Journal of the National Cancer Center 3 (2023) 93–99

Contents lists available at ScienceDirect

Journal of the National Cancer Center

journal homepage: www.elsevier.com/locate/jncc

Perspective

National Cancer Institute's early detection research network: a model organization for biomarker research

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ARTICLE INFO

Keywords:
Biomarkers
Early detection
Validation
Collaboration
Data sharing

ABSTRACT

For many cancers a primary cause of poor survival is that they are detected at a late stage when therapies are less effective. Although screening methods exist to detect some types of cancer at an early stage, there are currently no effective methods to screen for most types of cancer. Biomarkers have the potential to improve detection of early-stage cancers, risk stratification, and prediction of which pre-cancerous lesions are likely to progress and to make screening tests less invasive. Although thousands of research articles on biomarkers for early detection are published every year, few of these biomarkers have been validated and shown to be clinically useful. This reflects both the inherent difficulty in detecting early-stage cancers and a disconnect between the process of discovering biomarkers and their use in the clinic. To overcome this limitation the US National Cancer Institute created the Early Detection Research Network. It is a highly collaborative program that brings together biomarker discoverers, assay developers, and clinicians. It provides an infrastructure that is essential for developing and validating biomarkers and imaging methods for early cancer detection and has successfully completed several multicenter validation studies.

1. Introduction

For many cancers, treatment of an early-stage cancer results in a better outcome than treatment of a later stage cancer.[1] For example, the five-year survival for stage I colorectal cancer is 80–95%, but less than 15% when detected at stage IV. Fortunately, there are currently several methods available to screen for and detect early-stage colorectal cancer. Similarly, the 5-year survival for resectable stage IA pancreatic cancer is about 85%, but less than 10% when detected at a later stage.[2] Unfortunately, only about 15% of pancreatic cancers are detected at an early-stage, and unlike for colorectal cancer, there are currently no methods to screen for pancreatic cancer.

Currently, biomarkers or imaging methods to screen for early-stage cancers exist for several types of cancer (What cancer screening tests check for cancer? - NCI).

- Colorectal cancer: fecal occult blood test (FOBT), fecal immunochemical test (FIT), FIT plus stool DNA (Cologuard) and colonoscopy; ages 45–75.
- Hepatocellular carcinoma: ultrasound with or without alpha-fetoprotein (AFP); patients with cirrhosis.
- Lung cancer: low dose computed tomography (LDCT); 50–80 years of age with ≥20 pack years smoking and who are currently a smoker or have quit smoking within the past 15 years.
- Breast cancer: mammography (x-ray); women ages 40–74.
- Cervical cancer: pap smear (cytology) and human papilloma virus (HPV) DNA test; women ages 21–65.
- Prostate cancer: prostate specific antigen (PSA); men ages 55–69.

A critical criterion for a biomarker or imaging test to be used for cancer screening is that their use results in a reduction in cancer mortality. Unfortunately, for many cancers there are no biomarkers or imaging methods with sufficient accuracy to be used for screening or for the detection of early-stage cancers. Consequently, there is a significant need for biomarkers and/or imaging methods both to screen cancers where currently no screening method exists and for those cancers where the currently available biomarkers do not have sufficient accuracy. For example, the current biomarker for the diagnosis of pancreatic cancer is the serum marker, CA 19-9. In an asymptomatic population, this biomarker has a positive predictive value for pancreatic cancer below one percent, and screening for pancreatic cancer in an average risk population is not recommended. It is currently recommended to limit surveillance to those patients with a hereditary predisposition to pancreatic cancer using annual imaging of the pancreas with either endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI). Prostate-specific antigen (PSA) is frequently used to screen for prostate cancer. After review of available data, the U.S. Preventive Services Task Force (USPST) concluded that evidence from randomized clinical trials shows that PSA-

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https://doi.org/10.1016/j.jncc.2023.05.002
Received 13 January 2023; Received in revised form 26 April 2023; Accepted 8 May 2023

based screening programs may prevent approximately 1.3 deaths from prostate cancer per 1000 men screened and prevent approximately 3 cases of metastatic prostate cancer per 1000 men. However, fewer than one in four men with elevated serum PSA harbor clinically significant cancer. These men are directed to prostate needle biopsy, which results in excess morbidity,[3] and biomarkers are being developed and tested to determine which men with elevated PSA need to have a biopsy.

