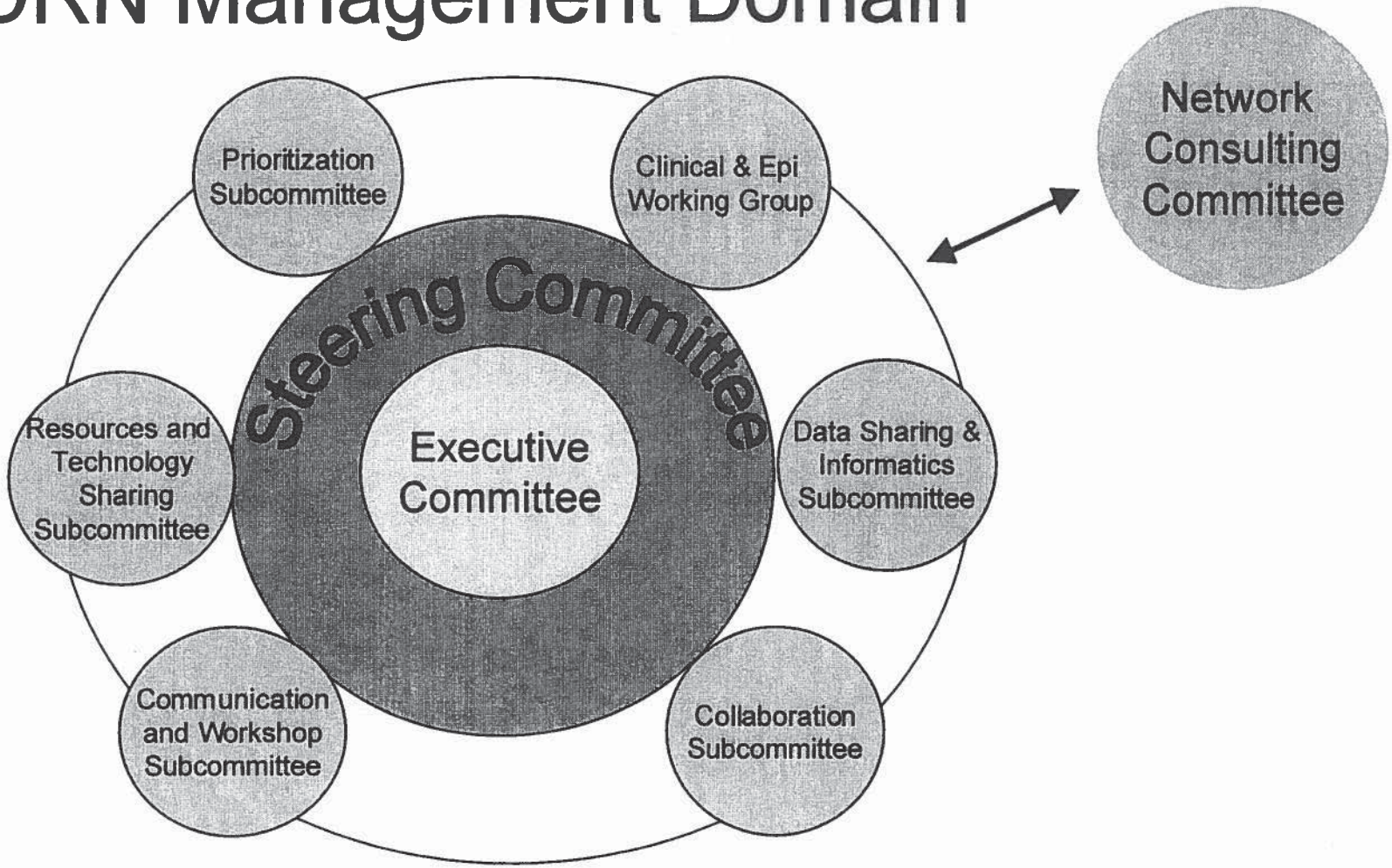


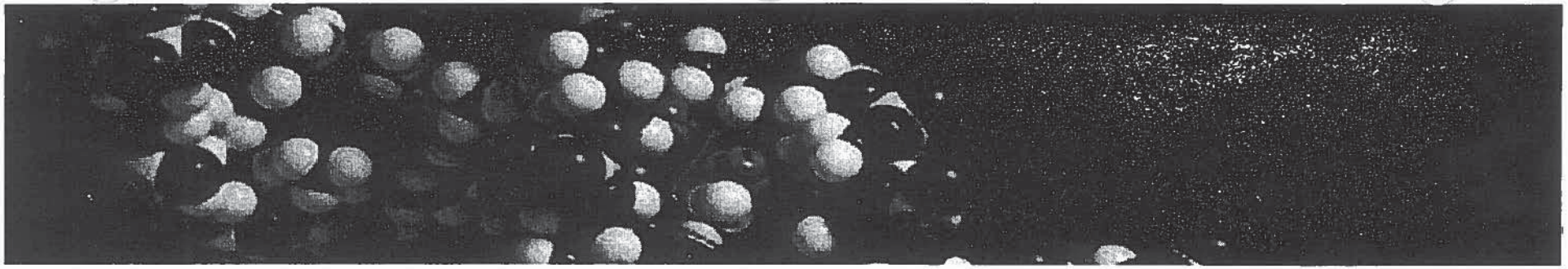
Management Challenges

- Define clear patterns of communications
- Develop strategy and management culture so everyone sees there is something in it for them
- Set the basis for priorities, strategies, and plans to bring stakeholders to work together



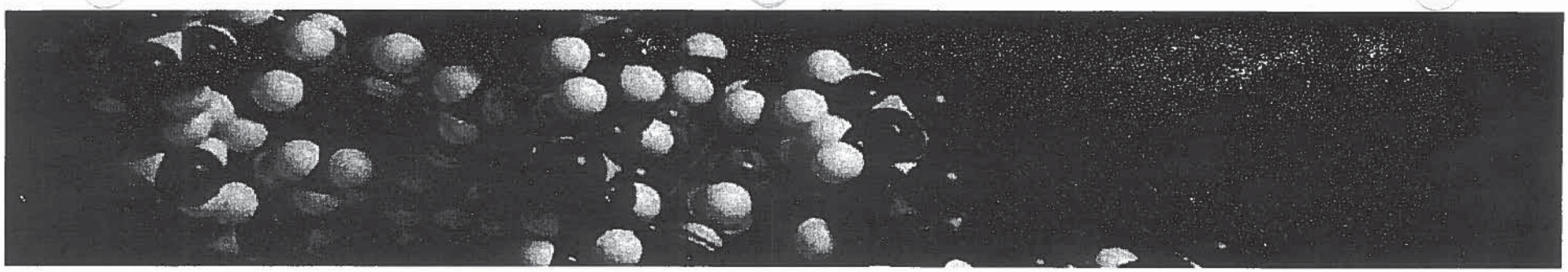
EDRN Management Domain





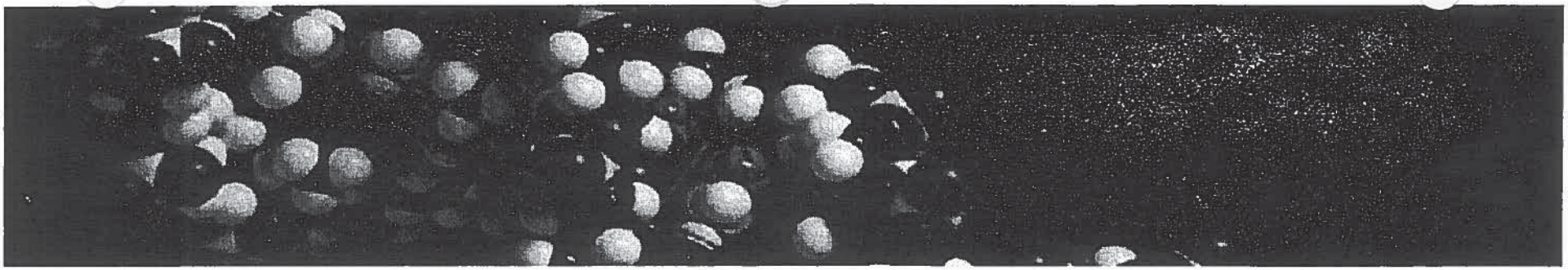
Managing Communication Across Domain

- EDRN Website launched (http://cancer.gov/edrn)
- EDRN Steering Committee meets three times a year
- 22 Listservs to facilitate dialogue among investigators; subscription open to public
- Network Consulting Committee members from scientific community, including Cancer Advocacy Groups, appointed; meets annually

