Precompetitive Collaboration on Liquid Biopsy for Early Cancer Assessment

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What is Liquid Biopsy?

A test performed on a sample of blood to look for circulating cancer cells from a tumor, or for pieces of DNA from tumor cells. A liquid biopsy may be used to help find cancer at an early stage.

For our purposes in this initiative, it is not just CTCs but all tumor-associated circulating cells, nucleic acids, and extracellular vesicles in all biofluids.

Why Liquid Biopsy?

- Noninvasive methods of cancer detection are advantageous.
- Use of many biofluids (blood, urine, sputum, saliva, etc.).
- Signatures of patients' tumors can be now be characterized and can aid in understanding tumor biology as well as prove to be the best tool for early detection and monitoring of therapeutic response.
- To date, there are **no standards** for capture, characterization, and evaluation of liquid biopsy markers for use in the setting of **screening or early detection.**

Advantages of Liquid Biopsy

- Repeated longitudinal sampling is possible. With tissue biopsy, this is difficult or impossible to carry out.
- Technologies enable researchers and clinicians to employ a simple blood draw that will enable analysis of defined biomarkers.
- Less invasive and generally less risk to patients, especially those who are not candidates for invasive biopsy.
- Can be performed in the **screening setting**.

Purpose of this Initiative:

- Establish a Public-Private Partnership Program to develop new and/or validate existing technologies, methods, and assays for the capture and quantification of tumor associated cells, DNA, RNA, or exosomes in body fluids of patients with **early stage disease** or those at high risk.

- Develop precompetitive alliances with industry to harmonize and validate technologies, methods, and assays associated with liquid biopsies.

- Emphasis on:

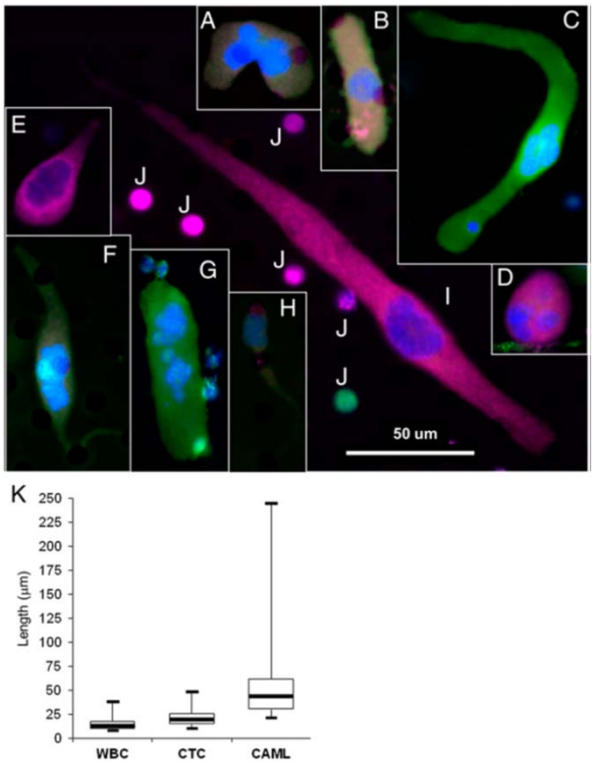
  - early cancer detection;
  - distinguishing benign disease from cancer;
  - distinguishing aggressive from nonaggressive cancers;
  - use with other classes of biomarkers to improve detection accuracy, reproducibility and predictability.

State-of-the-Science: Reach for the "HOLY GRAIL!"

- CTCs are used in monitoring minimal residual disease and therapeutic response; however, their use in **screening and early cancer detection** has been problematic.
- Recent studies identifying tumor-derived circulating endothelial cells *(1)* and circulating cancer-associated macrophage-like cells *(2)* hold promise as new targets for liquid biopsy analyses.
- Circulating tumor DNA (ctDNA) and circulating extracellular vesicles (exosomes) may overcome challenges posed by CTCs.

(1). Ref: Cima, et al, Sci Trans Med, (2016) 8(345): 345ra89
(2). Ref: Marks, et al, Cancer Epidemiol Biomarkers Prev (2016) 25(7):1037

Circulating Cancer-Associated Macrophage-like Cells CAMLs (3)