2. It takes a village: collaboration is essential for the development of clinically useful biomarkers

Solutions to grand challenges in science often require collaborations amongst many stakeholders.[4] Unfortunately, people often work in silos, which inhibits progress, and results are frequently not generalizable. The health care industry, while accounting for more than 18% of the U.S. gross domestic product and growing at triple the rate of inflation, remains a fragmented industry. In contrast, computer chip developers, where "big science" is always part of the equation, follow a collaborative business model that drives translation from "art to part". Health care organizations have generally grown organically, which typically results in structures that are organized along functional "silos", i.e., in areas of expertise where depth of knowledge in one area is critical. Such a "horizontal" structure fosters excellent solutions for primary scientific problems. However, it often generates barriers if knowledge must be shared between silos. In contrast, computer chip manufacturers are organized in a more "vertical" structure. In this structure, formal "hand-off" procedures have been designed to ensure that discoveries in one aspect of chip design and construction are rapidly and efficiently conveyed to others who require the information. This allows for rapid vetting of ideas, quickly culling out the poor concepts and fostering the rapid acceptance of good concepts.

Developing biomarkers for early cancer detection that can be used in the clinic involves a rigorous process that begins with discovery and leads to development, validation, and finally clinical application. The success of this process requires the expertise of basic scientists, population scientists, and physician scientists with expertise in clinical applications and a dedicated infrastructure to facilitate coordination amongst these diverse scientists and collaborations with academic institutions and industries. These collaborations are usually based on specific needs and leverage various types of expertise. The U.S. National Cancer Institute's Cancer Biomarkers Research Group (CBRG) has established several networks or consortia that incorporate these collaborative principles to discover and validate biomarkers and imaging methods to improve early cancer detection and to move biomarkers into clinical practice. These consortia include:

Early Detection Network (EDRN): Discovers, develops and validates biomarkers and imaging methods to detect early-stage cancers and to assess risk for developing cancer, and to translate these biomarkers and imaging methods into clinical tests. (Early Detection Research Network (EDRN) | Division of Cancer Prevention)

Translational Liver Cancer Consortium (TLC): Conducts studies to improve the surveillance of liver cancer in high-risk populations, increase the fraction of liver cancer detected at an early stage, and better stratify patients at risk of developing liver cancer. (Translational Liver Cancer (TLC) Consortium | Division of Cancer Prevention)

Pancreatic Cancer Detection Consortium (PCDC): Develops and tests new molecular and imaging biomarkers to detect early-stage pancreatic ductal adenocarcinoma (PDAC) and its precursor lesions. These biomarkers would be used to identify individuals who are at high risk of developing PDAC and are candidates for early intervention. (Pancreatic Cancer Detection Consortium (PCDC) | Division of Cancer Prevention)

Liquid Biopsy Consortium (LBC): An Academic/Industrial Partnership program designed to develop and advance liquid biopsy technologies specifically targeted for early-stage cancer detection. Liquid biopsy uses body fluids such as blood, urine, saliva, stool, and sputum from patients suspected to have early-stage cancer as well as those at high risk of developing cancer. (Liquid Biopsy Consortium | Division of Cancer Prevention)

Networks or consortia that support successful collaborations have similar properties and characteristics, including (1) clearly defined and agreed upon mission and goals, (2) specified roles for members and subgroups, (3) strong and engaged leadership, (4) effective communication, (5) funds to support collaborative projects, (6) willingness to share expertise and commitment to work with other investigators, and (7) development of shared resources. National Cancer Institute (NCI)'s EDRN serves as a model for the conduct of collaborative, translational research.[5]

EDRN serves as a hub for other networks and programs that conduct research to discover and develop biomarkers for specific cancers, e.g., pancreatic and liver cancers, to enrich the pipeline of biomarkers for EDRN to validate and for other programs that develop technologies to improve early detection, e.g., imaging, and liquid biopsies (Fig. 1). In addition, a number of external partners, i.e., government institutions, philanthropic institutions, and international institutions, actively participate in EDRN activities. These include:

