Early Detection Research Network (EDRN)
A National Infrastructure for Biomarker Development

Pre-Application Meeting
July 12, 2021

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NIH NATIONAL CANCER INSTITUTE

Disclaimer and Points to Note

- Today's presentation provides a high-level overview of EDRN and is not a substitute for the FOAs. Please read the relevant FOA for details.

- After today's orientation Webinar, any future questions must be directed via email to the contacts listed on each FOA. Phone calls are discouraged.

- All the slides will be posted on the EDRN Website (http://edrn.nci.nih.gov).

- Recordings of today's proceedings will be made available (http://edrn.nci.nih.gov).

EDRN Program Objectives

EDRN has established an infrastructure to:

- Support investigator-initiated research for the development and validation of biomarkers and imaging methods for detection and progression of early cancers;
- Conduct trials to demonstrate the clinical utility of biomarkers and/or imaging methods developed by the EDRN;
- Foster interaction and cooperation between academic, clinical, and industrial leaders;
- Establish and apply standardized biomarker validation criteria;
- Establish and apply standardized biomarker quality assurance;
- Facilitate the use of standardized biomarker validation and quality assurance protocols across the field; and
- Facilitate regulatory process to bring biomarkers rapidly into clinical use.

EDRN Milestones

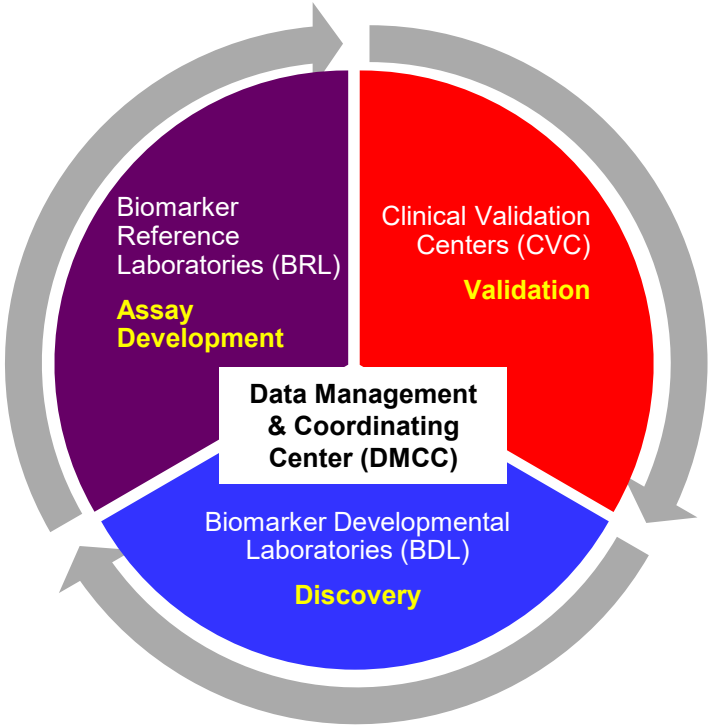
2000-2005 Coordinate, Communicate, & Collaborate	2005-2010 Learn, Improve, & Deliver	2010-2016 Productivity, Outcome, & Dissemination	2016-2021 Outreach, Productivity, & Dissemination
✓ 33 PIs; 32 Associate Members ✓ Steering Committee/Workshop Attendance: 85/300 ✓ EDRN-Gordon Research Tie-up (2002, 2003) ✓ Initiated EDRN-Human Proteome Organization Plasma Proteome Project ✓ Guidelines for Biomarker Discovery and Validation ✓ Project Management Tools Created ✓ Multi-center Trial Informatics Infrastructure created, verified ✓ Virtual Specimen Bank Established ✓ IRB Approvals Monitored: 38 sites	✓ 45 PIs; 123 Associate Members ✓ Steering Committee/Workshop Attendance: 120/300 ✓ 2 EDRN-Gordon Research Workshops (2005, 2007) ✓ MOUs signed with Canary Foundation, Lustgarten Foundation, and Turkey ✓ OVA1 FDA Approved ✓ EDRN-FDA Educational Biennial Workshop ✓ EDRN-NIST Workshop on Standards ✓ IRB approvals monitored: ~80 sites	✓ 57 PIs; 231 Associate Members ✓ Steering Committee/Workshop Attendance: 150/350 ✓ DCP and AFP-L3 FDA Approved for Liver Cancer and ROMA for Ovarian Cancer ✓ proPSA and PCA-3 FDA Approved for Prostate Cancer ✓ 11 CLIA-approved Diagnostic Tests ✓ 10 Clinical Reference Sets completed and stored at Frederick, MD ✓ IRB Approvals Monitored: 216 sites; 200 Protocols; 100 MTAs	✓ 58 PIs; >300 Associate Members ✓ Workshop attendance >400 ✓ Adoption of EDRN-supported tests (8 FDA and 19 CLIA approved cumulatively) are being offered and reimbursed through Reference Laboratories ✓ CancerSeek and EsoGuard receive FDA Breakthrough Designation ✓ Clinical Reference Samples expanded on colon, pancreas, prostate, uterine lavage ✓ Japan and US EDRN collaboration expanded to include joint annual meetings; China-EDRN formed

