The NCI Human Tumor Atlas Network (HTAN)

*Pre-application webinar slides for*

**RFA-CA-17-035**

*Pre-Cancer Atlas (PCA) Research Centers (U2C)*
The Cancer Moonshot Initiative

Goals

• Accelerate progress in cancer, including prevention & screening
  From cutting-edge basic research to wider uptake of standard of care

• Encourage greater cooperation and collaboration
  Break down silos within and between academia, government, and the private sector

• Enhance data sharing
  NCI Cancer Research Data Commons
  Annotated patient-level clinical and ‘omics’ data
The Process

Vice President’s Office

Federal Task Force

NIH/NCI

National Cancer Advisory Board

Blue Ribbon Panel (BRP)

BRP Working Groups (WG)

Cancer Immunology WG

Tumor Evolution and Progression WG

Pediatric Cancer WG
Blue Ribbon Panel Recommendations

A. Network for Direct Patient Engagement
B. Cancer Immunotherapy Clinical Trials Network
C. Therapeutic Target Identification to Overcome Drug Resistance
D. A National Cancer Data Ecosystem for Sharing and Analysis
E. Fusion Oncoproteins in Childhood Cancers
F. Symptom Management Research
G. Prevention and Early Detection: Implementation of Evidence-Based Approaches
H. Retrospective Analysis of Biospecimens from Patients Treated with Standard of Care
I. Generation of Human Tumor Atlases
J. Development of New Enabling Cancer Technologies
Cancer Funding in 21st Century Cures Act

Impact

• Allows for funding of the BRP Recommendations
  The cancer research portion is named the Beau Biden Cancer Moonshot Initiative®

• Specifies requirements for:
  Data sharing (Cancer Moonshot Public Access and Data Sharing Policy)
  Advancing health disparities research

“To support cancer research, such as the development of cancer vaccines, the development of more sensitive diagnostic tests for cancer, immunotherapy and the development of combination therapies, research that has the potential to transform the scientific field that has inherently higher risk, and that seeks to address major challenges associated with cancer.”
Recommendation I: Generation of Human Tumor Atlases

Create dynamic multidimensional maps of human tumor evolution to document the genetic lesions, molecular pathways and cellular interactions that guide tumor development from a pre-cancerous lesion to primary cancer, progression to metastasis, response to therapy and acquisition of resistance.

Combined recommendation from the Cancer Immunology, the Pediatric Cancer, and the Tumor Evolution and Progression BRP Working Groups

- BRP Pediatric Cancer Working Group Report (pdf)
- BRP Cancer Immunology Working Group Report (pdf)
- BRP Tumor Evolution and Progression Working Group Report (pdf)
- Final Blue Ribbon Panel Report (pdf)
Building the Human Tumor Atlas Network (HTAN)

Main Objective:

Construction of high-resolution, multidimensional, multiparametric, dynamic atlases of individual tumors over time.

- Atlases should describe the molecular, cellular and physiological events that occur during early stages of cancer development, progression and metastasis.
- Atlases should integrate data on the molecular, cellular, sub-cellular, tumor tissue composition and architecture, including the microenvironment and immune milieu.
- Atlases should enable predictive modeling to refine preventive and therapeutic choices.
- Atlases should include critical time points — transition from pre-malignancy to cancer, metastasis, response to therapy, and development of resistance to therapy.
- Atlases should focus initially on exemplary pediatric and adult cancers, including at least one adult cancer in which immunotherapy responses have been good and one in which such responses have been poor.
The Human Tumor Atlas Network (HTAN)

Components:

1. **Human Tumor Atlas (HTA) Research Centers** (U2C) focused on construction of dynamic, multidimensional tumor atlases for advanced cancers.  
   **RFA-CA-17-034**

2. **Pre-Cancer Atlas (PCA) Research Centers** (U2C) focused on construction of dynamic, multidimensional pre-cancer atlases.  
   **RFA-CA-17-035**

3. **HTAN Coordinating Centers** (U24s) focused on integration of the HTAN through administrative and scientific support.  
   - Data Coordinating Center (DCC)  
     **RFA-CA-17-036**  
   - Tissue Coordinating Center (TCC)  
     To be developed in FY2019

![Human Tumor Atlas Network Diagram]

**Human Tumor Atlas Network**

Transitions:
- Pre-cancer → Cancer
- Invasive → Metastatic
- Responsive → Resistant

HTAN Steering Committee – Leadership and Oversight
A human pre-cancer atlas is defined as a multidimensional cellular, morphological and molecular mapping of human pre-malignant tumors, complemented with critical spatial information (at cellular and/or molecular level) that facilitate visualization of the structure, composition, and multiscale interactions within the tumor ecosystem over time resulting in progression or regression of the tumors.
The information presented today is a general overview of the Request for Application (RFA) for the Precancer Atlas (PCA) Research Centers. Applicants must consult the PCA RFA (RFA-CA-17-035) as well as other companion RFAs (see Slide 8) for detailed information on the scope of each RFA, application procedures and requirements, and review criteria.