- *Jet Propulsion Laboratory (JPL)* supports EDRN informatics.
- *National Institute of Standards and Technology (NIST)* assists in the development of standards (including miRNA and ctDNA) and reference materials.
- *Pacific Northwest National Laboratory (PNNL)* supports the development of proteomic-based assays using high-sensitivity reaction monitoring mass spectrometry to rapidly identify the most promising candidate biomarkers.
- *Department of Defense's Center for Prostate Disease Research (CPDR)* assists in the development of specific monoclonal antibodies and provides valuable biospecimens collected from subjects with prostatic diseases with high representation of African Americans.
- *Japan Agency for Medical Research and Development (AMED)* (Overview | Japan Agency for Medical Research and Development (amed.go.jp)) holds joint scientific workshops with the EDRN.
- *Pancreatic Cancer Action Network (PanCan)* (Pancreatic Cancer Action Network – Research, Patient Support, Resources (pancan.org) collaborates with EDRN investigators on the early detection of pancreatic cancer.

3. EDRN: a vertical model for biomarker discovery and validation

3.1. Clearly defined mission

Without a defined mission and set of goals that all consortia members understand and agree with, individual members are likely to pursue their own interests and be less willing to share resources and participate in collaborative projects.

The overarching goal of the EDRN is to help reduce cancer morbidity and mortality by conducting research to discover, develop, and validate biomarkers and imaging methods to detect early-stage cancers and to translate these biomarkers and imaging methods into clinical tests. All EDRN investigators, who are funded by cooperative agreement awards from the NCI, are committed to achieving these goals.

3.2. Responsibility and accountability

Clearly defining the roles of each member of a consortia ensures that all participating members know what is expected of them and what they need to do to ensure that the mission and goals of the consortia are achieved. By defining the roles of individual members and subgroups, each member knows how they can use their expertise and resources to contribute to the success of the collaborative projects.

The development of a clinically useful biomarker for early cancer detection is a multistep process that begins with discovery, followed by

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
- Consortium on Translational Research for Liver Cancer (CRRLC)
- Pancreatic Cancer Detection Consortium (PCDC)
- Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC)
- Pre-Cancer Atlas (PCA)

Inter-Agency Agreements (IAA)

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

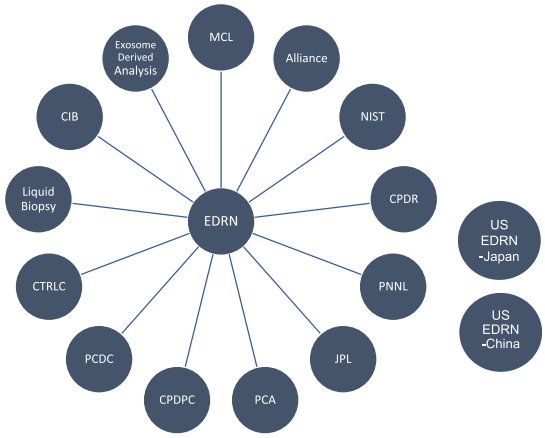

Fig. 1. EDRN functions a hub for related programs and networks. Over the years, the NCI's cancer biomarkers research branch has established a number of discovery-oriented research programs to enrich the biomarkers pipeleine to be considered for a large validation study. In this regard, EDRN serves a hub to several of these sister programs as illustrated in Fig. 1. EDRN, Early Detection Research Network.

development of a rigorous and reproducible assay, validation of the ability of the biomarker to accurately detect early-stage cancers and finally demonstration that their use has a positive effect on patient outcomes. This requires participation by investigators with a variety of expertise who are willing to perform one or more of these tasks and be willing to hand off the biomarker to investigators with different expertise.

The EDRN provides an infrastructure that fosters translational research by encouraging collaborations among basic scientists, population scientists, and physicians. Essential features of EDRN which help ensure its success include, (1) a coordinated process for discovering, developing, and validating biomarkers, (2) collaboration and resource sharing among institutions and investigators, and (3) active participation by basic scientists, assay developers and clinicians. Each EDRN laboratory or center is funded by a cooperative agreement award from the NCI. EDRN has three structural components (Biomarker Characterization Centers, Clinical Validation Centers, and a Data Management and Coordinating Center) with distinct but complementary roles that are integrated to facilitate the discovery and validation of cancer biomarkers and imaging methods. Every EDRN investigator is a member of one of these components (Fig. 2).

