RENEWAL

Precompetitive Collaboration on Liquid Biopsy for Early Cancer Assessment

RFA CA17-029

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Purpose

To seek your approval for the renewal of the **NCI Precompetitive Collaboration on Liquid Biopsy for Early Cancer Assessment (LBC)** initiative that was established in 2018 to address many of the challenges impeding progress in the implementation of liquid biopsy technologies in the ***early cancer detection*** space.

Support for Renewal Request

- Substantial progress toward developing technologies and associated adaptability toward clinical use (following slides)
- Strong endorsement from the External Program Evaluation Committee
  - Evaluators noted there was not enough time to evaluate the full potential of the consortium (2018 – present)
- Continuing research gaps remain (following slides)

External Program Evaluation

External Program Evaluation Committee Members: Meeting 12/6/2021

- **Chair**: Alan Pollack, MD, PhD - University of Miami
- Stephen Gould, PhD – Johns Hopkins University
- Angelo DeMarzo, MD, PhD – Johns Hopkins University
- Lance Liotta, MD, PhD – George Mason University

"We unanimously have concluded that the thoughtful and innovative structure of the program combined with the results of the partnership teams, has led to meaningful inter-team and Academic:Industrial collaborations. Significant advances toward the goal of much needed tests for early cancer detection and longitudinal assessment of response are in evidence."

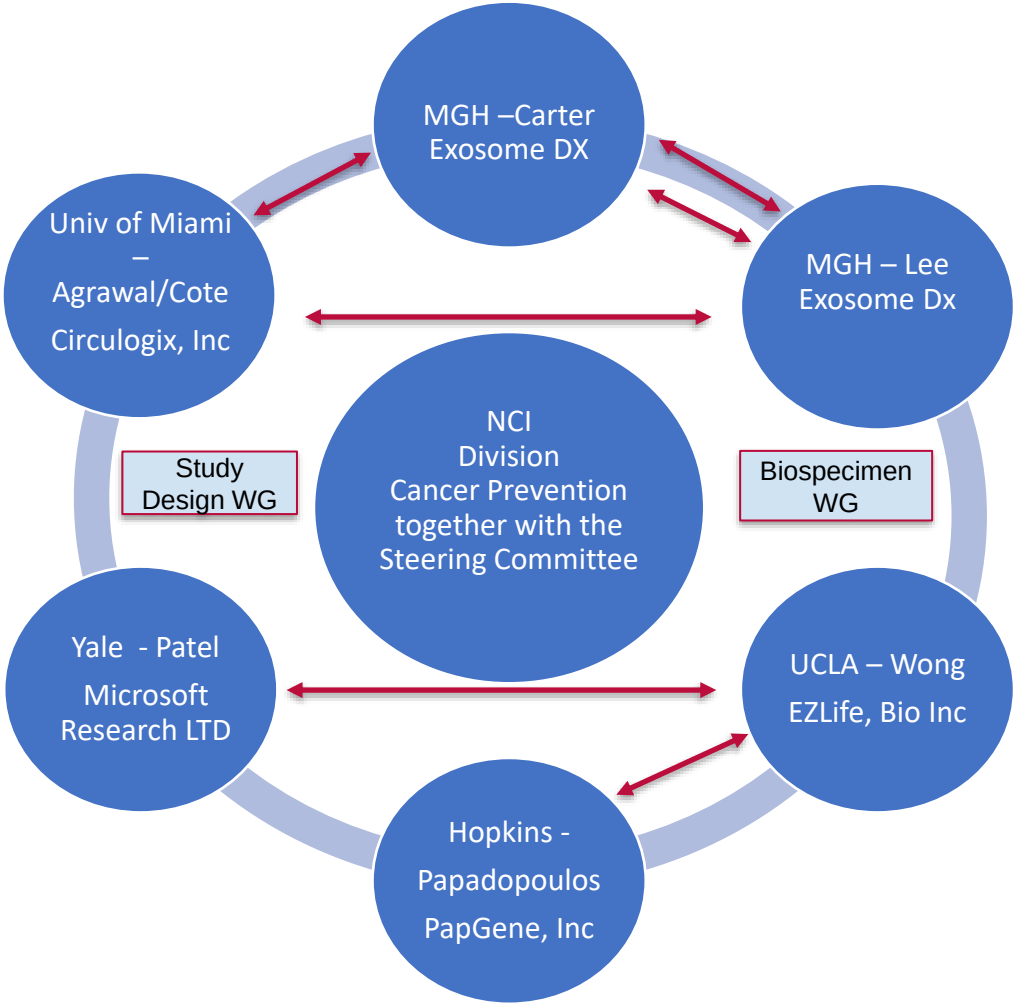
"We strongly recommend continued funding of the Liquid Biopsy Consortium."

Overview of the Current Program

- **Six "teams"** of academic and industry partners funded for the development or refinement of technologies/assays specifically for early cancer assessment.
- A **steering committee** and **working groups** were formed to guide/advise/assist in the study design and biospecimen accrual.
- **Model systems** utilized by the teams: lung, ovarian, breast cancers, and glioblastoma.
- A portion of funding was **"restricted"** (set-aside) for collaborative research within the consortium.
  - Collaborative studies - approved with the guidance of the steering committee.