**Definition of Pre-cancer:** A condition that may (or is likely to) become cancer, pre-malignant lesions where there is a clear evidence of association with increased risk of invasive cancer, chronological evolution of the lesions result in progression to invasive cancer or regression, lesions differ from normal cells and share molecular and phenotypic features with invasive cancer, invasive cancer originates from the pre-malignant lesion.
Objective of the PCA Research Centers

Each PCA Research Center will undertake comprehensive molecular, cellular and tissue characterization of human pre-malignant lesions with spatial resolution to construct comprehensive, dynamic, high-resolution, multidimensional, multiparametric, multiscale, temporal and scalable atlases of precancerous lesions and their surrounding microenvironment for select organ sites. The pilot-level precancer atlases should be built based on data from prospective, longitudinal, well-annotated clinical biospecimens representative of the racial/ethnic diversity of the United States population.

The atlases will provide a deeper understanding of the transition of premalignant to malignant cancer and identify markers for early detection and preventive interventions.

RFA-CA-17-035 : Part 2. Full Text of Announcement; Section I. Funding Opportunity Description; Research Objectives and Main Requirements.
Structure of the PCA Research Center

Molecular, Cellular and Tissue Characterization Unit (Characterization Unit)

Biospecimen Acquisition, Processing and Classification Unit (Biospecimen Unit)

Data Processing, Analysis and Modeling Unit (Data Analysis Unit)

Other PCA Research Centers

Administrative Core

HTAN Data Aggregator

HTAN Coordinating Centers (DCC, TCC)

HTA Research Centers

**RFA-CA-17-035**: Part 2. Full Text of Announcement; Section I. Funding Opportunity Description; Research Objectives and Main Requirements.
Required Capabilities of the PCA Research Center

• A multidisciplinary, collaborative team with expertise (clinical, cancer biology, imaging, computational) required to construct the pre-cancer atlas.

• Access to high-quality, well-annotated pre-malignant biospecimens (NIH programmatic emphasis to projects that utilize prospective human samples for atlas construction).

• Capability to perform comprehensive, longitudinal, multiparametric and multidimensional characterizations of the composition and architecture of human biospecimens.

• Access to innovative technologies and instrumentation.

• Demonstrable computational expertise that facilitates data analysis and atlas building activities, including advanced data visualization.

RFA-CA-17-035: Part 2. Full Text of Announcement; Section I. Funding Opportunity Description; Research Objectives and Main Requirements.
Selection of Organ Sites

The rationale for the selection of organ site(s) must be based on the following four criteria:

- **Impact on Public Health**: Public health burden, nature of the clinical question to be addressed, and if applicable, address health disparities in a variety of racially and ethnically diverse populations, and care settings.

- **Access to Technologies and Biospecimens**: The atlas construction will use a two-step hybrid approach; first use retrospective samples and different sample preservation methods from existing cohorts to broadly test emerging technologies, and then use uniformly collected, extensively annotated, longitudinal biospecimens and well-standardized and validated technologies for atlas building.

- **Feasibility of Atlas Construction**: The feasibility of atlas construction is based on the available cohorts, number of available biospecimens, rate of progression to cancer and the available tools and technologies.

- **Synergistic Partnerships for Maximizing Resources**: Partnership with ongoing initiatives in this area (federal, foundation, industry, etc.) is preferred for access to cohorts, technologies and any other resources deemed necessary for atlas construction.