Biomarker Characterization Centers (BCCs): Each BCC has two functional components (1) a Biomarker Developmental Laboratory (BDL), which discovers, develops, characterizes and tests new biomarkers or refines existing biomarkers, and (2) a Biomarker Reference Laboratory (BRL), which develops, refines and/or standardizes biomarker assays and provides resources and support for the validation of biomarkers developed by the EDRN. BCCs participate in collaborative projects with other laboratories and centers.

Clinical Validation Centers (CVCs): CVCs conduct research to validate biomarkers and/or imaging methods for risk assessment and detection of early-stage cancers. CVCs serve as resource centers for collaborative research within the EDRN by partnering with BCCs to provide high-quality specimens for biomarker refinement studies, as well as collaborating with other CVCs, BCCs and the DMCC for conducting network collaborative biomarker validation studies. The CVCs have the expertise and ability to conduct clinical utility trials of validated early detection biomarkers and/or imaging methods.

Data Management and Coordinating Center (DMCC): One of the major roles of the DMCC is to work with the CVCs to conduct validation studies. The DMCC assists with protocol design, monitors the validation studies, and maintains the data and biospecimen tracking system. The DMCC is responsible for analyzing the results of the trials, thereby reducing bias as they are independent from the laboratories that discovered the biomarkers.

Oversight committee: EDRN steering committee (SC) provides oversight of organizational operations, scientific research, and collaborations amongst the centers. SC is composed of all the EDRN principal investigators (PIs) and is responsible for overseeing the activities of EDRN and setting priorities. The SC meets in person twice a year. The executive committee, which consists of the chair and co-chair of the SC, chairs of the collaborative groups, and NCI project coordinator, have monthly conference calls.

Bringing stakeholders together: Within the EDRN there are four organ-specific collaborative groups—breast and gynecologic cancers, colorectal and other gastrointestinal cancers, lung and upper aerodigestive cancers, and prostate and other urologic cancers. Collaborative groups are an important aspect of the EDRN structure. These EDRN groups are organized around specific cancer types, and all EDRN PIs, co-investigators and many associate members are members of one or more of these collaborative groups. They have monthly conference calls and meet twice a year in person to update each other on their progress and to develop collaborative projects that use the resources of all the investigators. These projects frequently involve comparing the performance of biomarkers from different laboratories in a common set of biospecimens and when appropriate combining these biomarkers to create a panel.

3.3. Strong and effective leadership

An essential element for successful collaborative projects or consortia is strong and effective leadership. Without strong and active leadership, projects are likely to go uncompleted, miss critical deadlines or lose focus and have investigators more interested in their individual research than the agreed upon collaborative goals. The EDRN has two sources of leadership, the chairs and co-chairs of the EDRN SC and Collaborative Groups and the NCI project coordinator that work synergistically to ensure the EDRN achieves its mission.

The chair and co-chair of the SC are elected by the EDRN SC. They provide overall leadership, help set overall goals, monitor progress on collaborative projects and review requests to initiate new projects and validation trials. Chairs of the four collaborative groups are elected by the members of the groups. They monitor progress on collaborative projects being conducted by the collaborative group and lead the development and initiation of new collaborative projects. The NCI project coordinator, assisted by other NCI Program Officials, is responsible for the