Current EDRN Organizational & Operational Structure

Network Consulting Team ⟷ **Steering & Executive Committees**

Groups

- Prostate & Other Urologic
- Breast and Other Gynecologic
- Lung & Upper Aerodigestive
- Colon & Other GI



EDRN Collaborations & Partners

- Parallel, EDRN-Advised Initiatives
- Co-funding by PanCAN, Kenner Family Research Fund, Lustgarten Foundation, Canary Foundation, & CR-UK
- Independent, collaborative consortia: PCDC; CPDPC; LBC; CIB; TLC; Alliance of GBs; HTAN (PCA)
- Associate Members
- Federal Partners: NIST, CPDR/DoD; PNNL/DoE; JPL/NASA; CGH/NCI
- Pharma/Biotech Industry (15 active)

Infrastructure Administered Through Policy and Procedures

- Vertically integrated infrastructure for collective discovery, development and validation of biomarkers:
  - >200 active protocols; >100 MTAs and IRBs
  - >1650 candidate biomarkers prioritized for evaluation
  - ~950 moved forward to Phase 2 and Phase 3 validation
  - >100,000 subjects enrolled for the various validation studies
  - >12 clinical validation studies in progress
- Policy and Procedures in place for transparency and effective management
- Effective hand-off mechanism from BDL to BRL to CVC

EDRN cited as a model organization by AACR, NCI Translational Research Working Group, IOM, Nature, Science, and J. Proteome Research for project management driven by milestones and operational guidelines, manual of operations, and team approach.

Revised, Streamlined Funding Opportunity Announcements

Biomarker Characterization Centers: RFA-CA-21-035

- Each Biomarker Characterization Center will perform the functions currently being carried out by both a Biomarker Developmental Laboratory and a Biomarker Reference Laboratory to better align and integrate biomarker development with assay development and standardization.

Clinical Validation Centers: RFA-CA-21-033

- Conduct biomarker and/or imaging validation study(s) to detect early-stage cancers and/or distinguish aggressive from non-aggressive screen-detected cancers.

Data Management and Coordinating Center: RFA-CA-21-034

Collaboration, Resources and Networking Opportunities

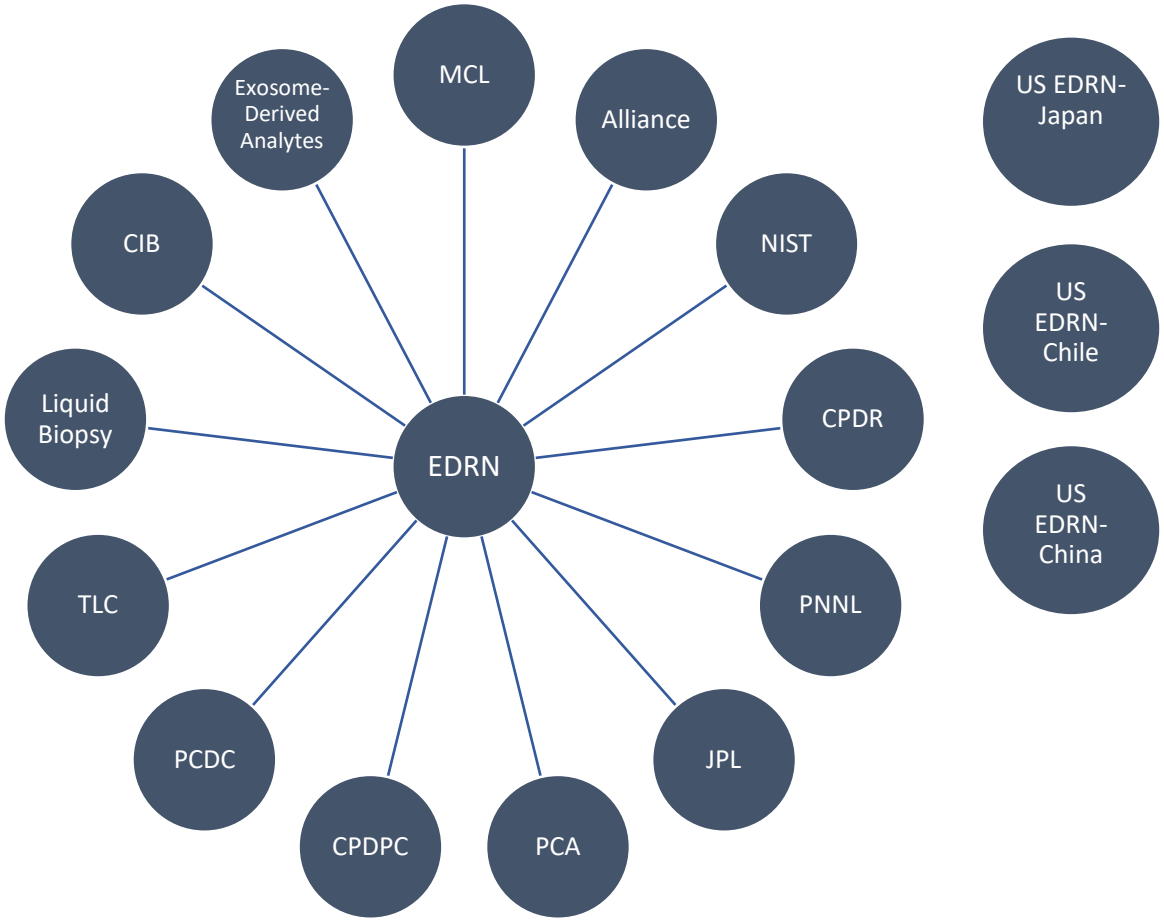
Opportunities to Collaborate with Other Programs: "Hub and Spoke" Model