LBC Structure and Synergy

Cross Laboratory Collaborative Projects



Major Accomplishments: Scientific Advances

- **The EFIRM technology (Electric Field-Induced Release and Measurement) can use 40-100 µL of saliva or plasma to detect somatic mutations in cfDNA for early lung cancer detection (academic: UCLA, industry: EZLife Bio, Inc.)**

- A new EV-assay platform, nPLEX **(**nanoplasmonic exosome), that can read out >100 EV proteins from a single sample load (academic MGH, industry : Exosome Diagnostics)

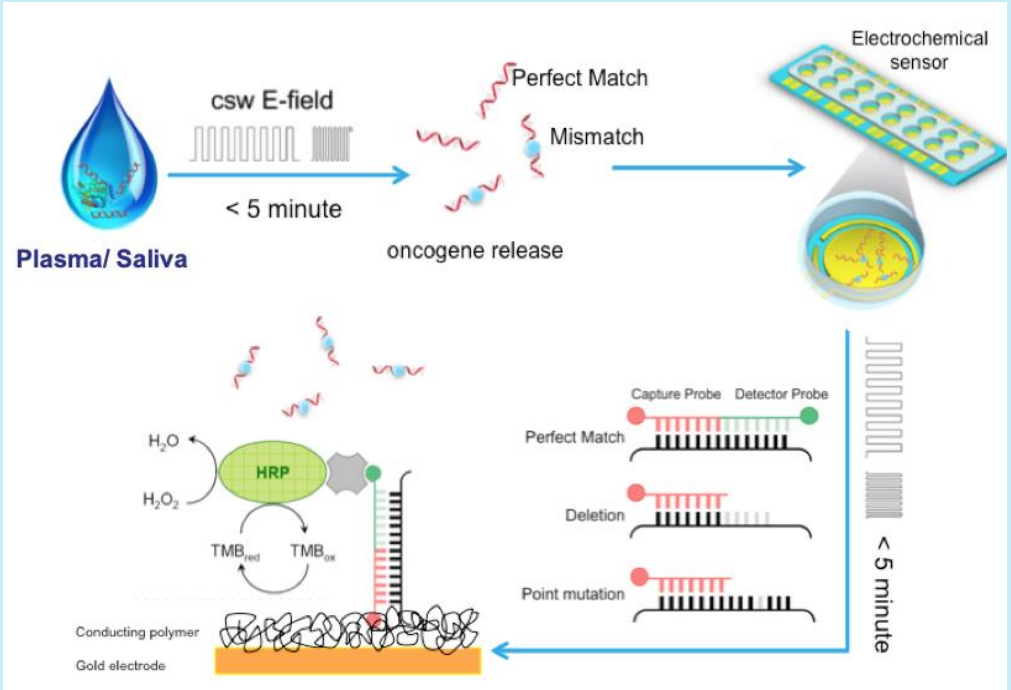
- A robust assay for medulloblastoma in CSF using a genome-wide aneuploidy score in saliva and stool (academic: MGH; industry: Exosome Diagnostics)

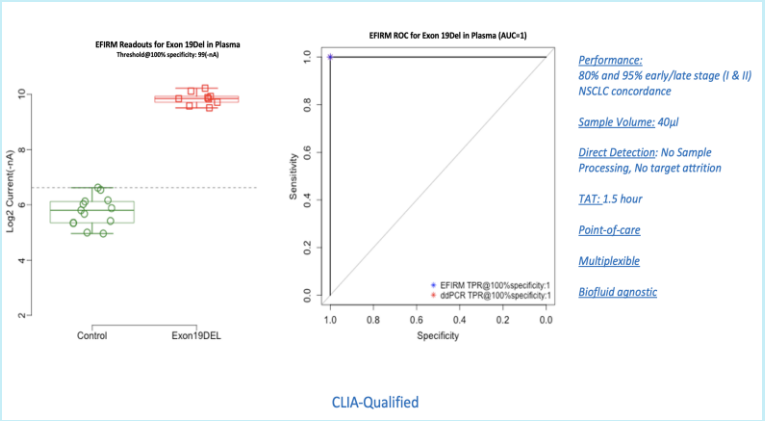
- Development of assays for detection of cancer-associated genome-wide methylation patterns in cfDNA for early lung cancer (academic: Yale; industry: Microsoft Research)

- Development of a unique imaging system using Fourier Ptychographic Microscopy for the capture and characterization of CTCs and circulating cancer-associated fibroblasts for a variety of cancer types (academic: Univ of Miami/WSU; industry: Circulogix and Google)

- **42 publications to date**

Example: eFIRM Technology for Lung Cancer Detection





Continuing Research Gaps for Liquid Biopsy In Early Cancer Assessment

Low Levels of Genetic Targets:

- **Low levels of mutant ctDNA** and other tumor associated circulating targets, requiring large volumes of blood/plasma;
- **Limit of Detection:** what level of the biomarkers must be present in blood?
- Low capture efficiency (ctDNA detection varies widely in patients with localized disease).
- **Issues with specificity, precision, accuracy**, etc.