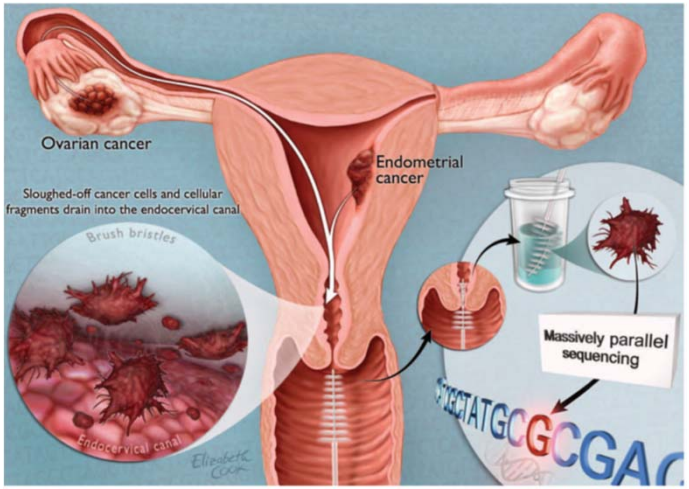


(A, F, and G) Pancreatic cells. (B, C, and D) breast cells. (E, H, and I) Prostate cells. (J) Typical WBCs. Morphology variants are as follows: amorphous (A), oblong (B and G), spindle-shaped (C, F, and I), round (D), and tadpole-shaped (E and H). Color differences result from varying degrees of staining for DAPI (blue), cytokeratins (green), EpCAM (red), and CD45 (violet)

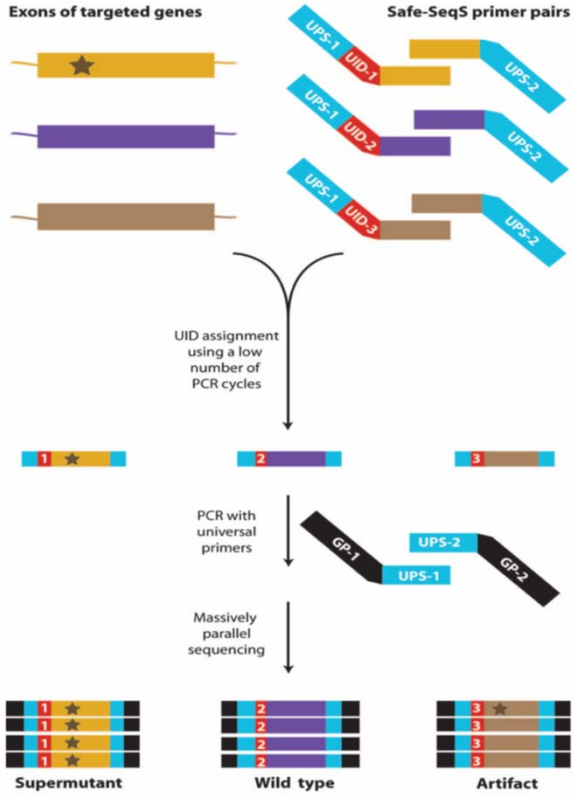
Whisker plot of cytoplasmic diameters showing diameters of WBCs, CTCs, and CAMLs (n = 75) from pooled prostate, breast, and pancreatic samples

(3) Adams, DL, et.al., PNAS (2014), 111:3510

Liquid Pap Smears (cervico-vaginal fluid) Capture and Sequencing of the DNA (4)



Detection:
Endometrial 100%
Ovarian 44%



Tumor cells shed from ovarian or endometrial cancers are carried into the endo-cervical canal. These cells can be captured by the brush used for performing a routine Pap smear. The brush contents are transferred into a liquid fixative, from which DNA is isolated. By means of massively parallel sequencing, this DNA is queried for mutations that indicate the presence of a malignancy in the female reproductive tract.

(4) Kinde, et. al., Sci Transl Med (2013) Jan. 9: 5(167)

Challenges: Technological and Biological

Low levels of genetic targets:

- Low levels of mutant ctDNA that is “diluted” with wild-type DNA; thus requiring large volumes of blood.
- Low capture efficiency (ctDNA detection varies from 49-78% in patients with localized disease).
- Issues with specificity.
- What is the clinically relevant fluid to sample?

Tumor heterogeneity:

- Is liquid biopsy representative of all the genetic clones of a tumor?
- Is there sample bias? (i.e., are all regions of the tumor the same?)
- What are the clinically relevant targets?

Liquid Biopsy Offers an Environment Suitable for Precompetitive Collaboration

- Opportunities for collaboration on data sharing, data integration and standards; results from the verification of a product and technology performance can be used to inform additional discovery efforts.

- Private sector will have opportunities to quickly improve their return on investment through collaboration on validating their technologies.

Why Precompetitive Collaboration?

- Precompetitive collaboration is a term used when competitors share early stages of research and development that are beneficial to all stakeholders.
- Pharmaceutical industry has employed this in the areas of standards, data, and processes to accelerate drug development.
- Accepted as a **driver** for improved efficiency, while simultaneously improving our understanding of increasing complexity.
- Efficient utilization and sharing of resources allows effective movement to market competition.