*Courtesy of the NCI Pre-Cancer Atlas Think Tank Meeting, June 15-16, 2017.*

**RFA-CA-17-035**: Part 2. Full Text of Announcement; Section I. Funding Opportunity Description; Research Objectives and Main Requirements.
Expectations from the PCA Research Center

At the end of a successful 5-year PCA initiative, a preliminary set of comprehensive human precancer atlases will be constructed that can:

• Provide an improved understanding of disease progression;
• Characterize heterogeneity of pre-malignant lesions;
• Quantify the dynamics and multidimensional architecture of the tumor ecosystem during transition to malignancy (or regression);
• Identify novel biomarkers for early detection, risk stratification and chemoprevention targets that will lead to better intervention options for patients;
• Facilitate predictive modeling of pre-malignant to malignant transition.
The Multi-Component Application

**RFA-CA-17-035**: Part 2. Full Text of Announcement; Section IV. Application and Submission Information. Instructions for the Submission of Multi-Component Applications.
Overall Component
(Please review the PCA RFA for detailed information/functions)

• Describe the overall vision and goals for the PCA Research Center.

• Define the pre-cancer atlas(es) that will be constructed within the PCA Research Center and a vision of the final structure of the atlas. If applicable, address how health disparity data will be integrated into the proposed studies.

• Provide a rationale for the selection of organ site(s) based on the four criteria described earlier.

• Describe how the research project will use the suggested hybrid study design:
  • Step 1: Use biospecimens from existing cohorts to broadly test and standardize emerging state-of-the-art technologies and lock down promising technologies to be used in Step 2.
  • Step 2: Apply the selected promising technologies on prospectively collected longitudinal biospecimens with uniform clinical/imaging annotation to build the atlas.

• Describe the Research Center organization and team integration.

• Provide an outline of the structure of each Research Unit. Describe the workflow from sample acquisition all the way to data aggregation, analysis and modeling.

• Describe the timeline and project milestones.

• Describe a Data Sharing Plan that is in compliance with the Beau Biden Cancer Moonshot Public Access and Data Sharing Policy.
Administrative Core

(Please review the PCA RFA for detailed information/functions)

• The Admin Core should be led by the contact PD/PI of the PCA Research Center.

• Describe plans for providing logistical and organizational support.

• Describe the leadership and management structure to establish a cohesive, integrated team, including communication with different Research Units.

• Describe plans for oversight and coordination for biospecimen and data collection in compliance with the agreed practices and principles of the HTAN Standard Operating Procedures (SOPs), Common Data Elements (CDEs) as approved by the HTAN Steering Committee.

• Describe plans for providing support to the HTAN-DCC by gathering all multi-platform data sources across the PCA Research Centers for data sharing and data integration purposes and support to the HTAN-TCC (when it develops).

• The Administrative Core will also ensure bidirectional exchange of findings and insights with other HTAN Research Centers.
Biospecimen Unit (Functional Unit Component)

(Please review the PCA RFA for detailed information/functions)

- Describe plans for collection of biospecimens, e.g., biopsy, blood, serum, plasma and any other cross-sectional and prospective, longitudinal specimens deemed necessary to support the construction of the proposed atlas(es).

- Describe the necessary expertise within the Unit (e.g., clinician(s), surgeon(s), a research coordinator, and pathologist(s) as outlined in the RFA).
  - The Biospecimen Unit should have expertise necessary for classifying/staging/grading specimens and for preparing and optimizing pre-analytical processing of tissue specimens to be used for extensive characterization of the lesions.

- Outline plans for working with other HTAN Biospecimen units to develop appropriate SOPs and CDEs for specimen collection and processing to reduce biases and allow comparison of independent data sets among the HTA/PCA Research Centers.
• Describe the research plan for conducting state-of-the-art molecular, cellular, non-cellular and tissue characterization for selected organ site(s) using biospecimens procured by the Biospecimen Unit, which must include plans for multidimensional/multiparametric characterization.
  • Applicants should note that the goal is to **not create a cellular and molecular catalog, but to contribute to a framework that provides an understanding of transition from pre-malignant to malignant cancer.**

• Describe the necessary expertise within the Unit (e.g., clinical, cancer biology, imaging and computational, as outlined in the RFA).

• Describe plans for working collaboratively with the Biospecimen Unit to optimize pre-analytical processing of tissue for the variety of imaging and omics assays proposed by the Unit.

• Describe plans for working collaboratively with the Data Analysis Unit as a tight integration is required between the Units to ensure adequate collection and sharing of metadata and multidimensional experimental data for processing, analysis, and atlas-building activities.
Data Analysis Unit (Functional Unit Component)
(Please review the PCA RFA for detailed information/functions)

• Describe plans for integrating and modeling the data generated by the Characterization Unit to visualize high-resolution structural, functional and temporal relationships as a dynamic, multidimensional, multiparametric atlas in a scalable and queryable format.

