Early Detection Research Network (EDRN)'s Biomarker Characterization Centers (BCCs): Frequently Asked Questions (FAQs) on the BCC FOA RFA-CA-21-035; U2C – Clinical Trial Not allowed

To potential applicants: We appreciate your interest in the EDRN BCC FOA and hope that you and your team will choose to submit an application. To maximize your chances of success, we have provided answers to the questions that were submitted to the NCI Program via email and during the July 12 pre-application webinar, assuming that these questions could be of interest to many additional potential applicants. For additional questions or clarifications, we encourage you to contact the NCI scientific staff mentioned in the BCC FOA.

Q: What is the url for the EDRN website?
A: https://edrn.nci.nih.gov/

Q: Are the pre-application webinar slide decks available?
A: Slides and webinar recordings have been posted on the EDRN website.

Q: Are there opportunities for individual bioinformatics investigators (not part of EDRN centers) to apply directly to EDRN?
A: Individual bioinformatics investigators can apply to the EDRN to become an associate member. Please check the EDRN website for details on associate membership (https://edrn.nci.nih.gov/work-with-edrn/associate-membership-program). However, proposals that are solely based on bioinformatic or in silico analysis or mathematical, computational and statistical modeling are not supported by EDRN, and needs to include a plan to support discovery and/or validation of biomarkers using human biospecimens.

Q: What is the process for becoming an associate member?
A: The process to become an associate member is described on the EDRN website. There are 3 types of associate membership, also described on the website. Associate membership information can be found on the EDRN website: https://edrn.nci.nih.gov/work-with-edrn/associate-membership-program

Q: Is this FOA one time or will last multiple years?
A: The BCC FOA and the companion EDRN FOAs will allow one time submission of applications. Please check the application due date mentioned in the FOA. No revisions are allowed and there will be no additional application due date.

Q: Will pancreatic cancer be of interest to this FOA?
A: Pancreatic and liver cancers have not been included in the BCC scope. For biomarker discovery studies focused on pancreatic and liver cancer, please see the Pancreatic Cancer Detection Consortium (PCDC) and the Translational Liver Cancer (TLC) Consortium. The PCDC FOA will be published later this summer. However, you may note that EDRN provides an infrastructure for biomarker validation and is supportive of biomarker validation studies for pancreatic and liver cancers. Biomarkers discovered and/or pre-validated in the PCDC and TLC can enter the EDRN validation pipeline. For interest in validating biomarkers for pancreatic and liver cancers, applicants are encouraged to see the companion EDRN CVC FOA (RFA-CA-21-033). Information on the PCDC and TLC can be found at https://prevention.cancer.gov/major-programs/.

Q: Can international candidates apply for this RFA?

A: Yes, but they cannot be the Contact PD/PI. They can join as a MPI or Co-I.

Q: Can a BCC proposal be in the lung cancer field?
A: Yes, lung cancer is within the scope of the BCC FOA. EDRN is organ agnostic, except for the cancer types mentioned earlier (pancreatic and liver cancers) where applicants are encouraged to review the CVC FOA.

Q: Are GI cancers of interest to this FOA?
A: Yes, esophageal, gastric and colon cancers are of interest to the BCC FOA. See above for information on pancreatic and liver cancers.

Q: Which RFAs are focused on pancreatic cancer?
A: The PAR FOAs for Pancreatic Cancer Detection Consortium (PCDC) will be published later this summer.

Q: With respect to this requirement: "Are there plans for effective interaction and coordination with other Network units (i.e., CVCs, DMCC), the Steering Committee, and the NCI?" -- what is expected, and is stating "we will be delighted to interact" sufficient?
A: Some specific examples of the nature of collaborations and interactions the applicant can foresee will be helpful to provide, not just agreeing to interact. Examples of types of interactions with CVC and DMCC may include, but are not limited to, biospecimen selection, quality control, pre-validation and validation of biomarkers.