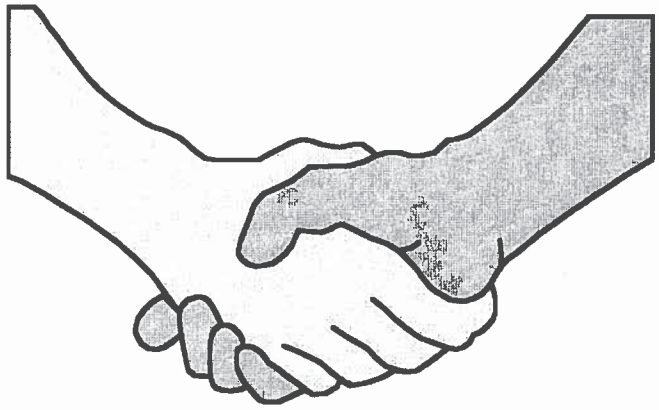


Goal

Provide semi-permeable network to facilitate collaboration

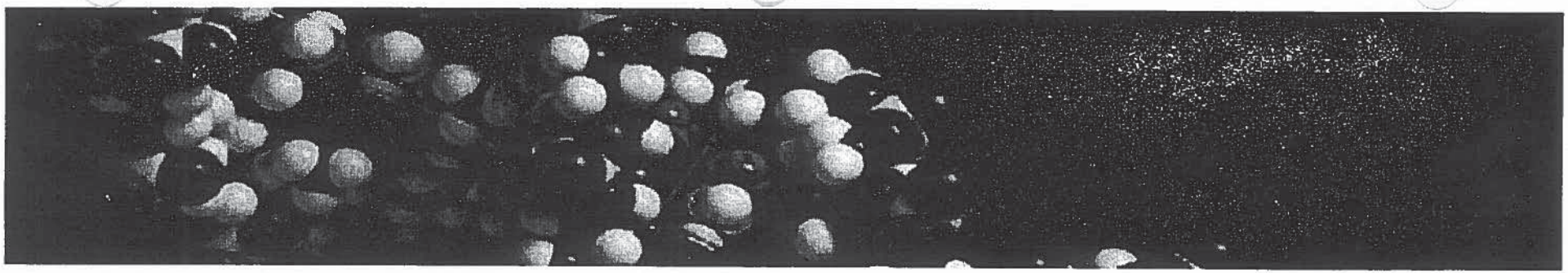


Facilitating Semi-Permeability



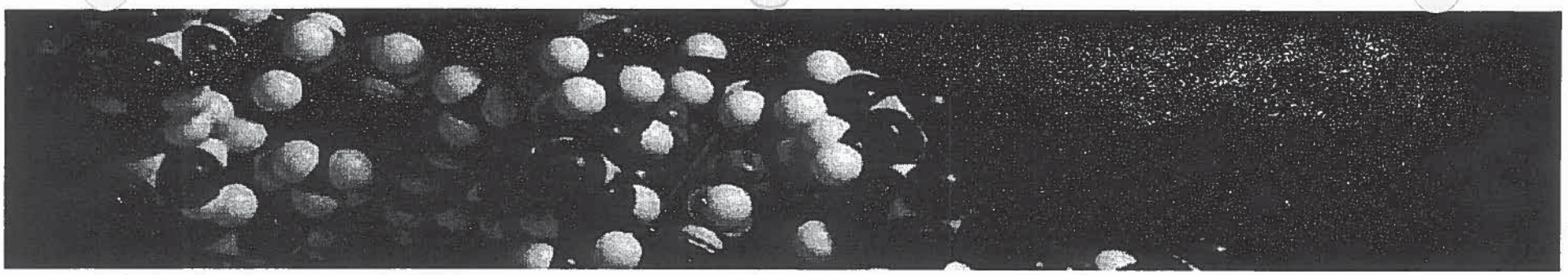
- **Associate Membership opportunity established**

- **Collaborative Groups established**
  - **Breast and Gynecologic**
  - **Prostate and Urological**
  - **Gastrointestinal and Associated**
  - **Lung and Upper Aerodigestive**



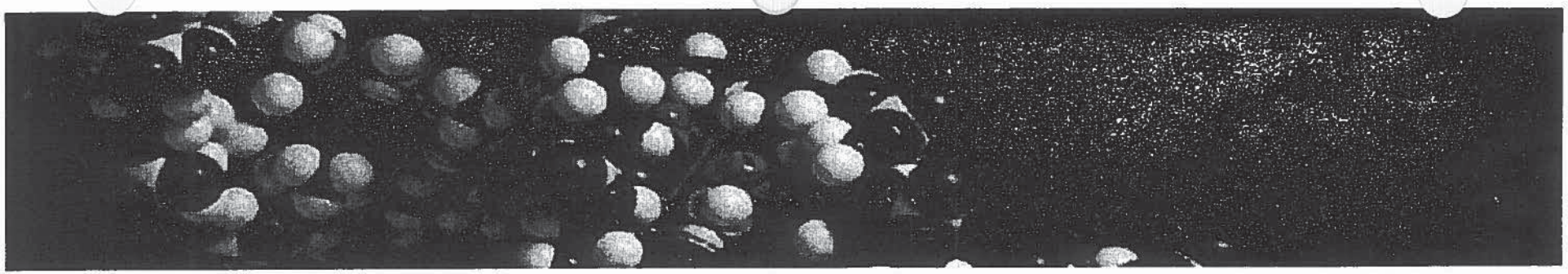
Six Associate Members Accepted

- Carolyn Muller, MD (Univ. of Texas)
- Jong Park, DrPH (Moffitt Cancer Center)
- Leonard Marks, MD (UCLA)
- Harvey Pass, MD (Wayne State Univ.)
- Ying-Hsiu Su, PhD (Thomas Jefferson Univ.)
- Karen Smith-McCune, MD, PhD (UCSF)