Programs

- **Early Detection Research Network (EDRN)**
- Molecular and Cellular Characterization of Screen-Detected Lesions (MCL)
- Alliance of Glycobiologists for Cancer
- Exosome-Derived Analytes for Cancer
- Consortium for Imaging and Biomarkers (CIB)
- Liquid Biopsy for Early Cancer Assessment
- Translational Liver Cancer (TLC) Consortium
- Pancreatic Cancer Detection Consortium (PCDC)
- Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC)
- Pre-Cancer Atlas (PCA) Research Centers of the Human Tumor Atlas Network (a Cancer Moonshot Program)

Inter-Agency Agreements (IAA)

- Jet Propulsion Laboratory (JPL)/National Aeronautics and Space Administration (NASA)
- National Institute of Standards and Technology (NIST)
- Pacific Northwest National Laboratory (PNNL)
- Center for Prostate Disease Research (CPDR)



https://prevention.cancer.gov/research-groups/cancer-biomarkers/about-cancer-biomarkers

Trans-Disciplinary Opportunities for Collaboration

Opportunity to collaborate with:

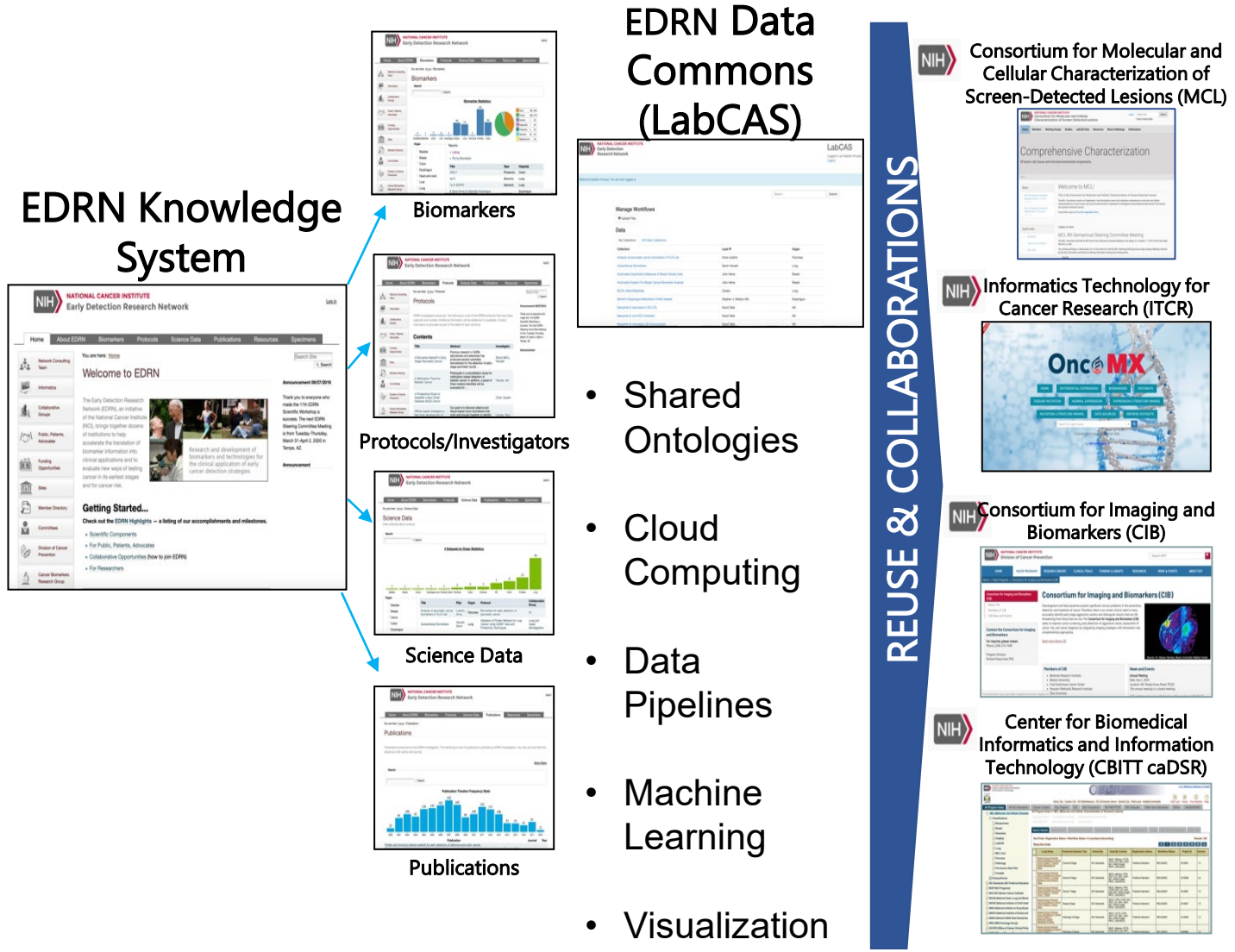
- EDRN Collaborative Groups
- Federal Agencies: NIST, JPL, DOD, DOE
- Non-Profit Foundations
- International Partners
- NCI- and NIH-sponsored programs
- NCI Statisticians on statistical issues
- EDRN Associate Members (>350) and privilege to sponsor new Associate members