Q: Is it necessary for BDL and BRL labs to be CLIA/CAP accredited?
The CLIA/CAP part has always been mentioned in the context of BRL, and not BDL. BRLs are responsible for standardization and refinement etc. of clinical-grade assays, and CLIA certification/CAP accreditation is applicable to such functions. We prefer that the BRL component be CLIA certified/CAP accredited (both not needed) but didn't want to impose conditions that could be too stringent for some applicants that may have other strengths, hence we ask that the applicant at least has access to a CLIA/CAP lab. In such a case, the applicant should include the CLIA/CAP collaborator as a PI in the application and a letter of support will not be considered sufficient. It is also helpful when biomarker researchers generally adhere to the CLIA/CAP/GMP/GLP principles. This is because EDRN is a translational program and the objective is to maximize the bench-to-bedside potential of the assays/biomarker tests.

Q: Can the BRL be a foreign component and include a foreign CLIA-type lab?
A: It is better to have a domestic BRL component and a US CLIA/CAP lab to safeguard your application from any concerns raised during the review.
However, foreign components are allowed, and an applicant can partner with foreign institutions for the BDL component and strengthen the discovery approach.

Q: If a group partners with a Biotech company to use a specific platform (device/system) for assay screening and validation, does that limit the ability to participate in the EDRN-directed standardization/validation studies of other biomarkers?
A: No, one does not preclude the other.

Q: Is there a role for industry partners and should they be specifically assigned as Co-I or collaborator?
A: Yes, industry partners can play an important role. Early interactions with industry and research collaborations are likely to benefit both EDRN investigators and the industry partners. We leave it up to the investigators regarding how the industry partners participate in the proposal and be an MPI, Co-I or a collaborator. Some guidance has been provided in the FOA for partnership with for-profit sector, industry

or diagnostic companies which could be for biospecimens, reagents, protocols, assay development and/or refinement, technology, any other resources. Such partnership also allows sharing of precompetitive data on the applicant's proposed research to avoid competition and foster complementarity.

Q: Because of NIDCR participation (NOT-DE-21-005), are head and neck cancers a key focus?
A: Head and neck cancers are included in the scope of the FOA.

Q: How much preliminary data is needed?
A: This is not an R21 or an R01 mechanism. In case of BCC, the application will need to include substantial preliminary data. As mentioned in the FOA:

- "Demonstrate the current capability within the BDL for biomarker discovery/development using the proposed technology platforms.
- Demonstrate adequate scientific evidence from epidemiologic, model systems (cell culture, animal models) or clinical studies warranting success of the proposed study.
- For projects proposing a novel combination/integration of several technology platforms, provide appropriate preliminary data for each individual platform as well as the entire combined approach."

Q: Is EDRN interested in the development of new screening assays? For example, new biomarker interactions with synthetic receptors?
A: Yes. Synthetic receptors/synthetic biomarker research area is of interest, as mentioned in the BCC FOA. We are interested in applications that may propose designing synthetic receptors for recognizing specific cellular markers and enhancing detection levels and/or design of synthetic probes and reporters leading to shedding of biomarkers and amplifying signals that could be easily detectable in biofluids. Please note that therapeutic use/purpose is not within the scope of EDRN.

Q: Will BCC fund pan cancer screening?
A: Yes. The FOA states "Focus on individual tests for more than one cancer type or on one test for simultaneous detection of multiple cancers is acceptable." The project size may allow an applicant to start a pilot study. There are several biomarkers in the EDRN that could be used in a multi-cancer study.

Q: How much preliminary data is needed for a multi-cancer test?
A: The applicant will need to emphasize the performance characteristics for each of the specific markers for multi-cancer detection. The applicant will need strong analytical data for each of the markers and organ sites included in the study. A sample size justification will be needed and it needs to be weighted towards earlier stages as the focus of EDRN is on early detection of cancers.

Q: Can you clarify if applications for the detection of early cancers, but not the early detection premalignant lesions, are eligible for this initiative or for CVC?
A: This is debatable. Premalignant lesions may be indolent and may not lead to consequential cancers. For the BCC FOA, premalignant lesions with consequential clinical implications could be included. Early-stage cancers are ones that are amenable to treatment that can improve patient outcomes/survival. This is not a standard rule. Under this definition, early-stage cancer will depend on the cancer type being considered. A stage shift of cancer detection that can improve survival could be considered early stage. BCC includes discovery (phase 1), but can also include phase 2 biomarker development depending on what stage of discovery the study is at. CVC is focused on taking the biomarkers beyond phases 1 and 2. Any application that proposes phase 2 or 3 would require preliminary data to support pre-validation and validation studies. If your goal is discovery and assay development, then apply to BCC. If your goal is validation, then apply to CVC. Please see the FAQs for CVC as well.