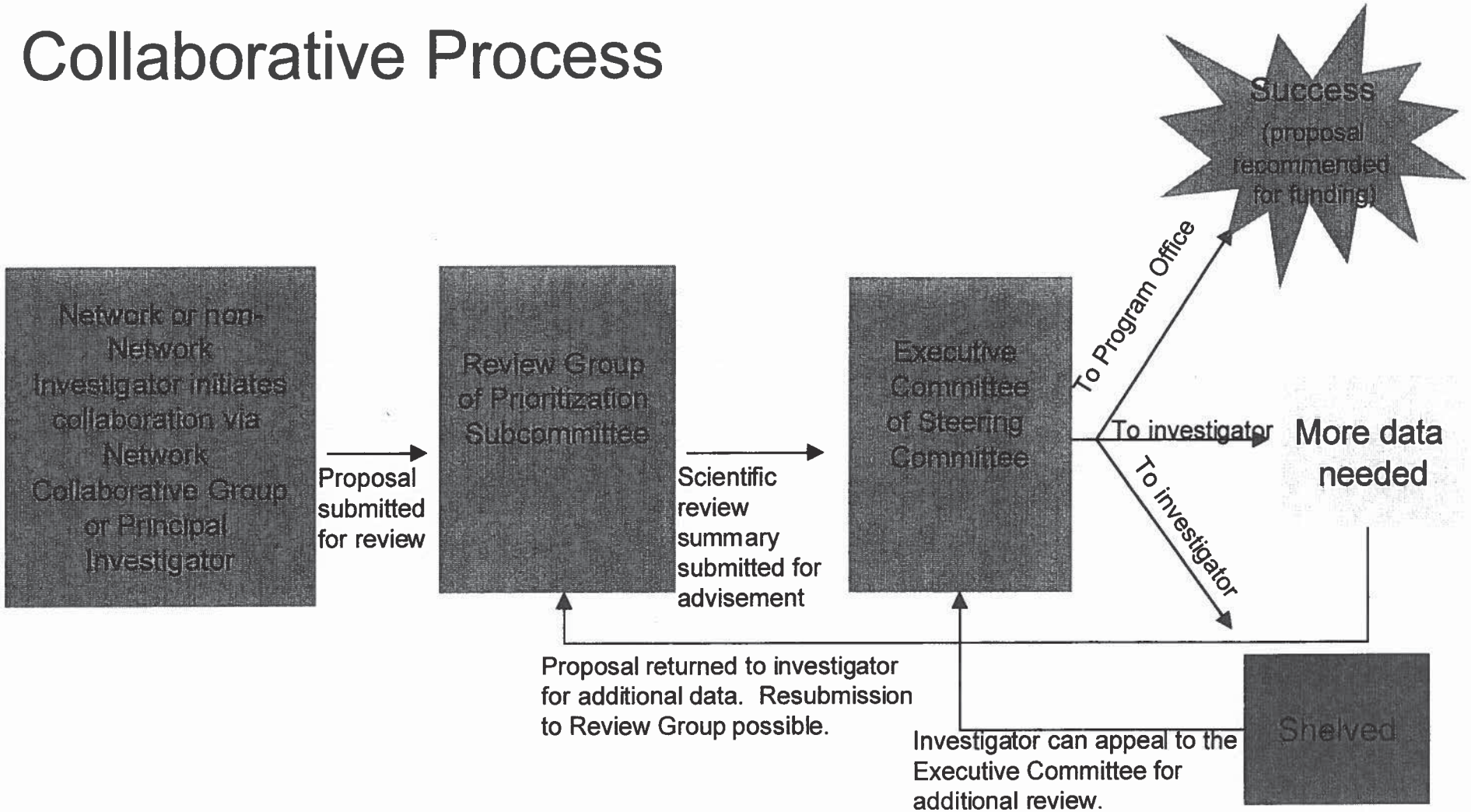


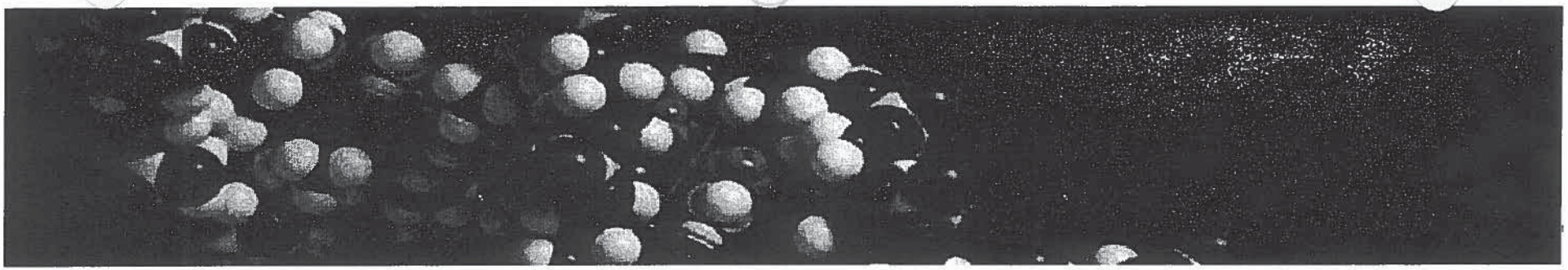
Collaborative Groups as a Gateway to Collaboration

- Consider areas of research where collaboration will enhance technology, resource, and information sharing
- Meet formally three times a year
- Discuss collaborative matters each month through conference calls, emails, and listserv

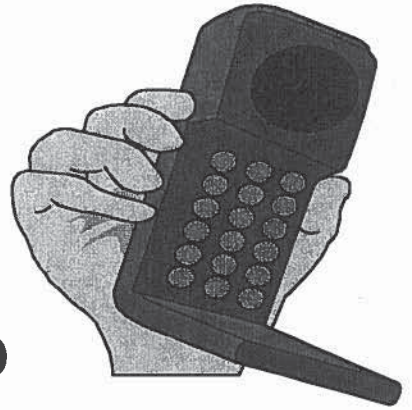


Collaborative Process



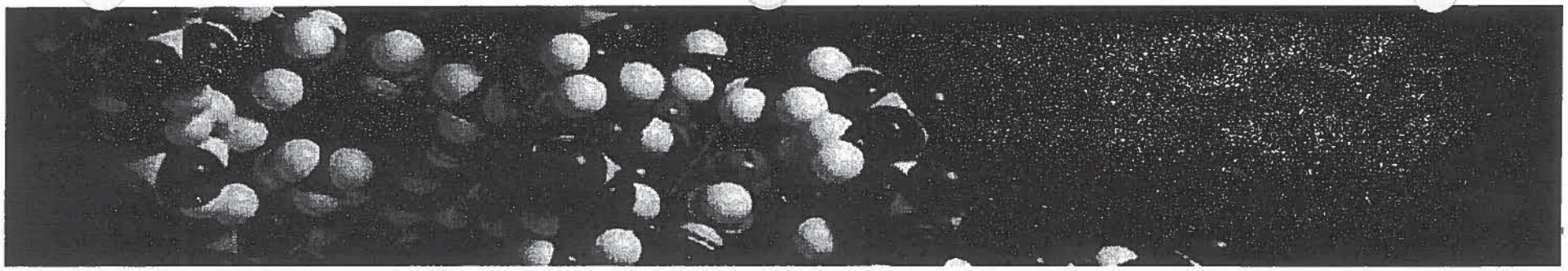


Communicating with the Scientific Community:



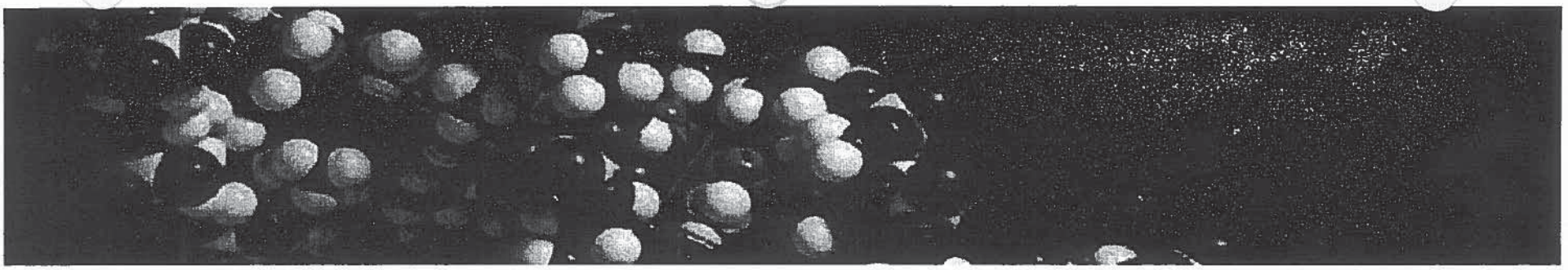
EDRN Communication and Workshop Subcommittee established

Member Liaisons for relevant professional societies appointed



Communicating With Community

- EDRN Website launched (http://cancer.gov/edrn)
- 22 Listservs to facilitate dialogue among investigators; subscription open to public
- Annual workshops/conferences held: Gordon Research Conference on *New Frontiers in Cancer Detection and Diagnosis*, March 10-15, 2002, Ventura, California
- Collaborative opportunities published in major journals