https://edrn.nci.nih.gov/work-with-edrn/associate-membership-program

Privilege to use EDRN Resources for Biomarker Research

Develop systems and tools to support biomarker research available on EDRN secure and public access portals:

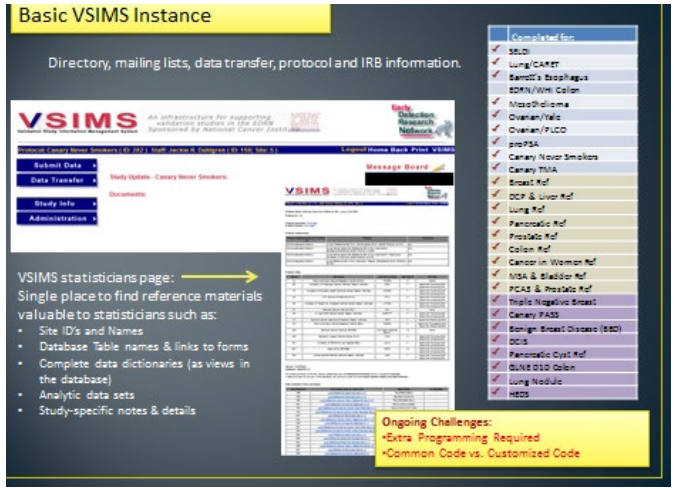
- Biomarker Database (EDRN supports data capture and curation of your data)
- Interactive, CLOUD-based Workspace/Data Commons (LabCAS) for secure, pre-publication data capture, sharing and analysis
- Use of automated data analytic pipelines
- Data-files, Publications and Protocol Archiving Systems (eSIS; eCAS)

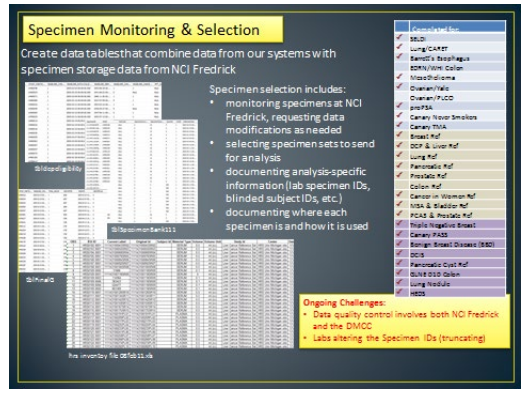


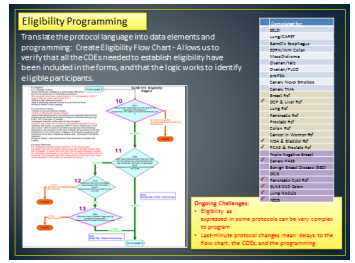
http://edrn.nci.nih.gov/informatics/informatics

Privilege to use Data Science Resources for Clinical Studies: Informatics and Bioinformatics (DMCC and Jet Propulsion Lab)