Q: Are applications with multiple biomarkers at different stages of discovery, development, validation reviewed more favorably? That is, the more biomarkers with preliminary data, the better it is?
A: If someone is looking for multi-cancer detection, they can make a case for it, but if someone is looking for more biomarkers for a given cancer type, then they can make a case for improving the diagnostic performance. For example, many biomarkers can be added to an assay to improve the negative predictive value, but the applicant needs to be mindful of how they justify the inclusion of multiple biomarkers.

Q: Are biomarkers that predict future cancer risk (instead of occult existing cancer) responsive to this FOA?
A: Yes, biomarkers for risk prediction are very much within the scope of EDRN. However, new genome-wide association studies will be considered non-responsive, as stated in the FOA.

Q: Are junior investigators encouraged to apply for BCC funds? How are junior investigators defined?
A: We encourage that junior investigators be included in the BCC team. This is to train the next generation of biomarker researchers and give them the necessary exposure and learning experience. For the purpose of this FOA, junior investigators can include senior graduate students and/or postdoctoral fellows, including those who are on a path to becoming independent, and can also include assistant professors. As stated in the FOA "The BCC team must include early-stage/junior investigators, and describe briefly a plan for their professional development and/or training."

Q: Does an applicant need to already have a set of biomarkers? Will it be acceptable to propose to explore the discovery of new biomarkers?
A: Please note that this is different from R21/R01-type grant mechanism. In case of biomarker discovery within EDRN, there needs to be some indication that the applicant has worked on the proposed biomarker(s), may not necessary be for early detection or preliminary data may not be based on human specimens collected using SOPs, but these biomarkers could be tested and further developed in the context of early detection. Please review the references mentioned in the FOA for a phase-based biomarker development approach.

Q: Is there a list of current BCCs?
A: This is the first time BDL and BRL are being combined to form an integrated BCC. Therefore, we do not have any prior awards for the BCC. You can find previously funded BDLs and BRLs on the EDRN website (edrn.nci.nih.gov).

Q: Can a small-business company apply for this award? What is the difference between SBIR and this award?
A: Yes, they can. This is different than SBIR awards, but we strongly encourage moving SBIR-funded projects forward to the EDRN BCC or CVC.

Q: Can someone from a partnering company serve as an MPI?
A: Yes, they can.

Q: Would it be acceptable for multiple BCC applicants, i.e., BDL components from 3-4 sites propose to use the same BRL? If so, would it be acceptable for that single BRL to receive budget from each participating BCC site?
A: The BCC FOA states "An investigator designated as a Contact PD/PI of an application under this FOA must not be the designated Contact PD/PI of another application under this initiative or under any of the companion FOAs. The Contact PD/PI can be an MPI or Co-I on another application, whether for this FOA or its companion FOAs. An MPI on a BCC application may be an MPI or a Co-I on another application,

whether in response to this FOA or any of the companion FOAs." This allows some flexibility, but also has a caveat. Applicants need to avoid scenarios that can lead to budget reductions post award because of using the same BRL functions in different applications. Therefore, if one BRL team is providing service to multiple BCCs with same assay development capabilities, then we advise against it. However, if the different BCC U2C applicants have distinct BDL projects, say for example, using completely different technological platforms, and describing distinct assay capabilities for the BRL team without overlaps in functions among the applications, then that would be acceptable. Please note that overlaps in BRL components among applications will be identified during review and by the NCI, and budget reductions will be imposed post-award for those applications, if selected for funding.

Q: What if the applicant team has a blend of some biomarkers ready for validation and other biomarkers in an earlier stage of development, i.e., use of a known biomarker, for example, PET imaging tracer that has been validated in later stage disease now being applied to new platform in earlier stage disease.