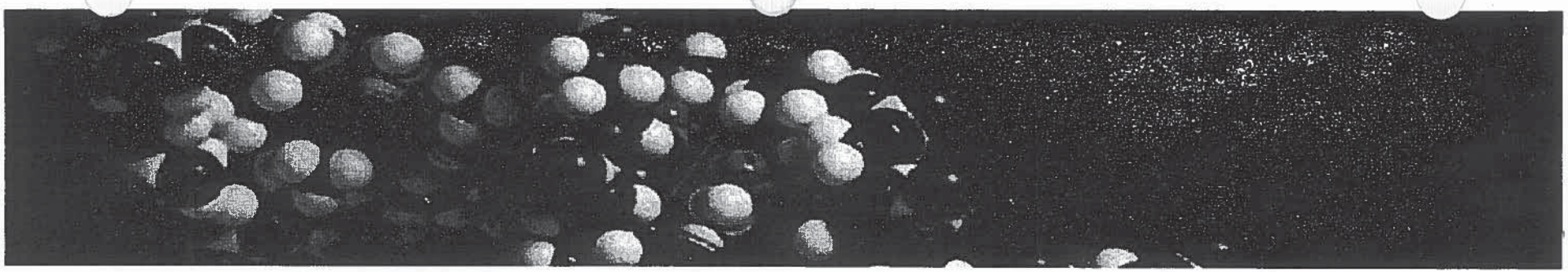
GOAL

Support Biomarkers Validation

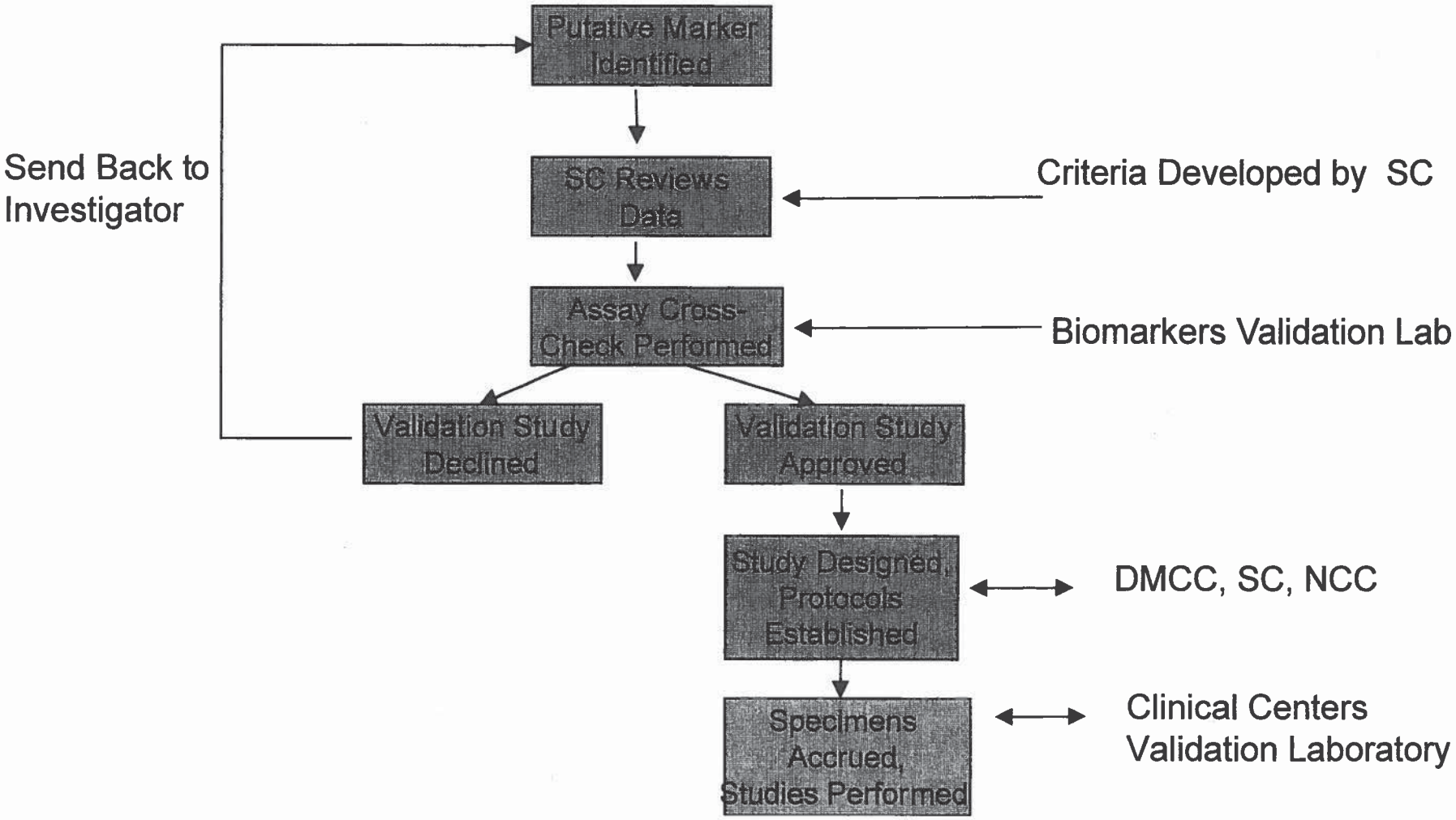
Guiding Principles

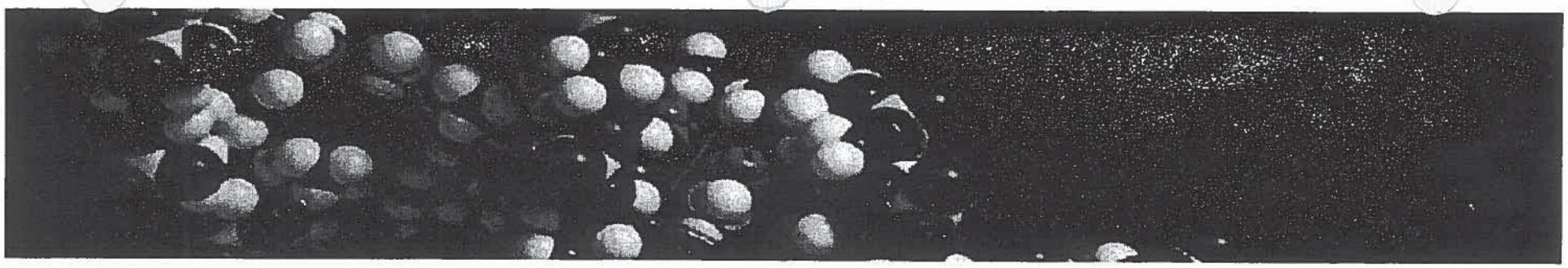
Phases of Biomarker Development

Preclinical Exploratory	*PHASE 1*	*Promising directions identified*
Clinical Assay and Validation	*PHASE 2*	*Clinical assay detects established disease*
Retrospective Longitudinal	*PHASE 3*	*Biomarker detects preclinical disease and a "screen positive" rule defined*
Prospective Screening	***PHASE 4***	*Extent and characteristics of disease detected by the test and the false referral rate are identified*
Cancer Control	*PHASE 5*	*Impact of screening on reducing burden of disease on population is quantified*



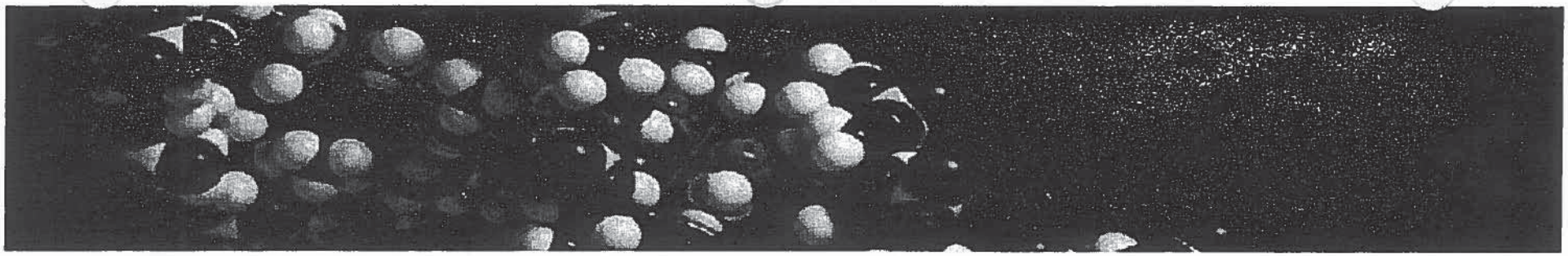
Supporting Systematic Validation: Process