- LIMS (VSIMS) for multicenter validation studies
- eSIS for study management
- ERNIE for Virtual Specimen Banks (tracks >100,000 biospecimens)
- Biomarker Database
- >2600 Common Data Elements
- Data Storage, Archival, Analytical Pipelines through LabCAS (proteomic and genomic data) and eCAS
- Integration of AI/MLL into data analytic pipelines to support analysis
- Crowd-sourcing Opportunity on stored data







http://edrn.nci.nih.gov/informatics/informatics

Opportunity to Use Resources for Biomarker Verification: Reference Sets

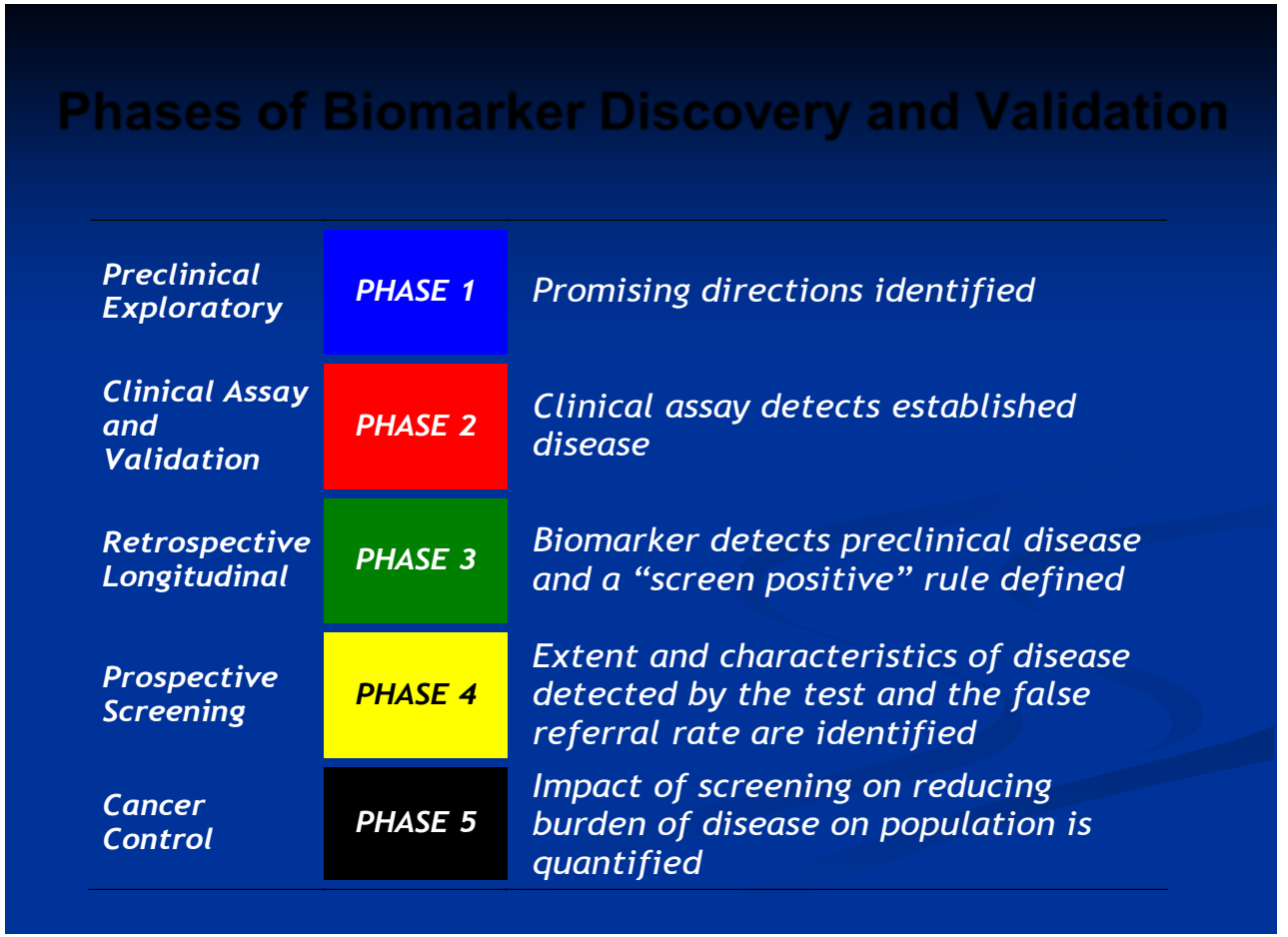
Housed at NCI Frederick Central Repository

