Early Detection Research Network (EDRN)
A National <u>Program</u> for Cancer Biomarker Development

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On behalf of Division of Cancer Prevention
and the EDRN Team

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NIH NATIONAL CANCER INSTITUTE

EDRN Program Objectives

EDRN (2000-) has established an infrastructure to:

- Support investigator-initiated research for the development and validation of biomarkers for early detection and progression;

- Foster interaction and cooperation between academic, clinical, and industrial leaders;

- Establish and apply standardized biomarker validation criteria and quality assurance; and

- Facilitate regulatory process to bring biomarkers rapidly into clinical use.

EDRN is NCI's core program on biomarker discovery & early validation for screening/early detection of cancer.
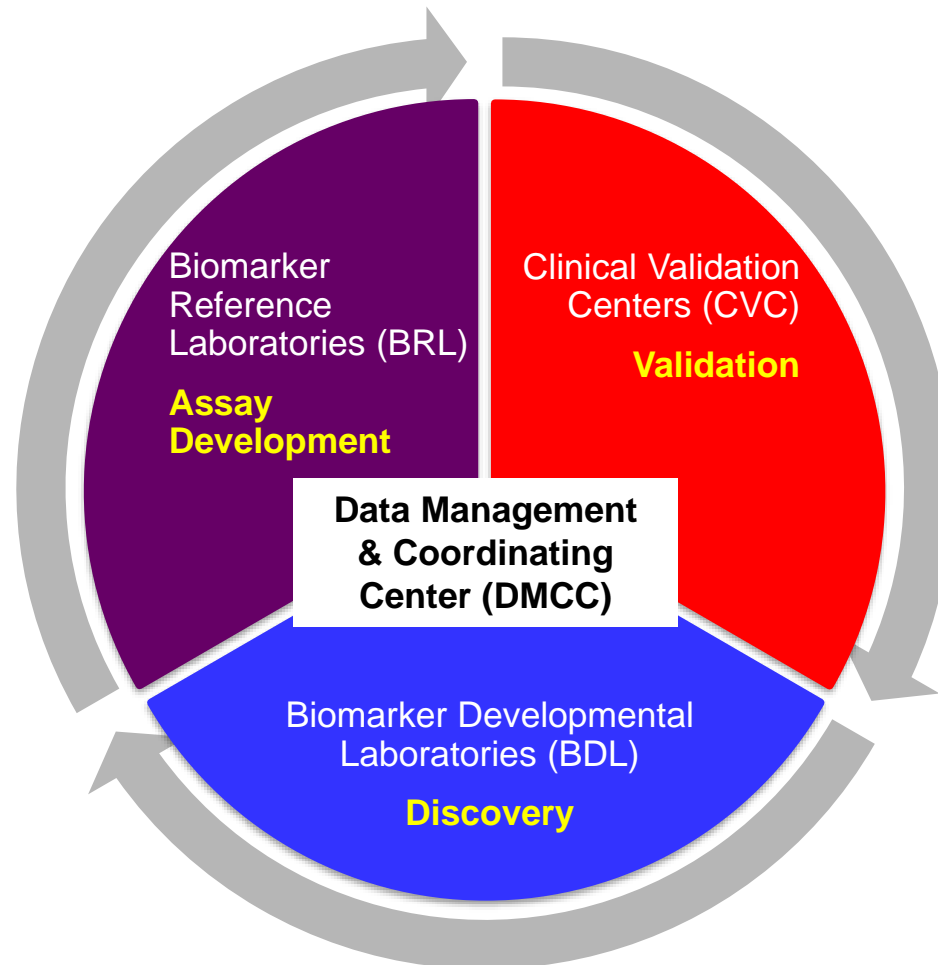
EDRN Organizational & Operational Structure

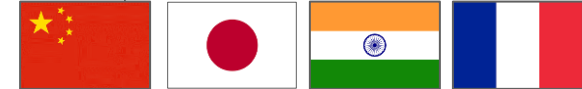**Network Consulting Team** ⟷ **Steering & Executive Committees**

Research Groups

➢ Prostate & Other Urologic

➢ Breast and Other Gynecologic

➢ Lung & Upper Aerodigestive

➢ Colon & Other GI

Biomarker Reference Laboratories (BRL)
Assay Development

Clinical Validation Centers (CVC)
Validation

Data Management & Coordinating Center (DMCC)