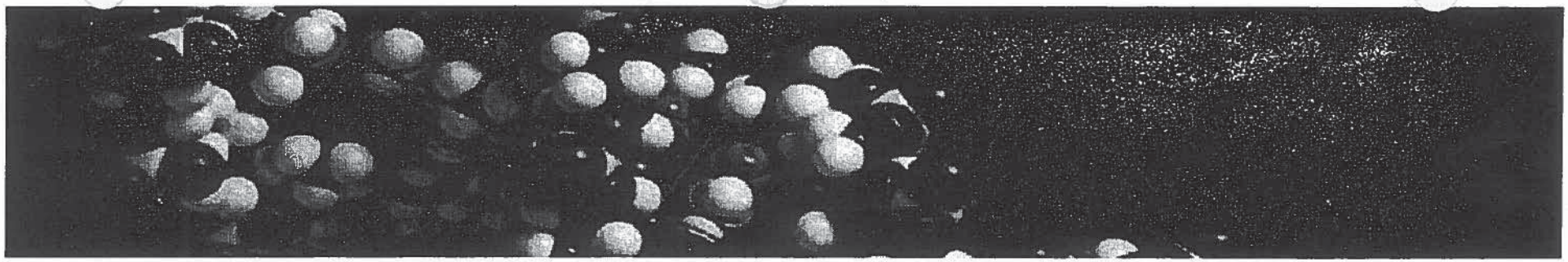
Goal

Novel Biomarkers Identified and Evaluated



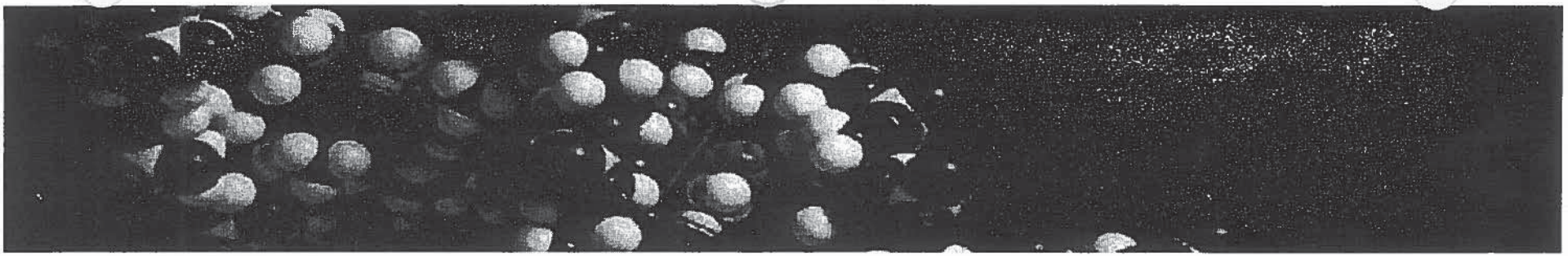
LUNG

- Hypermethylation of CpG islands in genes like p16 and RAR-β2 (Sidransky, Gazdar, Franklin).
- Facile detection of mtDNA mutations in sputum and bronchioalveolar lavage. (Sidransky)
- Protein Markers Discovery (Hanash)
- Assessment of TGF-bR, hnRNP, SMAD 2,4,7 in sputum; p53 and ras in biopsies (Tockman, Bigbee)



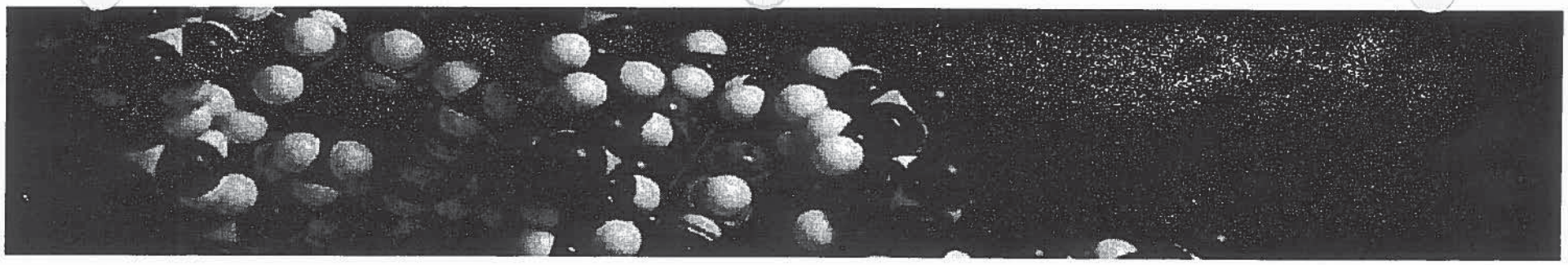
PROSTATE

- Protein biomarkers (33Kd, 8.5Kd, 9.5Kd) in seminal plasma from early stage prostate cancer patients identified using Ciphergen Proteomics Chip and SELDI mass spectroscopy (Wright)
- Serum-based protein-pattern analysis (using Heuristic approach) as potential paradigm for early detection (NCI:Liotta, Petricoin, EDRN:Zhao, Trock)
- Assessment of IGF-1 and androgen receptor polymorphism (Thompson)



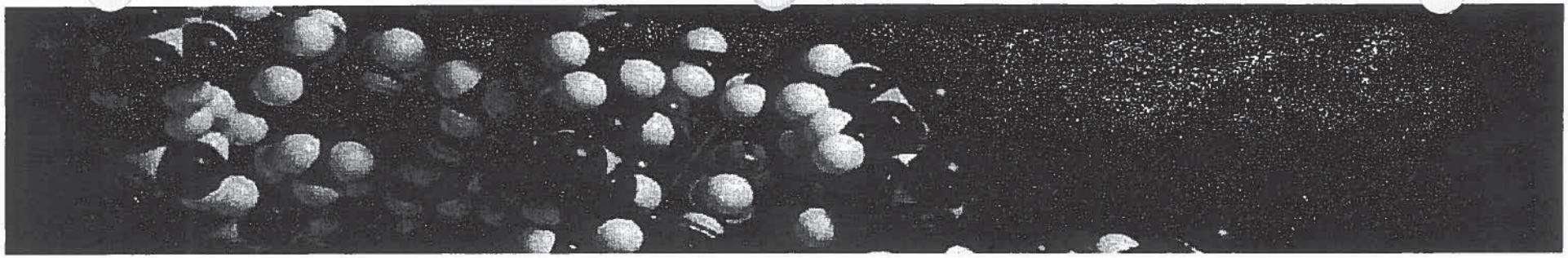
BREAST

- Secretory Protein Trapping Technology (Beach)
- Unique proteins identified in breast nipple aspirates using proteomics-based approaches.
- Reproducibility of LCM and SELDI results are being validated. (Trock, Liotta, Petricoin)



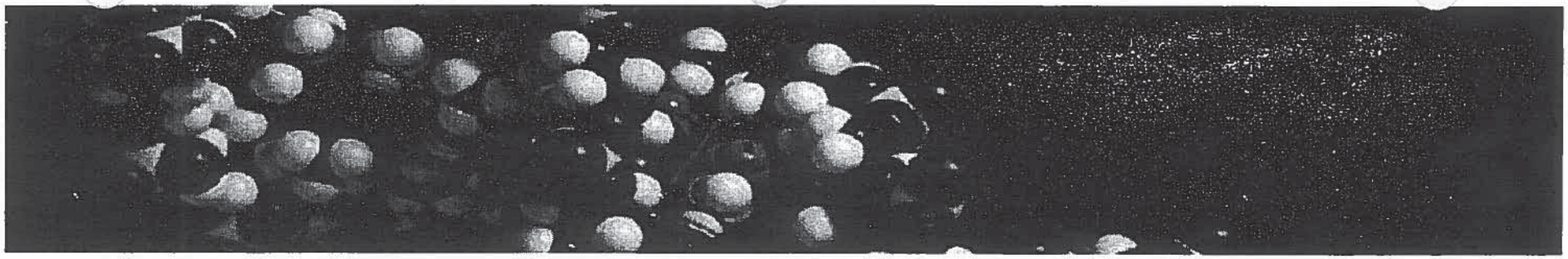
OVARY

- Ovarian Pap Smear Test developed and poised for evaluation for molecular testing for early diagnosis. Accrual of high-risk cohorts is underway. (Fishman)
- Panel of biomarkers (p53, MMPs, plasminogen activators, CA-125, BRCA-1&2, LPA, Her-2) being tested (Fishman, Cramer, Kiviat, Kazinski)