- Bladder
- Breast
- Colon
- Lung
- Liver
- Pancreas
- Prostate
- Ovary

http://edrn.nci.nih.gov/resources/sample-reference-sets

Guidelines for Biomarker Development

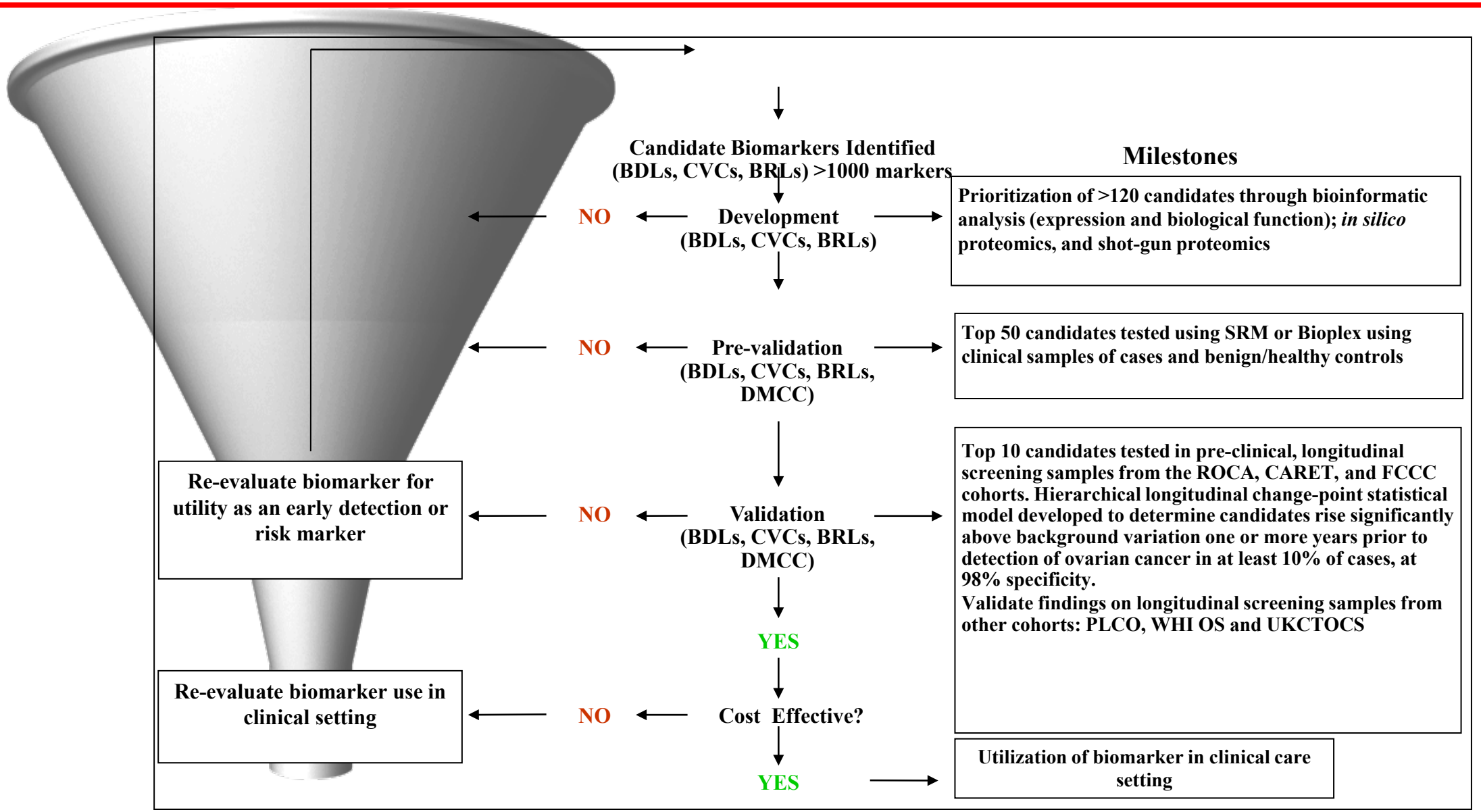
PRoBE Study Design:
Prospective-Specimen-Collection,
Retr**o**spective-**B**linded-**E**valuation



Pivotal Evaluation of the Accuracy of a Biomarker Used for Classification or Prediction: Standards for Study Design
Margaret Sullivan Pepe et al.
J Natl Cancer Inst 2008; 100:1432-1438

Phases of Biomarker Development for Early Detection of Cancer
Margaret Sullivan Pepe et al.
J Natl Cancer Inst, Vol. 93, No. 14, July 18, 2001

Participation of EDRN Scientific Components in Biomarker Validation: Ovarian Cancer Markers as an Example



19 Biomarker Tests in Clinical Laboratory Improvement Amendments (CLIA) Laboratories (*9 in current cycle*)

Biomarker Assay	Purpose	EDRN Principal Investigator CLIA Laboratory
MiCheck (Glypican-1 protein and related signaling molecules)	Differentiate aggressive prostate cancer from non-aggressive cancer and no cancer	Daniel Chan, Ph.D. Minomic, Inc
Videssa (a multi-protein biomarker blood test)	Distinguish benign from malignant breast lesions	Joshua LaBaer, M.D., and Karen Anderson M.D. Provista
DetermaVu	Liquid biopsy test intended to facilitate clinical decision making in lung cancer	Louise Showe, Ph.D. OncoCyte
Percepta (23-gene expression panel)	Detection of lung cancer	Avrum Spira, M.D. Veracyte Inc.
Esoguard (methylated vimentin and cyclin A1)	Detection of Barrett's esophagus	Sanford Markowitz, M.D. Lucid Diagnositcs
Decipher Prostate Cancer Classifier Test (SChLAP1 and other lncRNAs)	Determination of prostate cancer aggressiveness	Arul Chinnaiyan, M.D., Ph.D. GenomeDx
Mucin panel (MUC4, MUC5AC, MUC16 and MUC 17)	Detection of pancreatic cancer	Surinder Batra, Ph.D. Sanguine Diagnostic and Therapeutics
MiPS (Mi Prostate Score Urine test), Multiplex analysis of TMPRSS2:ERG gene fusion, PCA3 and serum PSA	Detection of prostate cancer	Arul Chinnaiyan, M.D., Ph.D. Gen-Probe
IHC and FISH for TMPRSS2:ERG fusion	Detection of prostate cancer	Arul Chinnaiyan, M.D., Ph.D. Roche