Biomarker Developmental Laboratories (BDL)
Discovery

EDRN Collaborations & Partners

- Parallel, EDRN-Advised Initiatives:

- **Co-funding** e.g., PanCAN, Canary Foundation, & Cancer Research UK

- **Independent, collaborative groups** e.g., Pancreatic Cancer Detection Consortium, Consortium for Imaging and Biomarkers, Human Tumor Atlas Network (Pre-Cancer Atlas), & Center for Global Health (NCI)

- **Associate Members (>350)**

- **Federal Partners** e.g., NIST, FDA, & Jet Propulsion Lab (JPL)

- **Pharma/Biotech Industry** (15 active)

BSA Subcommittee Review

- *"The subcommittee indicated concurrence with the one-time re-issuance…. stated that the concept was well-written, the documents were well-prepared, the external reviewers' report was excellent, and the progress and productivity of the program has been substantial…"*

- *"In particular, the subcommittee recommended that the validation trials include representation of diversity and inclusion; implementation science, and imaging and apply AI and machine learning. The subcommittee stated that strong consideration be given to increasing collaboration across institutions and biotech companies, nationally and internationally."*

BSA Subcommittee Review: Questions

- What is the return on investment? **(Slide 6 and 17 [Supplemental])**

- What EDRN-supported products/devices have had the greatest clinical impact? Which are being used in clinical practice? Are any of the Cooperative Groups using any of the EDRN resources and/or products? **(Slides 7-9, 11)**

- Since the last review, how many devices have been developed for non-diagnostic tests? **(Slide 12)**

- Does the NCI fund other mechanisms and/or programs that promote biomarker development, validation, and translation? **(Slides 3, 11)**

- What are considered the best examples of how this program has changed the practice of cancer prevention and clinical oncology outcomes? **(Slide 10 & 20 [Supplemental])**

- What are the best examples of biomarkers currently under development/evaluation by EDRN that are viewed as being highly transformative over the next 5 years? **(Slide 10)**

- What would the potential impact be if this program would no longer be funded? **(Slide 6 & 17 [Supplemental])**

- In the next funding period, what major shift in terms of priority and procedures is expected? (**Slide 13 & 23 [Supplemental]**)

Scientific Milestones: Return on Investment

- 8 FDA-approved (**3 in this cycle**) and19 CLIA-certified (**9 in this cycle**) tests;

- Clinical Reference Samples expanded on colon, pancreas, prostate, and uterine lavage;

- EDRN grants outperformed a comparable number of R01 grants that focused on biomarkers for early cancer detection in terms of*:

  - ➤ 32 vs. 1 patent

  - ➤ 19 vs. 0 CLIA-approved protocols/tests

  - ➤ 2,169 (>550 publications this cycle) vs. 1,149 publications; 850 vs. 494 with impact factor ≥7

- EDRN is a platform and coordination center for investigator-initiated, rigorous, unbiased research on biomarker discovery and validation.

Source: EDRN Quantitative Analysis of Productivity Report 10262020 Full Report Final; Analyses conducted by an independent contractor, ICF

Diagnostic Tests Being Used and Reimbursed

Test	Tissue	CPT Code	Offeror	PI	Remarks
PHI (proPSA) Test	Prostate	84153, 84154, 86316	ACCU Reference Laboratory, Mayo Clinic, Innovative Diagnostic Laboratory	Daniel Chan	Beckman
OVA1, Overa	Ovary	81503, 0003U	BCBS, CIGNA, CMS	Wei Zhang/Daniel Chan	2,700 physicians in the US ordering OVA1 or its reflex test (OVA1 followed by Overa/OVA2).
PCA3	Prostate	81313	Hologic/LynxDx/Mlabs/ other CLIA labs	Arul Chinnaiyan	----
MiPS	Prostate	0113U	MPS LynxDx/Mlabs	Arul Chinnaiyan	1,623 tests
ERG IHC U-M/other pathology CLIA labs across US	Prostate	88342/only IHC 88342	University of Michigan and Several CLIA laboratories across USA	Arul Chinnaiyan	IHC Interpretation (pro fee) CPT= 88321 >300 year just for U-M CLIA lab
DCP with AFP-L3	Liver	82107	LabCorp	Jorge Marrero	More than 1 million kits
DCP	Liver	83951	LabCorp	Jorge Marrero	
GP73	Liver		Not available in the US	Tim Block	China FDA Approved for Cirrhosis
ROMA (premenopausal)	Ovary	2012619, 69569-2	Fujirebio, LabCorp	Steve Skates	FDA Approved
ROMA (post-menopausal)	Ovary	2012620, 69570-0	Fujirebio, LabCorp	Steve Skates	FDA Approved
ROMA, HE4	Ovary	2012622	Fujirebio	Steve Skates	FDA Approved
ROMA, CA125	Ovary	2012622	FujiRebio	Steve Skates	FDA Approved