BLADDER

- Allelic loss of 3q21-23 reported in 30% tumor samples, 20% urine samples (Czerniak)
- STK15/BTAK over-expression induces abnormal centrosome duplication and distribution in early stage bladder cancer. Studies using larger sample size are underway. (Czerniak)
- Comprehensive mapping of molecular alterations with the natural history of bladder cancer. (Czerniak)
- Assessment of BLCA-4 protein immunoassay in urine (Bigbee)

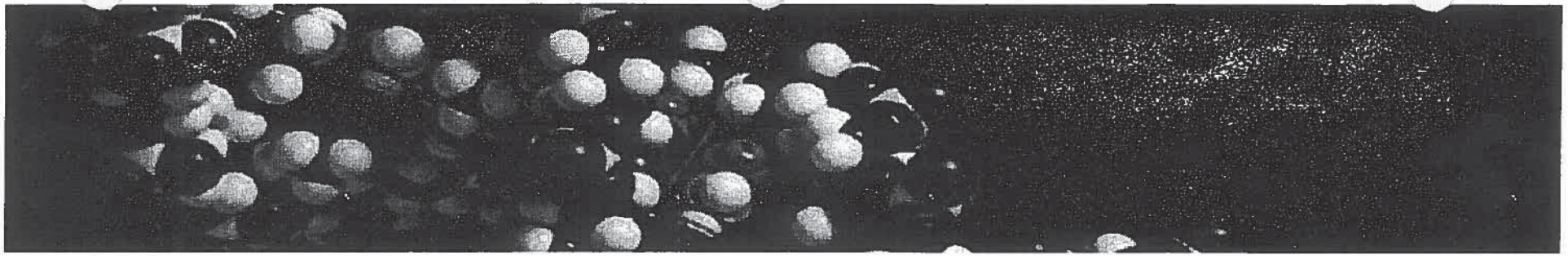


COLORECTAL

- 5q LOH, K-ras and exon 15 of APC mutation, iNOS and prostaglandin synthase-2 expression (Bigbee)
- Expression patterns for secreted and cell surface proteins (Beach)
- Serum markers (S-1000 proteins, Galectin-3, MUC5AC) and aberrant crypt foci (Brenner/Hanash)
- Cancer-prone families, such as carriers of germ-line HNPCC mutations and FAP (Lynch)

Goal

Support Analytical Validation of Biomarkers



Validation of Gene Hypermethylation

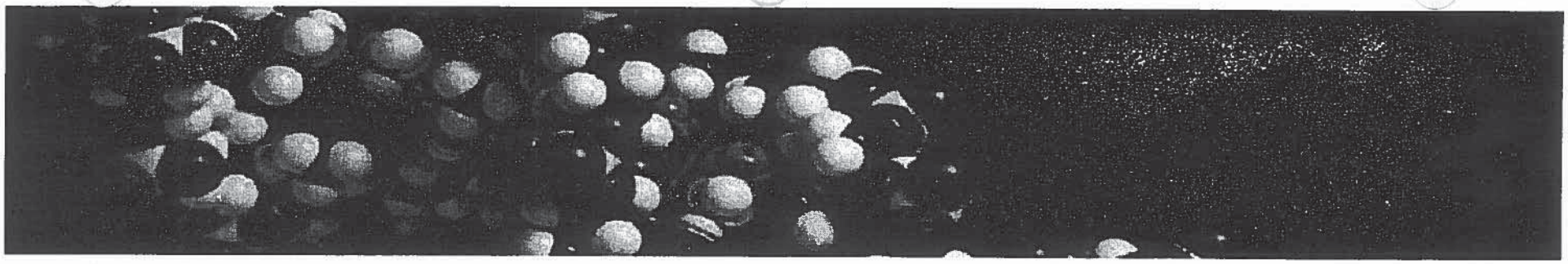
- **Markers that detect 100% of lung cancers have been developed for aberrant methylation evaluation.**
  RARβ, DAP kinase, GSTP1, FHIT, RASSF1, MGMT, E-cadherin, APC, and p16

- **RASSF1 and RARβ are frequently deleted (3p21.3) in lung cancer and methylated in 70-100% small cell cancers. APC is methylated in 71% NSCC.**

Promoter hypermethylation working group established to cross-check results from four labs, using same set of primers and coded samples

Working Group Members

Melvin Tockman
Adi Gazdar
Wilbur Franklin
David Sidransky
Jim Herman



Analytical Validation Studies with the National Institute of Standards and Technology (NIST)

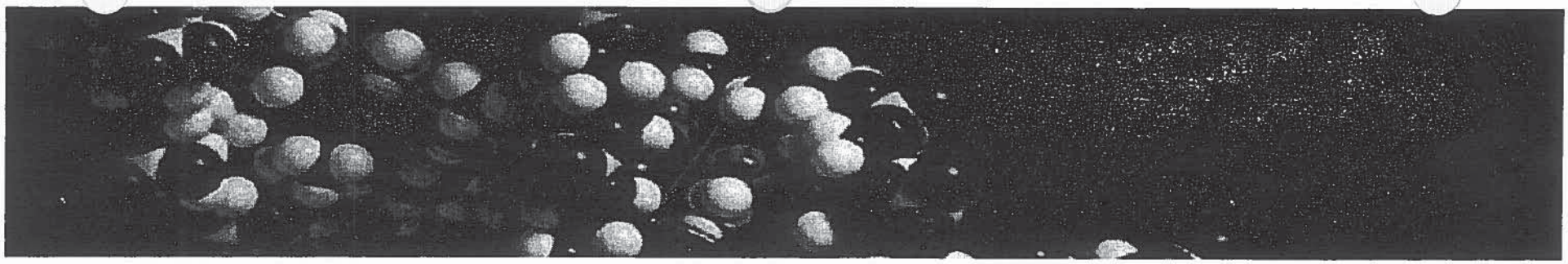
Validation of Mutagen Sensitivity and Chromosomal Hotspot Assays (Spitz, M.D. Anderson)

Mutation Detection in Mitochondrial DNA in Solid Tumors (Sidransky, Johns Hopkins University)

Serum Telomerase with Capillary Electrophoresis (Highsmith, University of Maryland)

Analytical Validation Study: Chromosome Breakage Assay

- Determine basal level and variability in the number of chromosomes and chromatid breaks in simultaneously repeated assays from cells of the same biologic source
- Evaluate break number changes with blood storage
- Evaluate assay performance under different conditions, including cell culture conditions, hypotonic treatment, and slide preparation treatment.

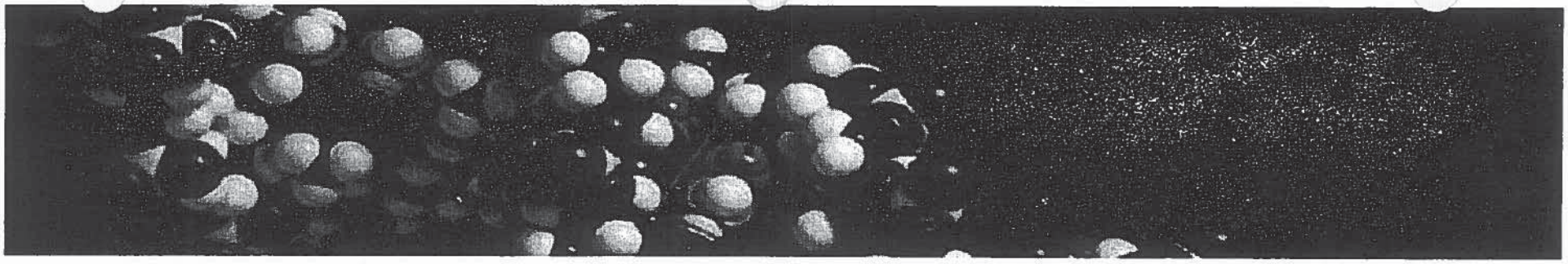


Analytical Validation Study: Mitochondrial DNA

- Powerful marker for early detection: readily detectable in body fluids, more abundant than other molecular changes
- Check for heteroplasmy using various technologies.
- Establish threshold concentrations below which mtDNA cannot be reliably sequenced.
- Determine if standard PCR/sequencing protocols faithfully detect mtDNA present in original DNA sample and are optimal for primer pair sequences chosen by NIST and EDRN.