Issues Regarding Cancer Biology and Screening:

- Approximately, 2/3 of all cancer deaths occur in cancers **outside of standard of care** screening.
- Is liquid biopsy representative of all the genetic clones of a tumor? Is there sample bias?

Data Sharing and Verification:

- Currently available technologies are **proprietary** and do not allow data sharing and verification
- Data sharing would empower inter-lab validation and verification
- **Developed algorithms** are a blackbox and does not permit federated modeling

Continuing and New Research Areas to Address Gaps

(1) **Expand the capacity** of the new liquid biopsy technologies/assays/methods; accurate assessment of **low variant allele frequency (<0.5%)** suitable for early-stage disease detection.

(2) **Validate** current and/or new technologies/assays in **different biofluids** in patients with early-stage disease or those at **high risk** of cancer. Include detection/screening for **multiple types of cancer** from a single blood draw.

(3) Untargeted (discovery) and targeted (quantification) identification of **protein-based analytes** for inclusion in liquid biopsy panels.

(4) Development of algorithms for **tissue of origin determinations**.

(5) Build on the established **Public-Private Partnerships infrastructure** to address the continuing challenges of LB technologies/assays

Justification for Use of RFA and Cooperative Agreement Mechanism

An RFA for a Cooperative Agreement Mechanism is requested as **substantial scientific and/or programmatic involvement by NCI staff** is required for the operation of this program and to leverage and collaborate with existing NCI programs, i.e., EDRN, TBEL as well as organizations/advocacy groups (BloodPAC) and gov't agencies (NIST).

The use of this mechanism is required to allow:

- The continuation of the already established collaborative infrastructure; formulated and accepted SOPs; and, accrued and shared biospecimens and other resources;

- For high quality applications that can meet the challenges of accuracy, precision, specificity, etc. of liquid biopsy and MCED assay development for common usage by allowing collaborations and further validation toward clinical implementation.

Rationale for Data Management and Coordinating Unit (DMCU)

Data Management and Coordinating Unit would:

- Be responsible for overall **data management, monitoring and communications** among all sites.
- Provide coordination for **cross-validation studies, blinding/unblinding and distribution of samples.**
- Develop **computational and ML/AI tools** for the analysis of complex data originating from multiple technology platforms.
- Develop **common data elements** (CDEs) for collection of physical, demographic and biospecimen data in a Data Commons for subject enrollment from all sites.
- **Educate** sites about applicable NIH/NCI policies on data sharing and reporting requirements.

Questions from the BSA Review Team that were Satisfactorily Answered by NCI Staff

(1) ✓How do you envision facilitating validation of findings and what is the mechanism to provide access to samples from impacted populations? *Completed and reviewed*

(2) ✓How are collaborations with industry established? Are there specific criteria that must be met to engage an industrial participant? *Completed and reviewed*

(3) ✓What new strategies will be utilized to facilitate the continuation of and/or establish new collaborations? *Completed and reviewed*

(4) ✓What steps are taken to engage and maintain collaborations? Specifically, how are the industrial partners evaluated, i.e., what are the criteria? How can the process be improved? *Completed and reviewed*

(5) ✓How does the set-aside budget process work and what portion of the budget is designated for set-aside? *Completed and reviewed*

Further Explanation to a BSA Question

(6) What is the process for accessing the virtual biorepository? What are the challenges that have been encountered with the sharing of biospecimens and what mechanisms and process are utilized to overcome those challenges?

- In 2019, the LBC consortium established an internal virtual biorepository of retrospective specimens that reside at the institutions of individual LBC sites and/or their collaborators.
- The virtual biorepository is supported with short term assistance from the Division of Cancer Prevention through the end of the current cycle of the consortium.
- Eventually, these samples will be transferred to the NCI Frederick biorepository for cataloging, storage, distribution and tracking.
- In the renewed LBC consortium, the DMCU will take on these responsibilities, among others, including the development of a policy for biospecimen sharing both with internal and external investigators.
- In the meantime, samples have already been shared among LBC investigators for their ‘bake off’ studies.

Current Portfolio Analysis

We conducted an NIH-wide and NCI-focused portfolio analysis on ***liquid biopsy technology development*** for FY 20 and FY21 together: $24 million

Of the total funds awarded by the NIH, the NCI awarded **42** of those grants in FY 2020 and FY 2021, with a total investment **of $10 million.**

LBC is included in this amount.

Requested Budget

Requested Budget for First Year:	$ 6.7 million
Total for Program (5 Years):	$33.5 million

- Liquid Biopsy Research and Development Sites (U01):
  6 (up to $1 M total cost per site per year)
- Data Management and Coordinating Unit (U24):
  1 (up to $700K total cost per year)

Thank you

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