• Demonstrate expertise in advanced computational biology, including statistical and mathematical analysis, as well as the ability to develop new methods/tools/models for data integration research relevant to the pre-cancer atlas.

• Describe plans to conduct at least one preliminary study that illustrates how the resulting human tumor atlas dataset could be utilized to build a predictive model of cancer.
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Proposed Data Flow for HTAN

Research Center → HTAN DCC → GDC → Cancer Data Aggregator → Community
Research Center → HTAN DCC → TCIA
Research Center → HTAN DCC → etc. → Other Data Commons
U2C Funding Mechanism

**U2C = Resource-Related Research Multi-Component Projects and Centers (Cooperative Agreement)**

- This mechanism is to support multi-component research resource projects and centers that will enhance the capability of resources to serve biomedical research.

- Substantial federal programmatic staff involvement is intended to assist investigators during performance of the research activities, as defined in the terms and conditions of the award.
Budget

- Direct costs may not exceed $1.6 million/year.
- The contact PD/PI must commit a minimum of 1.8 person-months effort per year. For multiple PD/PI applications, all other PDs/PIs must devote a minimum of 1.2 person-months effort per year.
- Set aside $200,000 (Direct Cost) for trans-Network projects. These funds should be presented in the Other Direct Costs category under the heading "HTAN Collaborative Project Fund". Funds will be released pending approval by NCI following discussion of proposed projects by the HTAN Steering Committee.
- Travel funds should be requested to support travel for Network activities, including but not limited to supporting the travel and participation of PD(s)/PI(s) and other PCA Research Center members in the bi-annual HTAN Steering Committee Meeting and annual site visits.
A Few Helpful Tips for Preparing an Application

• Please read the PCA RFA carefully to understand the requirements; failure to follow the instructions will result in a ‘non-responsive’ application, which will not be reviewed.

• Please also read the companion HTAN RFAs (HTA Research Centers and DCC).

• For different components, specific sub-sections are described in the RFA in lieu of the standard Research Strategy subsections (Significance, Innovation, and Approach), however, applications must highlight aspects of the proposed activities that speak to the significance and innovation of the approach.

• Please pay attention to review criteria, including the criteria listed in “Specific to this FOA” section, and address those criteria in the body of your application, in appropriate places.

• Please demonstrate your knowledge of and experience with extensive tumor characterization to address specific clinical questions.

• Describe your experience with working in multidisciplinary teams/projects.

• Please read carefully the Cooperative Agreement Terms and Conditions of Award; compliance with these are required and must be clearly stated in application.

• For any specific questions, contact relevant Program Directors listed on the RFA for guidance on your application.
Application Review*

• Reviewers will provide an overall impact score for the entire PCA Research Center (Overall component). In addition, assigned reviewers will provide individual "criterion scores" for the Overall criteria but not for the other components.

• The Biospecimen Unit, Characterization Unit and Data Analysis Unit – each will receive only one overall numerical score.

• Administrative Core – will receive only one overall adjectival rating.

*Please contact the Scientific Review Officer (listed below and in the RFA) for any review-related questions for the PCA RFA.

Lambratu (Bree) Rahman Sesay, PhD, Telephone: 301-905-8294, Email: rahmanl@csr.nih.gov
Important Dates

• **Letter of Intent (LOI) Due Date: December 18, 2018**
• **Information required in the LOI:**
  • Number and title of the FOA
  • Title of the proposed research
  • Organ site
  • Name, address, and telephone number of the PD(s)/PI(s)
  • Names of other key personnel
  • Participating institutions
  • Ballpark estimate of the budget

LOI for PCA RFA ([RFA-CA-17-035](#)) should be sent to Dr. Sharmistha (Sharmi) Ghosh-Janjigian (mentioned in the RFA; Section IV. Application and Submission Information)

**Earliest Submission Date:** December 18, 2017

**Application Due Date:** January 18, 2018

**Earliest Start Date:** September, 2018
NCI Program Contacts for the PCA RFA (RFA-CA-17-035)

Sudhir Srivastava, PhD, MPH
Sharmistha (Sharmi) Ghosh-Janjigian, PhD
Jacob Kagan, PhD
Richard Mazurchuk, PhD
Asad Umar, DVM, PhD

All team members can be reached at NCI_HTAN_PCAU2C@mail.nih.gov
Thank you!