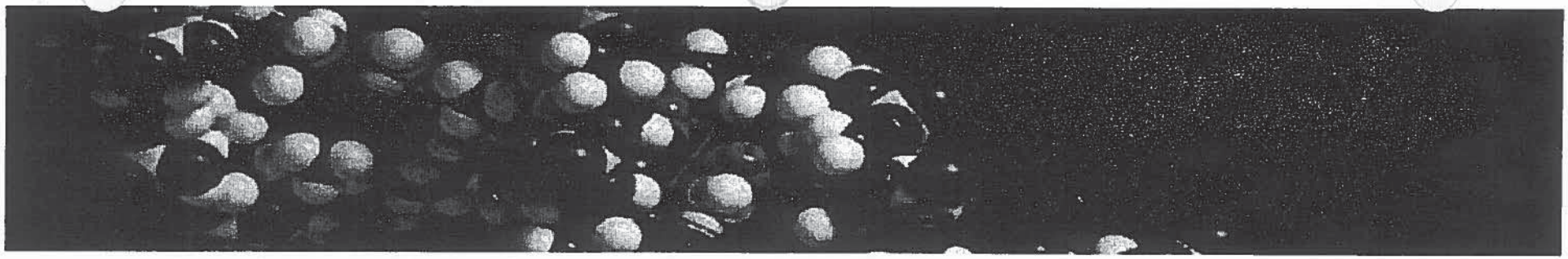
Analytical Validation Study: Serum Telomerase

- Develop a high-throughput capillary electrophoresis (CE) method for analysis of PCR products of the Telomerase Repeat Amplification Protocol (TRAP). Current assays are not high-throughput.
- Streamline validation of TRAP assay system with increased sensitivity, reproducibility, and automation over slab-gels.
- Enable accurate telomerase analysis of large numbers of tissue and blood samples in early detection of cancer.



Goal

Provide informatics and facilitate information flow across the Network

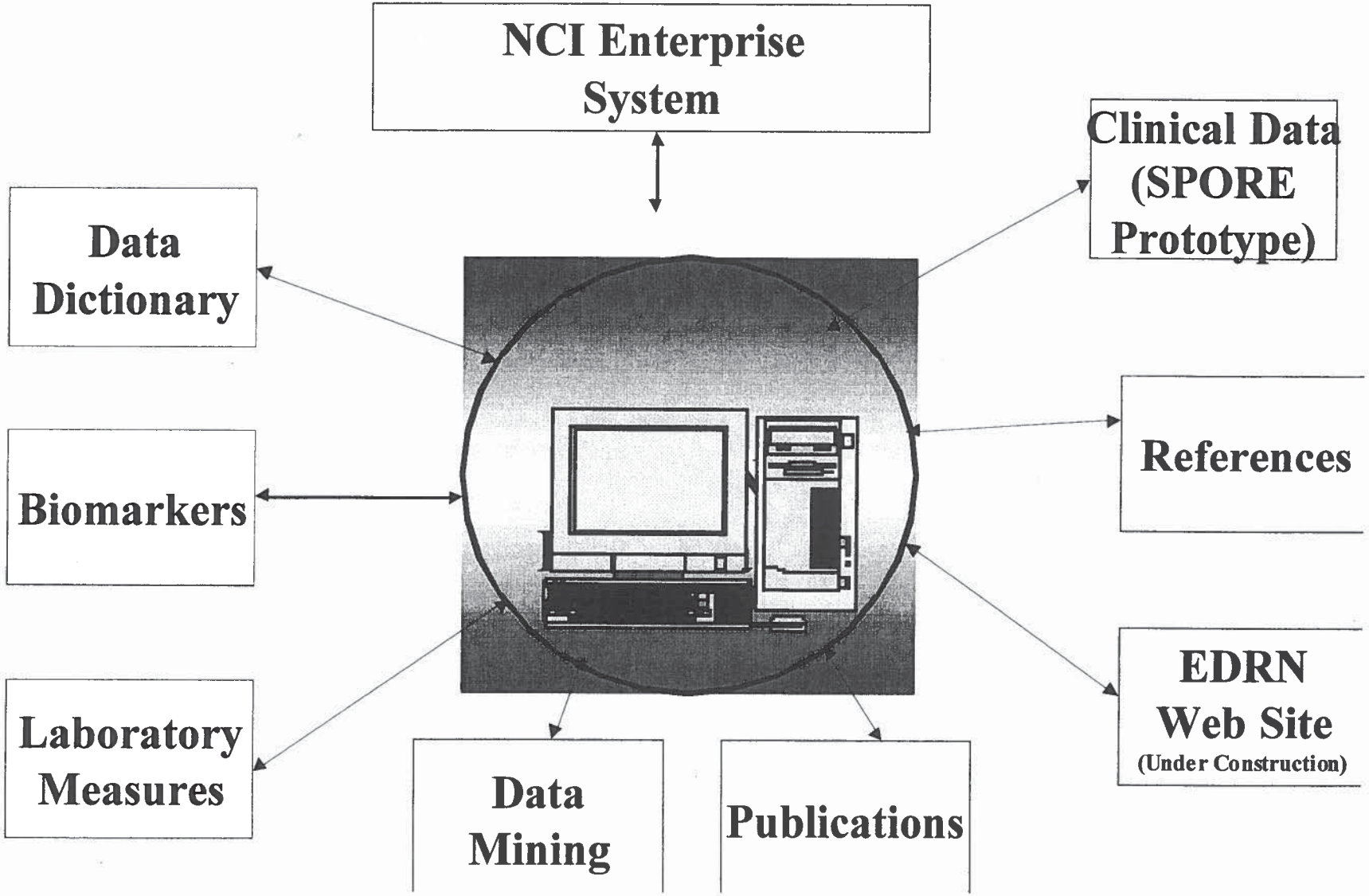


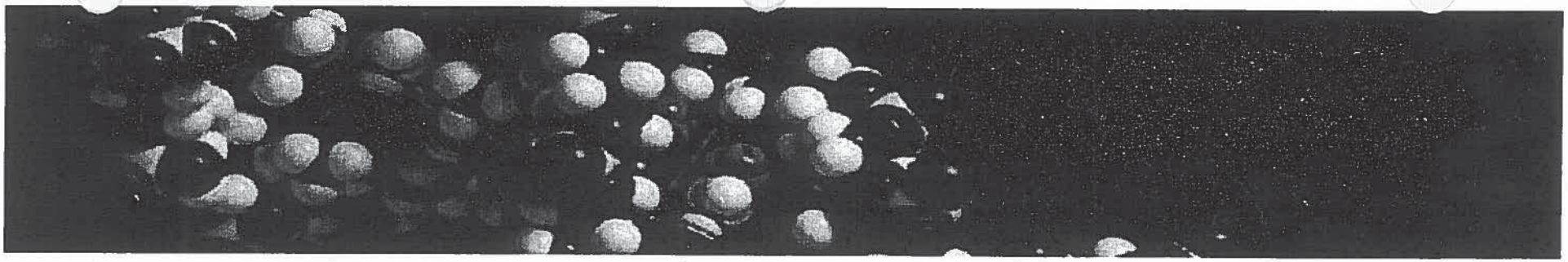
Why EDRN Bioinformatics

Bioinformatics is likely to lead to a qualitative change in clinical medicine, diagnostic, and prognostic practice.