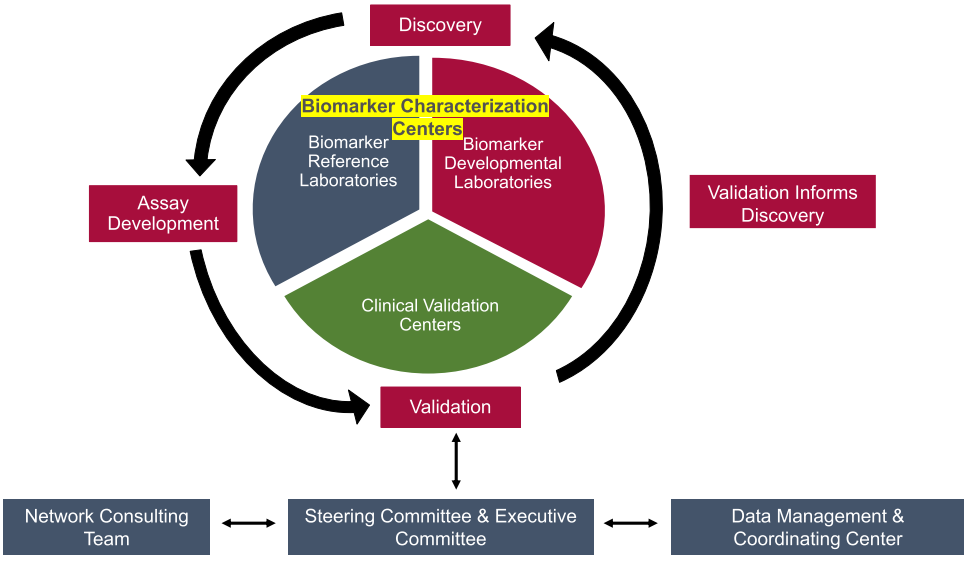

Fig. 2. Organizational structure of the Early Detection Research Network (EDRN). EDRN has three functional units: (1) Biomarker Characterization Centers (BCCs), each of which has two components—a Biomarker Developmental Laboratory (BDL) and a Biomarker Reference Laboratory (BRL); (2) Clinical Validation Centers (CVCs); and (3) a Data Management and Coordinating Center (DMCC). BCC and CVC are highly integrated components and dependent on each other's expertise and resources requiring the paring of at least one CVC with BCCs. There are two oversight committees: EDRN steering committee, which is composed of EDRN principal investigators and a network consulting team, which is composed of independent investigators who provide advice to EDRN on scientific directions. The workflow is shown by directional arrows. Discoveries from BDL are handed over to a BRL for assay development and verification and then handed over to an appropriate CVC to conduct a large validation study.

overall coordination of the network, oversight of collaborative projects, and ensures that the network is meeting NCI's expectations.

3.4. *Effective communication*

For any collaborative consortia or network to function effectively, there must be an established communication plan and mechanisms for individual members to discuss the status of projects, resolve issues, and plan future projects. The EDRN infrastructure is designed to foster communication. This includes the monthly Collaborative Group calls, the bi-annual SC meetings and the monthly executive committee calls.

EDRN has both a public and a secure website to facilitate communication both within the EDRN and with non-EDRN investigators and patient advocates. The public website (edrn.nci.nih.gov) contains information on EDRN's biomarker database, biospecimen reference sets, research tools, informatics tools, common data elements, study protocols, status of current research, and upcoming meetings.

The EDRN secure website contains information on EDRN investigator's research interests so that they can be identified by other EDRN members looking for potential collaborators. EDRN investigators enter data on project protocols, biospecimen collections, and progress on their research projects. This information can be accessed by other EDRN investigators.

3.5. *Innovative mechanisms for collaborative projects*

The EDRN has two innovative funding mechanisms (set-aside and core funds) to drive collaboration within the EDRN and with investigators outside of the EDRN.

Set-aside funds: EDRN cooperative agreement awards include funds that can only be used for new team and other collaborative projects that take advantage of the expertise, resources, and platforms of several different laboratories or centers. These funds account for thirty percent of EDRN investigators' awards. Requests for the use of set-aside funds are reviewed by the EDRN SC and the release of the funds is contingent upon the advice of the EDRN leadership and authorization by the NCI. Set-aside funds have been used to support projects that compare the performance of biomarkers developed in multiple EDRN and non-EDRN laboratories using a common set of biospecimens. The results of these studies are used to identify which biomarker or combination of biomarkers should be moved forward to validation. Set-aside funds have also been used for a biomarker discovery technique developed for one type of cancer to be used to discover biomarkers in another type of cancer.

Core funds: These funds are used to support post-award projects. They are used primarily to support large multi-center biomarker validation studies that involve patient accrual, biospecimen collections, and assays of defined biomarkers. Core Funds are also used to support the collection of biospecimens from multiple centers (both EDRN and non-EDRN) to be used for future biomarker verification and validation. Applications for these funds are reviewed by the appropriate collaborative group and the EDRN SC. The EDRN executive committee then recommends to NCI which project should be funded. The final decision rests with the NCI.