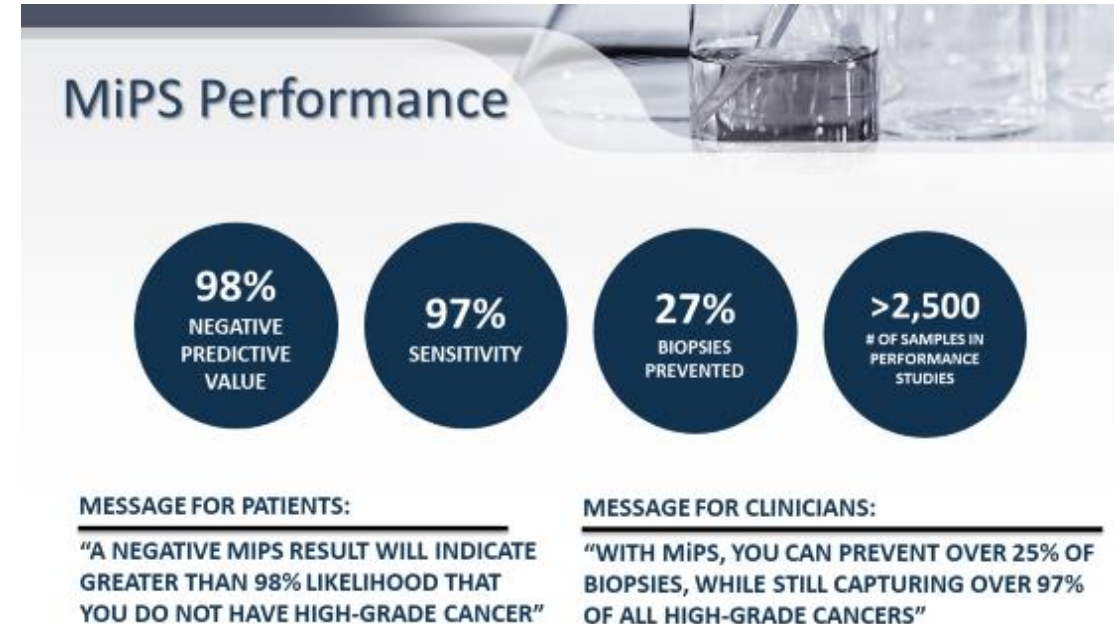# FDA-approved Tests with Significant Clinical Application

Two FDA-approved assays for determining risk of ovarian malignancy in women with an adnexal pelvic mass, who will be referred to a gynecologic oncology surgeon:

- OVA1/OVERA (5 analytes each) offered by Vermillion, Inc.
  2700 physicians in the US ordering OVA1 or its reflex test (OVA1 followed by Overa/OVA2)

- ROMA (2-analytes plus menopausal status) offered by Fujirebio, LabCorp.