Food and Drug Administration (FDA) Approved

Biomarker	Purpose	Year of Approval	EDRN Principal Investigators Industrial Partner
EsoCheck	Allows patients to undergo a non-invasive five-minute office-based procedure to detect Barrett's Esophagus	2019 FDA-cleared tool	Sanford Markowitz, M.D. Lucid Diagnostics
CancerSEEK	Detection of genetic mutations associated with pancreatic and ovarian cancer.	2019 FDA break through device	Ken Kinzler, Ph.D., Robert Schoen, M.D., Randall Brand, M.D., Peter Allen, M.D., and Samir Hanash, M.D. Thrive Detection Corp.
Overa (5 analytes: CA 125, apolipoprotein A-1, transferrin, follicle-stimulating hormone, human epididymis protein 4)	Prediction of ovarian cancer risk in women with adnexal mass.	2016	Zhen Zhang, Ph.D. and Daniel Chan, Ph.D. Vermillion
%[-2]proPSA	Reduce the number of unnecessary initial biopsies during prostate cancer screening.	2012	Daniel Chan, Ph.D. Beckman Coulter
PCA3 (Prostate Cancer Antigen 3) RNA in urine	Determination of need for biopsy or repeat-biopsy in patients at risk for prostate cancer.	2012	John Wei, M.D. Gen-Probe
Risk of Ovarian Malignancy (ROMA) algorithm	Prediction of ovarian cancer risk in women with pelvic mass.	2011	Steve Skates, Ph.D. Fujirebio Diagnostics
DCP and AFP-L3; a combined panel of biomarkers	Risk assessment for development of hepatocellular carcinoma.	2011	Jorge Marrero, M.D. Wako Diagnostics
OVA1™ (5 analytes: CA 125, prealbumin, apolipoprotein A-1, beta2 microglobulin, transferrin)	Prediction of ovarian cancer risk in women with adnexal mass.	2009	Daniel Chan, Ph.D. and Zhen Zhang, Ph.D. Vermillion

Flexibility to Adapt to the Changing Landscape of Biomarker Science

- Multi-analyte, multi-cancer detection approaches
- Changing regulatory requirements for biomarker qualifications (FDA)
- Responding to regulatory needs, e.g., how to set a threshold for multi-analyte assay(s) for acceptable diagnostic performance, e.g., Sensitivity, Specificity, PPV and NPV
- Close collaboration with Pre-Cancer Atlas of the Moonshot Initiative on Human Tumor Atlas Network for promising leads on biomarkers
- Focus on multiplexing biomarker assays for improved diagnostic performance

New Scientific Priorities

EDRN will work closely with other NCI-Sponsored Programs on:

- Data science and artificial intelligence;
- Better integration of imaging and biomarkers;
- Clinical utility trials;
- Pan-cancer/multi-cancer screening/early detection tests;
- Increased efforts on inclusion/diversity of studied populations; and
- Increased efforts on training of early-stage/junior investigators.

Collaboration with NIDCR on Oral, Head & Neck Cancer

National Institute of Dental and Craniofacial has joined EDRN to support a Biomarker Characterization Center. See the following: NOT-DE21-005

https://grants.nih.gov/grants/guide/notice-files/NOT-DE-21-005.html

For details, contact:
Zhong Chen, MD, Ph.D.
National Institute of Dental and Craniofacial Research
Telephone: (301) 529-7083
Email: zhong.chen@nih.gov

General Requirements Pertaining to all FOAs

- Adhere to the FOA-specific scope, specific requirements, page limitations, and other details.
- Describe study designs.
- Describe statistical analyses.
- Collaborate with Cohort Consortia, HMOs, Cooperative Groups, and other relevant entities for “shovel-ready” biospecimen collections , if applicable.
- Pay attention to review criteria when preparing your application.
- Describe licensing and IP management plan, if applicable.