3.6. *Shared expertise and commitment to work with other investigators*

The success of collaborative projects in EDRN, especially those supported by set-aside and core funds, depends on the expertise and commitment of multiple investigators with different expertise. Frequently, these projects include investigators from BDLs, which provide the biomarkers, BRLs, which perform the assays, CVCs, which provide biospecimens, and the DMCC, which coordinates the project and analyzes the data.

Crucial to success of these projects is a dedicated lead PI, assisted by NCI staff. Biomarker validation trials and biospecimen collections involve multiple accrual sites. The lead PI needs to be in frequent contact with sites' PIs and other staff involved in patient accrual to ensure that accrual goals are being met. When the lead PI takes a more hands-off approach, accrual goals are not met, and the project fails.

3.7. *Development of shared resources*

EDRN biospecimen reference sets: To facilitate the rapid testing and verification of biomarkers developed both within and outside the network, EDRN has created 15 organ-based biospecimen reference sets.[6]

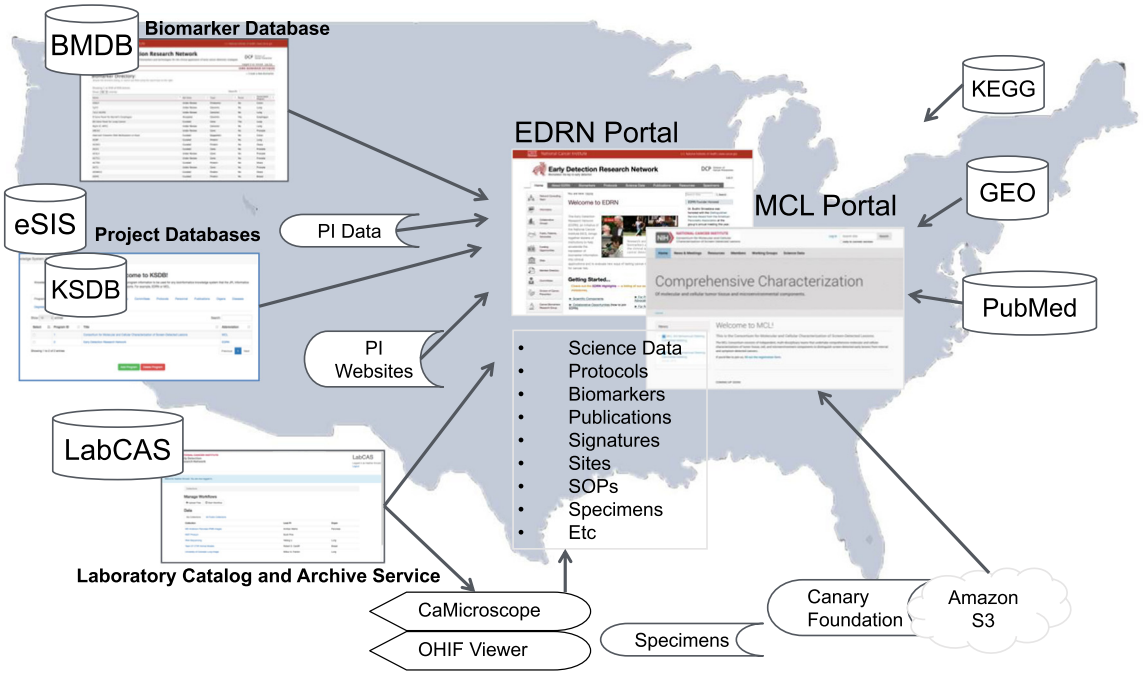

Fig. 3. EDRN knowledge system. This figure illustrates the integration of various modules within the EDRN knowledge system that is seamlessly accessible through the EDRN public portal. For example, if someone wants to query a biomarker by name, all of the associated properties of that biomarkers along with data and protocols will be displayed without any need to access an individual module. BMDB, Biomarker Data Base; CaMicroscope, an independently developed web-based module for biomedical image and data viewer, with strong emphasis for applications in cancer pathology; EDRN, Early Detection Research Network; eSIS, database of EDRN protocols; GEO, Gene Expression Omnibus; KEGG, Kyoto Encyclopedia of Genes and Genome; KSBD, Knowledge System Biomarker Database; LabCAS, Laboratory Catalog and Archive System; MCL Portal, Molecular and Cellular Characterization of Screen-Detected Lesions; OHIF, Open Health Imaging Foundation; PI, principal investigator; SOPs, standard operating procedures.