A: For BCC applications, the main objective should be towards biomarkers at earlier stages of development. Biomarkers that are ready for validation are more appropriate for the CVC FOA. You want to be specific about that when proposing a BCC or a CVC. Two applications could be submitted as long as the Contact PD/PI are different in the BCC and CVC applications, as stated in the FOA. The applicant may note that a funded team can always propose new validation or discovery efforts post award as part of the collaborative studies.

For the imaging part of the question, if one is using a validated biomarker in comparison to an unknown entity, for example, if one is using imaging to improve the diagnostic performance of a validated biomarker, there is a separate NCI program called Cancer Imaging and Biomarkers (CIB). The CIB PAR FOA will be coming out later this summer. The CIB program does not support large validation studies. If you are proposing a validation study where molecular biomarkers are being integrated with imaging approaches to improve performance of tests, reduce false positive rates, and improve detection of clinically significant cancers, this is acceptable and within the CVC scope.

Q: Can imaging be the primary method for CVC?

A: Yes.

Q: Can imaging be the primary method for BCC?

A: Yes.

Q: Is it appropriate to use cohort samples from EDRN in the proposal to validate new biomarkers?

A: We do not have large cohorts within EDRN. There is a limited number of reference samples which are used to bring a biomarker forward or test a biomarker(s) performance after they have successfully completed phase 1 and phase 2.

Q: For pan cancer screening, is the proposal required to determine the cancer of origin, i.e., the location of the cancer.

A: The cancer of origin can be studied in different ways, for example, using MRI, PET or CT. This is something that the applicant needs to determine. Having a multi-cancer screening test without the cancer of origin would not be very helpful.

Q: Is it okay to submit BCC and CVC from the same institution?

A: Yes. As long as you do not have the same Contact PD/PI on both applications.

Q: Are there any preferred sample types for biomarker validation?

A: Early detection requires the use of non-invasive techniques and development of biomarkers using

bodily fluids (e.g., blood, urine, sputum) and easily accessible samples such as stool. This can be compared to ground truth, and may include biopsy samples, when the standard of care permits that.

Q: Does early detection of recurrence of 2nd tumor fit the FOA?
A: No, discovery and development of biomarkers using recurrence samples will not be supported by EDRN. Early detection of primary cancers is the main focus of EDRN and should be the major focus of all BCC applications. However, if an applicant would like to test the usefulness of the biomarkers in a recurrence setting, it can be a minor objective of the study. Please note that developing biomarkers for cancer recurrence is outside the scope of EDRN.

Q: How are these applications reviewed? Is it in standard study sections? BCC or BRL applications reviewed together?
A: BCC and BRL are not separate entities. A BCC application will include both BRL and BDL components, and will be reviewed as one application. BCC applications will be reviewed by a SEP (special emphasis panel). The CVC and DMCC will be reviewed by separate SEPs.

Q: Can we apply as an associate member and then apply to this FOA? Will the timeline for review as an applicant be conducted in time for this submission?
A: An applicant does not need to be an associate member to apply for the FOA. We are not accepting new associate members until after the applications are due.

Q: Are applicants allowed to have international (Canadian for example) MPI, Co-I and/or collaborators?
A: As mentioned earlier, the FOA allows foreign components, so international MPI, Co-I and/or collaborators are acceptable, but we discourage developing a foreign BRL component, as mentioned earlier. The Contact PD/PI also cannot be an international investigator and needs to be US based.

Q: Who are the EDRN program directors an applicant can contact for questions on different tumor types?
A: See https://prevention.cancer.gov/research-groups/cancer-biomarkers/staff
EDRN lead: Dr. Sudhir Srivastava
GU cancers: Drs. Jacob Kagan and Richard Mazurchuk
GI cancers: Drs. Matthew Young, Jo Ann Rinaudo, and Sharmistha Ghosh-Janjigian
Lung cancers: Drs. Lynn Sorbara and Karl Krueger
Breast and Ovarian cancers: Drs. Christos Patriotis and Sharmistha Ghosh-Janjigian
Head and Neck cancers: Drs. Wendy Wang and Karl Krueger
Q: What is the basic requirement of the overall size for a BCC? Are we allowed to propose one PI with two to three co-PI?
A: There is no specific requirement to have a certain number of PDs/PIs and or collaborations. However, it is encouraged that the BCC applicants are multi-PD/PI applications (could be a contact PD/PI and one MPI or 2 MPIs – this is up to the applicant) as the structure is multi-component in nature. We do not have any opinion on the structure of the team, i.e., completely internal or mix of internal and external. Collaboration is an important tenet of EDRN.