Highlights of FOAs

- **Biomarker Characterization Centers**

  RFA-CA-21-035 (U2C)

Two components

  - **Biomarker Developmental Laboratory**
  - **Biomarker Reference Laboratory**

- **Clinical Validation Centers**

  RFA-CA-21-033 (U01)

- **Data Management and Coordinating Center**

  RFA-CA-21-034 (U24)

These RFAs are funded through Cooperative Agreement Mechanisms in which there is substantial involvement of NCI staff

Biomarker Characterization Center (U2C): Scope

Each Biomarker Characterization Center (BCC) will have two main functional components.

(1) Biomarker Developmental Laboratory (BDL) will discover, develop, characterize and test new biomarkers or refine existing biomarkers.

(2) Biomarker Reference Laboratory (BRL) will (i) develop, refine and/or standardize biomarker assays and (ii) provide resources and support for the validation of biomarkers developed by the EDRN.

BCCs will participate in collaborative projects with other laboratories and centers.

BCC Biomarker Developmental Laboratory (BDL): Expectations

- Investigators with extensive laboratory skills and experience with biomarker research:
- Knowledge of the principles of biomarker discovery, e.g., EDRN's 5-phase criteria, PRoBE Design and other relevant guidelines
- Availability of quality specimens for discovery as opposed to "convenience samples"
- Statistical analysis plan to analyze multiplicity and minimize false-discovery rate, (e.g., multiple platforms, multiple biomarkers, plan for avoiding chance, bias, over-fitting)
- Biomarkers addressing a specific question(s) in the realm of early detection (Phase 1 and Phase 2)

BCC Biomarker Reference Laboratory (BRL): Expectations

- Experience with GLP/CLIA/CAP practices and principles
- Experience with laboratory medicine
- Collaboration with diagnostic/biotech/industrial scientists for clinical grade assays and scale-up
- Provide a clear assay development pipeline for markers meeting EDRN Phase 2 criteria
- Ability to create CLIA-compliant assay protocols, conduct assay for EDRN validation studies and laboratory resources in one or more “Omic” technologies
- Achievable timeline for the project period with decision criteria for triaging assays and technology

Clinical Validation Center (U01): Scope

1. Conduct research to validate biomarkers and/or imaging methods for risk assessment and detection of early- stage cancers.
2. Serve as resource center for collaborative research within the EDRN by providing high-quality specimens for phase 1 and 2 biomarker refinement studies to other EDRN scientific units.
3. Participate in Network collaborative biomarker and/or imaging validation studies.
4. Have the expertise and ability to conduct Phase 4 clinical utility trials of validated early detection biomarkers and/or imaging methods.

Clinical Validation Center (CVC): Expectations

- Patient populations and resources for conducting multi-institute, multi-discipline clinical validation studies
- Sound knowledge and expertise in principles and practices for conducting clinical trials
- Partnerships with Cooperative Groups, HMOs, Cohort Consortia for accessing and collecting specimens, if applicable
- Supportable clinical questions on early detection and/or related issues with decision criteria for inclusion of proposed biomarker panel
- Achievable timeline for proposed study to be completed in 5 years with a provision of an interim analysis in years 3 and 4

Data Management and Coordinating Center (U24): Scope

1. Network Coordination and Outreach
2. Data Science, Data Management and Study Protocol Development
3. Validation Study Infrastructure and Services
4. EDRN Core Fund Management

Data Management and Coordinating Center (DMCC): Expectations

- Demonstrate experience in managing complex biomedical consortia, networks, or equivalent entities with multi-discipline, multi-site activities
- Ability to manage, improve, maintain laboratory management systems for conducting multi-center trials
- Strong background and experience in statistical study designs, protocol management, informatics, BIG data
- Ability to maintain confidential communication on patient data (storage, retrieval, dissemination) through Web Portal, Secure Website, etc.
- Ability to coordinate meetings, workshops, virtual meetings through Webinar and conference calls
- Ability to conduct auditable site visits

PD/PI: Individual Responsibilities

- Define scientific objectives and approaches
  - Study design & protocol development
  - Data collection & accrual of patients (safety monitoring)
  - Data analysis
  - Quality control & quality assurance
- Registration of protocols with DMCC
- Data deposition in EDRN databases (LabCAS)
- Publications & presentations – acknowledge EDRN support

PD/PI: Collaborative Responsibilities

- Develop collaborations with other EDRN BCCs and CVCs
- Participate in Collaborative Group(s) meetings and team projects
- Participate in EDRN Steering Committee Meetings and Scientific Workshops
- Participate in Network collaborative studies (set-aside projects, validation studies, and clinical utility trials, if applicable)
- Collaborate with DMCC on common research designs and protocol development (apply EDRN CDEs)
- Data sharing

Application Checklist

- Is application organized per instructions in the RFA?
- Have the special requirements been followed in developing the proposal, e.g., page limits, team structure, study designs, etc.?
- Are the proposed specific aims achievable in the given time frame?
- Have collaborations been established and are partners on board?
- Has a contact PI been identified for multi-PI proposals and communication and management plans developed?

NCI EDRN Team

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THANK YOU!

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