Multiple EDRN sites contribute specimens to these sets, which is critical as single sites rarely have a sufficient number of early-stage cancers. These sites use a common standard operation procedure to collect, process and store the biospecimens, and they collect clinical information on the subjects using common data elements. These sets are stored at NCI Frederick, which ensures their availability to the entire research community Specimen Reference Sets — Early Detection Research Network (nih.gov). They allow direct comparison and assessment of the performance characteristics of different platforms, as well as the performance characteristics of individual candidate biomarkers using the same specimens in a blinded fashion. For example, the EDRN pancreatic cancer reference set is comprised of serum and plasma samples from subjects with pancreatic cancer (n = 60 early stage and 40 late-stage cancers), chronic pancreatitis (n = 63), acute benign biliary obstruction (n = 31), and healthy controls (n = 61).

Also, in most instances when the EDRN undertakes a biomarker validation study, additional aliquots of specimens are collected to allow for the validation of future biomarkers. For example, biospecimens from a hepatocellular carcinoma (HCC) biomarker validation study were used to create a biospecimen validation set that contains specimens from 400 patients with HCC and 400 cirrhosis controls.[7]

Informatics infrastructure and data repository: In collaboration with NASA's Jet Propulsion Laboratory, EDRN has developed a novel informatics infrastructure (Fig. 3) and tools that permit interrogation of diverse databases.[8] This bioinformatics infrastructure is used to manage the large amounts of clinical and biological data generated by both EDRN and non-EDRN laboratories and centers. The EDRN knowledge system allows both EDRN and non-EDRN investigators secure access to the programmatic and scientific results of EDRN research. It provides seamless linking of the various modules of validation systems, including study protocols, biomarker database, data analytics, and visualization. The laboratory catalog archiving system is an infrastructure for both EDRN and non-EDRN investigators to securely capture, process, and disseminate data to other investigators.

4. Ongoing challenges

The EDRN, like other collaborative networks that conduct translational research, faces the following challenges:

- Academic culture—independence and individual achievement hallmarks of academic scientists, can be incompatible with the teamwork needed to successfully grow a vertically integrated organization. The push-pull of collaboration versus the requirements of academic scientists to individually excel creates stress among investigators. Within the EDRN, this type of stress impacts CVC and the BRL investigators disproportionately. While BDL investigators have frequent discoveries that they can report in high prestige journals, CVC and BRL investigators are frequently middle authors, a less prestigious position.
- Perception that translational research is less prestigious than basic research, which results in insufficient number of investigators pursuing careers in fields such as developing early detection biomarkers.
- Culture of industry—small companies are attracted to organizations such as the EDRN due to the availability of well annotated biospecimens. Unfortunately, not all companies understand the need for NCI to negotiate fairly and transparently. This can lead to significant negotiations that do not result in a formal agreement. There may not be an alternative to this issue, but it creates major problems for CVCs and other translational investigators.
- Communication among scientists with diverse backgrounds—biochemists, clinicians, epidemiologists and statisticians have different approaches to scientific inquiry and views

on importance of their respective disciplines. They often do not use the same language. The struggle to enable effective communication and mutual respect is a major one for any vertically integrated organization such as EDRN.
- "Going against the grain" of silo-oriented or horizontal research structures.