Q: May certain researchers (not only limited to PI and co-PI) take responsibilities in both BDL and BRL?
A: Contact PD/PI, other PDs/PIs, Co-Is, subcontract PIs etc. – all senior/key personnel tend to have substantial roles/responsibilities for the different components. How you wish to distribute the roles is

your call, but as mentioned in the FOA, one thing we require is the contact PD/PI of BCC be the main PI of the Admin Core.

Q: May BDL and BRL share research facility/ equipment?
A: Yes, but clinical grade assay development requires blinding of samples and those processes must be in place to avoid any conflict. Blinding may also involve statisticians from the EDRN Data Management Coordinating Center.

Q: We have been actively preparing to apply CLIA certification via CAP accreditation. Our plan is to get our CLIA certificate within 2 years. Will this be viewed as a weak position?
A: Per RFA, CLIA certification or CAP accreditation is a prerequisite.

Q: Will additional funds be viewed as a weak position?
A: No. On the contrary, external source of funding could be viewed as a strength as long as you clearly explain how the proposed research is complementary to your ongoing research and how you leverage additional resources to accelerate progress.

Q: What are the basic requirements for publishing research papers during executing the study?
A: Please review the NIH guidelines provided in the FOA.

Q: Are we allowed to keep our IP associated with the proposed study?
A: NIH policy states that "Inventions arising from federally funded research projects are required to be reported to the government agency that funded the project, per the Bayh-Dole Act (the Patent and Trademark Law Amendments Act). The Act permits businesses (large and small) and nonprofits (including universities) to retain ownership of the inventions made under federally funded research and contract programs, while also giving the government the license to practice the subject invention. In turn, the organizations are expected to file for patent protection and to ensure commercialization upon licensing for the benefit of public health. Read the regulations at Bayh-Dole Act (37 CFR 401)." Please also see the IP section in the FOA.

Q: Can indirect costs be included in addition to the direct costs? If so, what is the limit?
A: Yes, indirect costs can be included. The F&A charges vary among institutions, and also depends on the subcontracts. The main requirement is to not exceed the direct cost cappings for Year 1 and Years 2-5 mentioned in the FOA.

Q: Can the purchase of certain instruments/equipment be a part of the direct costs? If so, what are the restriction and limits?
A: It is expected that the applicants have resources to carry out the proposed research. Major capital improvements (equipment, facility, etc.) exceeding $5000 is not permissible.

Q: Does NCI-EDRN have good resources to use or recommend for acquisition of high-quality human samples, especially deidentified urine and whole blood/ serum from patients with early-stage cancers?
A: Applicants are required to identify their biospecimens sources. The FOA has some guidelines that you may review, but we do not direct applicants to EDRN biospecimens before they are funded, because even when EDRN has the necessary biospecimens, they are reserved for validation studies, not for initial biomarker development purposes.

Q: What are the regular sample sized recommended by NCI-EDRN for early-detection biomarker studies based on targeted omics for Phase I (preclinical exploratory), Phase II (clinical assay and validation) and Phase III (retrospective longitudinal) studies?
A: It depends on prevalence of the cancer types and how many markers/types of markers are included in the panel and what would be an adequate sample size to avoid overfitting. There is no simple/ straightforward answer to this question and applicants need to consult their own statisticians to come up with a solid study design.

Q: We will follow the "hypotheses – specific aims – milestones" style for the approach part of the study strategy/plan for both BDL and BRL cores, right?
A: Please follow the instructions and structure laid out in the FOA. The BDL and BRL cores have slightly different sub-sections, as you may have noted, and applicants are required to provide information on the requested sections.