Scope: How does this Initiative Address these Challenges?

Encourage development:

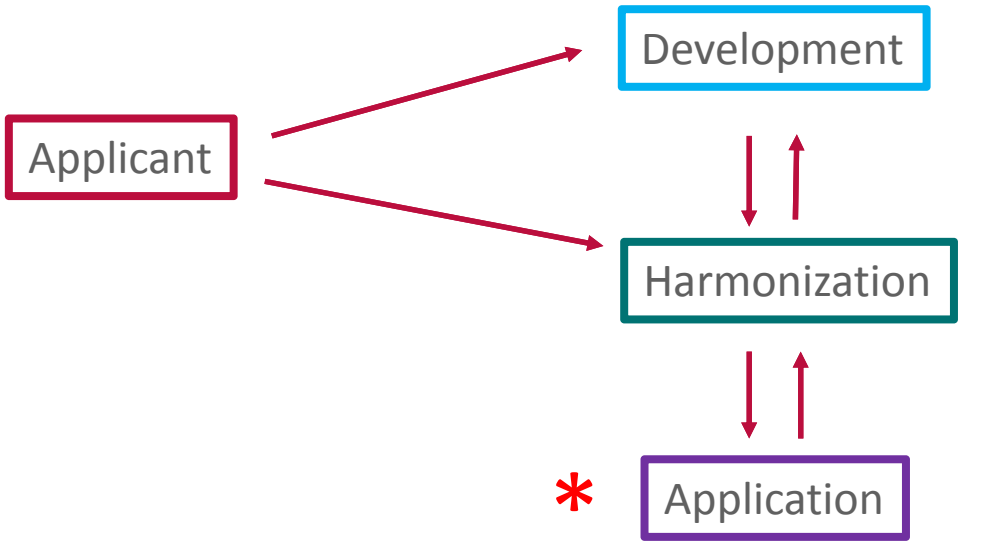
- to **enhance technology** for circulating cells, DNA, RNA, and exosomes and that the enriched analysts are tumor-specific and meet the requirements of early detection.
- of assays that can detect/screen for **multiple types of cancer** from a single plasma sample (e.g. colon, lung, pancreas, breast, prostate). The assays would need to distinguish the cancer type or have viable imaging or biopsies for a definitive diagnosis.
- of **single cell assay** for CTCs to identify molecular heterogeneity; use next-generation sequencing or new technology for mutational analysis, copy number changes, and other genomic aberrations.
- of assays for **isolation and characterization** of cancer-associated cells, such as tumor associated macrophages, platelets or tumor regulating stroma cells.
- of assay to capture and characterize tumor cells, DNA and extracellular vesicles from other bodily fluids.

Encourage Proposals Where Liquid Biopsy May be Most Beneficial

Examples:

- Where problems exit that are associated with current screening methodologies;
- Where no tools exit for noninvasive detection/monitoring of disease progression;
- Where no noninvasive tools exit for early detection in “high risk” populations (genetic and/or familial predispositions).

Three Stages of Focus for Liquid Biopsy



Need to modify or develop the Technology/methods/assays

Technology/methods/assay are fixed and established

Leveraging of other programs and resources

* Requires Steering Committee recommendation and guidance. Criteria for this: (1) Does this technology have overarching implications for other technologies within the consortium; (2) Is the technology portable and reproducible; (3) Does the technology advance the field…etc.

Funding Mechanism

An RFA for a U01 Cooperative Agreement Mechanism is requested as substantial scientific and/or programmatic involvement is required for the operation of this program.

NCI Staff will be involved in:

- Assisting in the coordinating interactions and collaborations among the investigators and industrial partners;
- Ensuring access to other NIH relevant programs;
- Facilitating collaborations with others who have relevant platforms;
- Promoting exposure to resources, specimens, and epidemiological expertise.

Justification for an RFA

- High priority for NCI and NIH:
  - Perspective published by the NCI/NIH Leadership identified liquid biopsy as a means of advancing early detection. (5)
  - Consistent with the recommendations by the Blue Ribbon Panel of the Moonshot Program **"for development of new cancer technologies and increased public-private sector collaborations."** (6)

- NCI's commitment of funds to this initiative will encourage investigators expand their research to include early detection and accelerate clinical adoption of these promising technologies.

(5) Lowy, DR, and Collins, FS, NEJM (2016) 374:20

(6) www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel

Budget:

- Request $6 M per year to support 6-8 applications for up to 5 years.

Thank you

www.cancer.gov **www.cancer.gov/espanol**