FEMALE REPRODUCTIVE SYSTEM

OVARY

FALLOPIAN TUBE

UTERUS

CERVIX

VAGINA
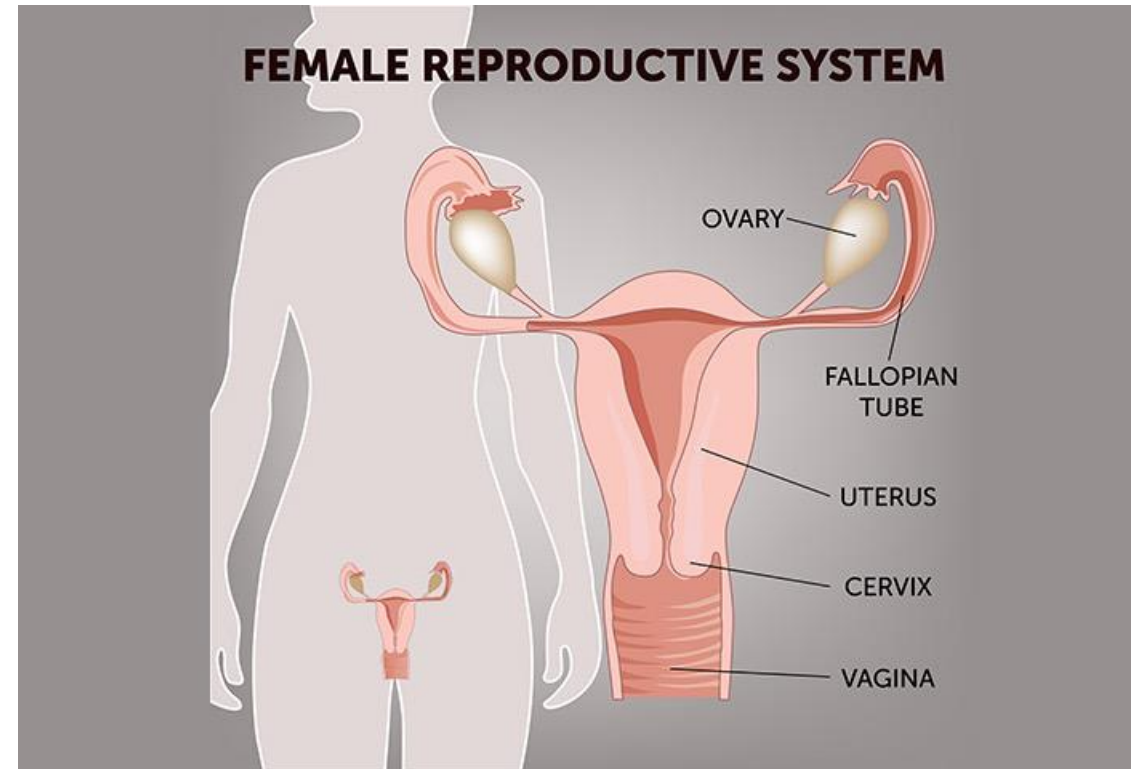
Diagnostic Tests Having Clinical Impact:
MiPS

- Mi-prostate score (MiPS), serum PSA, urinary PCA3, and urinary TMPRSS2:ERG, helps evaluate a patient's risk of having prostate cancer and the degree of its aggressiveness; it is usually performed after an abnormal PSA test and a digital rectal exam.

- This test has been shown to avert 27% of unnecessary biopsies. EDRN investigators have made significant contributions to its discovery and validation.

- More than 1,600 tests have been performed at LynxDX, a reference laboratory, to date.

MiPS Performance

98% NEGATIVE PREDICTIVE VALUE

97% SENSITIVITY

27% BIOPSIES PREVENTED

>2,500 # OF SAMPLES IN PERFORMANCE STUDIES

MESSAGE FOR PATIENTS:
"A NEGATIVE MIPS RESULT WILL INDICATE GREATER THAN 98% LIKELIHOOD THAT YOU DO NOT HAVE HIGH-GRADE CANCER"

MESSAGE FOR CLINICIANS:
"WITH MiPS, YOU CAN PREVENT OVER 25% OF BIOPSIES, WHILE STILL CAPTURING OVER 97% OF ALL HIGH-GRADE CANCERS"

EDRN-Supported Transformative Research and Its Impact on Clinical Practice

- EDRN findings inform ACS guidelines on early age screening for colon cancer (Sandy Markowitz)

- Blood-based biomarkers to screen for colorectal cancer with sensitivity and specificity comparable to FIT. The investigators and industry collaborators are in discussions with the FDA (Sandy Markowitz)

- Combining LDCT and biomarkers to better risk stratify patients in need of lung cancer screening (Avi Spira, Pierre Massion)

- Liquid biopsy test (Multi-Cancer Early Detection) – originated within EDRN (Ken Kinzler)

- Circular RNAs in Body Fluids – discovered as biomarkers through EDRN support (Arul Chinnaiyan)