- Foster exchange and sharing of data and tools among EDRN investigators located at diverse places: 25 active listservs also open to non-EDRN subscribers
- Provide standardized vocabulary, common data elements, and other decision support tools and research databases
- Provide NCI leadership with timely information for planning and evaluation of research programs

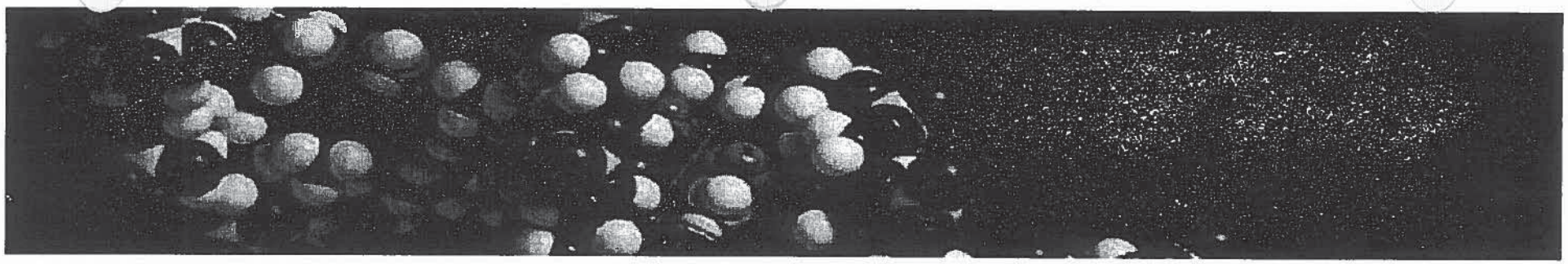
Plans for EDRN Informatics





Bioinformatics is Being Pursued

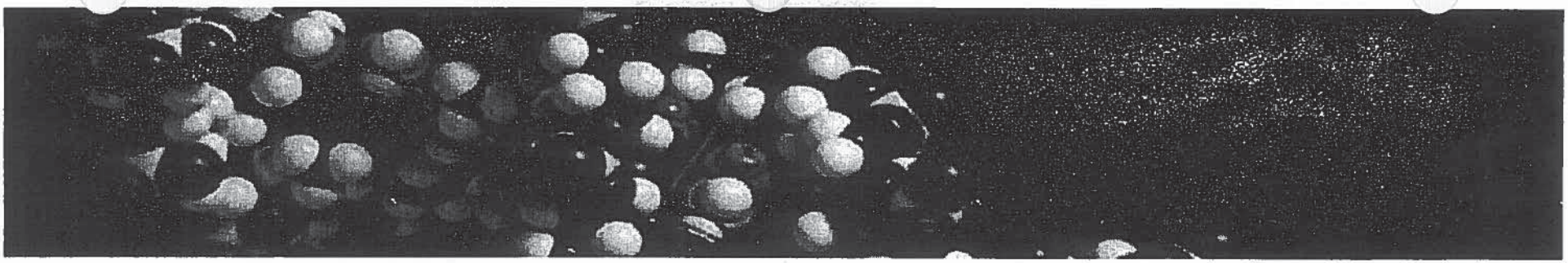
- **Knowledge Engineering**: Algorithm development to perform tasks requiring expert knowledge, e.g. medical diagnosis, array data analysis. Facilitated by Data Management and Coordinating Center.
- **Knowledge Integration**: **Biomarkers Knowledge Center** would integrate information from several sources into a **knowledge resource** for hypothesis generation, duplication minimization, and patient management.
- **Knowledge Representation**: Representation of knowledge to facilitate problem-solving program, e.g., meta-analysis of biomarkers data.



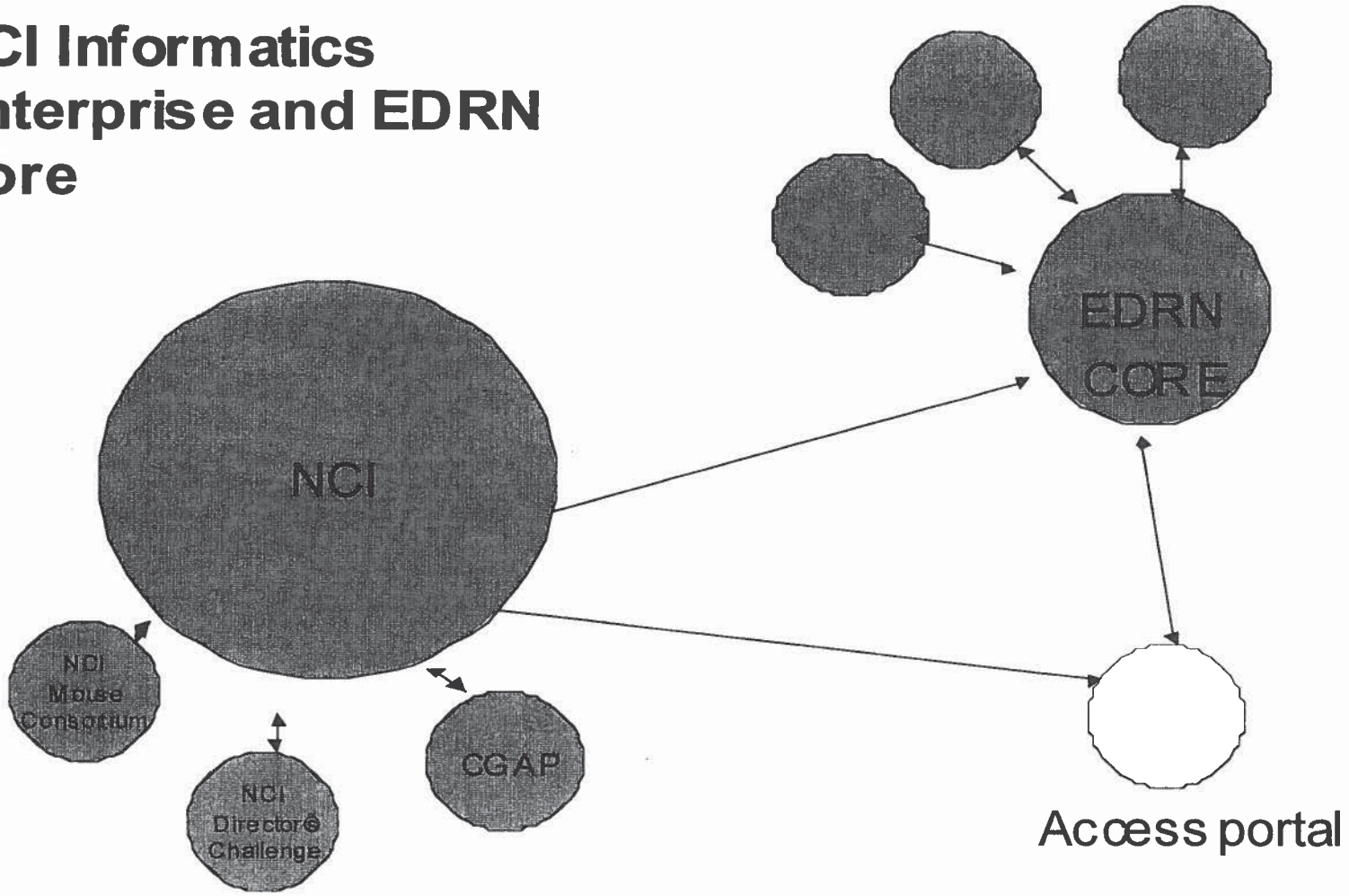
Biomarkers Knowledge Center

Develop a prototype in collaboration with JPL:

- Mock Implementation: January 2001
- Feasibility Implementation (2 sites): August 2001
- Pilot Implementation (6 sites): January 2002



NCI Informatics Enterprise and EDRN Core



The Early Detection Research Network

EDRN

Translational Research to Identify Early Cancer and Cancer Risk