5. How does EDRN address these challenges?

EDRN's organizational structure helps manage and mitigate conflicts and barriers. It ensures that good science prevails without any pecuniary interest. Processes that EDRN employs to mitigate challenges include:

- Collaborative research projects: All members of an organ-based collaborative group participate in the development and conduct of collaborative research projects, which are supported by the set-aside funds in their awards. These projects frequently lead to joint publications in high impact journals, and the results used to apply for additional funding. Each of the four collaborative groups have developed a portfolio of products and technologies that can exploit the translational research resources of the group.
- EDRN executive committee: This committee, which consists of the chair and co-chair of the SC, chairs of the collaborative groups, and NCI project coordinator, reviews all proposed collaborative projects developed by the collaborative groups to ensure both the significance of the research proposed and equitable participation of all members of that group. This committee also reviews requests for the use of EDRN core funds to ensure that the best science is being supported and that the proposed research include the participation of as many EDRN investigators as possible.
- Scientific workshops: The EDRN sponsor workshops to educate investigators both within and outside of EDRN as to the imperatives of collaboration and on methods to resource, prioritize, and ultimately, grow a cohesive collaborative longitudinal research pipeline without destroying the individualism that characterizes excellence in scientific discovery.
- Encourage more investigators to enter the field of early detection: All EDRN BCCs include at least one early-stage investigator, and the EDRN has formed an early career investigators forum. The objective of this forum is to facilitate cross-exchange of knowledge, skills and experience in furthering biomarker science, cancer early detection, and data science.

The EDRN has overcome many of these obstacles by facilitating the development of a cadre of collaborative investigators who are committed to working together to move biomarkers from the laboratory to clinic.

6. Conclusions

In many aspects the EDRN is unique. There are no similar collaborative groups capable of supporting longitudinal research projects from basic discovery to validation to clinical studies. EDRN has the requisite expertise and resources to create an evidence-driven pipeline for developing cancer biomarkers with academic rather than commercial goals.

Unlike most other organizations, EDRN promotes a *"vertical approach"* for conducting biomarker research, whereby biomarkers are developed in the BDLs, refined and cross-validated by the BRLs, and validated in collaboration with the CVCs, all within one organization. EDRN follows an *adaptive model* in which all players work coordinately toward the goal of developing biomarkers for early cancer detection to ultimately improve health outcomes and decrease mortality.

The best evidence of the success of the collaborative approach adopted by the EDRN is its achievements.[5] To date, EDRN has prioritized 1675 biomarkers, completed more than 10 multisite validation studies, is currently conducting 15 biomarker and/or imaging validation studies, and made major contributions to 8 diagnostic cancer tests or devices that have been approved by the U.S. Food and Drug Administration (FDA) and 19 diagnostic tests that are available in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories. An example of an FDA approved device test developed by an EDRN investigator is EsoCheck, which allows patients to undergo a non-invasive five-minute office-based procedure to detect Barrett's Esophagus, which is a precursor lesion to esophageal cancer. This device was developed by Sanford Markowitz and is currently marketed by Lucid Diagnostics. The distal esophageal cells recovered by this approach are then assayed for 2 methylation markers, CCNA1 and vimentin, which are biomarkers highly associated with the presence of Barrett's Esophagus.[9] An example of a biomarker test developed by an EDRN investigator, which is available in a CLIA-certified laboratory, is MPS (MyProstateScore). The test measures two biomarkers in urine (T2-ERG and PCA3) and PSA in serum and is used to evaluate a patient's risk of prostate cancer and aggressive prostate cancer.[10] The higher the levels of these biomarkers, the more likely the patient has prostate cancer. The test is currently marketed by LynxDX.

Other significant accomplishments include:

- 954 biomarkers developed by the EDRN have moved forward for Phase 2 validation and 353 of these have moved forward to Phase 3 validation;
- More than 28 team-science projects on the verification and validation of biomarkers are ongoing; and
- 75 patents and more than 12 licenses have been developed, an indicator of the robustness of the biomarkers and the belief of diagnostic companies in their commercial potential.

EDRN investigators have made significant contributions to early cancer detection by obtaining patents, developing diagnostic tests that are available in CLIA certified laboratories, and contributions to FDA approved tests.

Declaration of competing interest

The authors declare that they have no conflict of interests. The opinions expressed by the authors are their own and this material should not be interpreted as representing the official viewpoint of the U.S. Department of Health and Human Services, the National Institutes of Health, or the National Cancer Institute.

Acknowledgement

The authors would like to thank the members of the Cancer Biomarkers Research Group, Division of Cancer Prevention, National Cancer Institute for their tireless efforts to support the Early Detection Research Network. Their participation has been essential to the success of the Network.

Author contributions

Both authors contributed to writing the manuscript, designed and prepared the figures and legends.

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