EDRN Collaborative Community

Application for EDRN as an FDA Collaborative Community** is pending

- **Investigators funded through other mechanisms participate in EDRN:**
  - ➢ 2 SPOREs, 2 DOD Lung Programs, 4 CPTAC, 1 FDA, and >30 R01s and R21s;
  - ➢ Active collaborations with SPORE, ECOG (Pancreatic Cyst Surveillance Study), NCORP, and Diagnostic Companies; EDRN scientific workshops attract more than 400 participants.
  - ➢ EDRN Associate Membership Program (>350 members): a mechanism for non-EDRN investigators and industry partners to pre-validate/validate their biomarkers (e.g., via R01s).
- **Biospecimens:**
  - ➢ Reference Sets: Breast, Colon, Lung, Liver, Pancreas, Prostate, and Ovary; expansions of early-stage/precursor specimens via NCORP, Cancer Centers;
  - ➢ Provided to >75 non-EDRN investigators, mostly for R01 and industry research (http://edrn.nci.nih.gov/resources/sample-reference-sets)
- **Methodologies, Guidelines, and Novel Approaches (Next Slide)**
- **Technologies and Resources (e.g., informatics and data analytics with JPL)**
- **22 out of 26 funded grantees are from Major Comprehensive Cancer Centers**

***"a continuing forum in which private- and public-sector members, which can include the FDA, work together on medical device challenges to achieve common objectives and outcomes."*

Contributions Toward Non-Diagnostic Devices
Methodology, Approaches and Technologies for Wider Applications

- Melt-analysis of methylated DNA;

- Refinement of the Nucleic Acid-Programmable Protein Arrays (NAPPA) that contain glycosylated proteins;

- High-sensitivity reaction monitoring mass spectrometry-based assays to rapidly identify the most promising candidate biomarkers using single cells;

- Personalized oncology through integrative high-throughput sequencing (MiOncoSeq) to capture circular RNAs;

- Radiomics methods to detect early-stage cancers;

- Development of methods, data, and reference samples for liquid biopsy methods for cancer biomarker (RNA, DNA or proteins) present in extracellular vehicles (EVs) by the National Institute of Standard and Technology; and

- Development of reference materials and interlaboratory testing to improve the confidence in measurement of methylated DNA.

Priorities Going Forward

EDRN will work closely with the Pre-Cancer Atlas Centers of the Human Tumor Atlas Network to identify molecular targets, neoepitopes, neoantigens and other molecular and cellular features of the evolving precancerous lesions.

Other priorities in the next cycle, based on NCT recommendations, will include:

- Data science and artificial intelligence;

- Better integration of imaging and biomarkers;

- 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

EDRN Funding Request†

	Year 1	Year 2*	Year 3	Year 4	Year 5	Total
12 CVCs	$10.5M	$15.0 M	$15.0 M	$15.0 M	$15.0 M	$70.5.0 M
18 BCLs**	$9.5 M	$13.5 M	$13.5 M	$13.5 M	$13.5M	$63.5. M
1 DMCC	$3.0 M	$3.0 M	$3.0 M	$3.0M	$3.0 M	$15.0 M
CORE Fund	$4.2 M	$6.0 M	$6.0 M	$6.0 M	$6.0 M	$28.2 M
Total	$27.2 M	$37.5 M	$37.5M	$37.5 M	$37.5 M	$177.2 M

*Consortium collaborative projects will commence in Year 2

**Biomarker Development Labs (BDLs) and Biomarker Development Labs (BRLs) will be issued as a single FOA as Biomarker Characterization Laboratories (BCLs)

CVCs=Clinical Validation Centers; DMCC=Data Management and Coordinating Center

†Past budget of $25M per year; does **not** include mandatory 20% budget cut

Staggered to reflect the greater resources needed for a greater emphasis on validation (i.e., more clinical studies) and initiation of collaborations in Years 2-5 and limited remaining set-aside dollars in FY22 budget (Year 1)

Justification for Reissuance Request

- *EDRN's value and ROI is likely to increase from its already high ROI given the maturity of the infrastructure, potential to tackle even more complex questions, etc.;*

- Maintain collaborative, comprehensive **infrastructure** and resources critical for biomarker discovery and validation that does not exist without EDRN;

- Accelerate the development of biomarkers that will change practice – critical to the mission of the NCI;

- Ensure data **reproducibility and integrity**; negative findings are as important as positive ones; and

- Checks and balances for unsubstantiated claims and data reproducibility, **economy of scale** compared to individual efforts

Proposed budget increases will cover costs of 1) additional clinical utility studies; 2) more support for junior investigators; 3) increased investment in data analytics and modeling; 4) expanded research on radiomics and image analysis; and 5) increased accrual of under-represented populations

Actual programmatic costs are dependent on the number of meritorious awards

Thank You

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