Human Tumor Atlas Network (HTAN)
Precancer Atlas (PCA) Research Centers

Pre-Application Webinar for RFA-CA-23-040

- The PCA webinar will start at 2:00 PM EST
- All participants are muted upon entry to the webinar
- Please submit your questions in the Q&A box
- HTAN pre-application webinars will be recorded and posted on https://www.cancer.gov/about-nci/organization/dcb/news/past-events

NIH NATIONAL CANCER INSTITUTE

November 9, 2023

Human Tumor Atlas Network (HTAN)

Agenda for Precancer Atlas Orientation Meeting

1. Welcome to Orientation: Sudhir Srivastava
2. Overview of HTAN: Shannon Hughes
3. Overview of Precancer Atlas Program: Sudhir Srivastava
4. Guidance on Application Submission and Requirements: Indu Kohaar
5. Fielding of Question and Answers: Nick Hodges

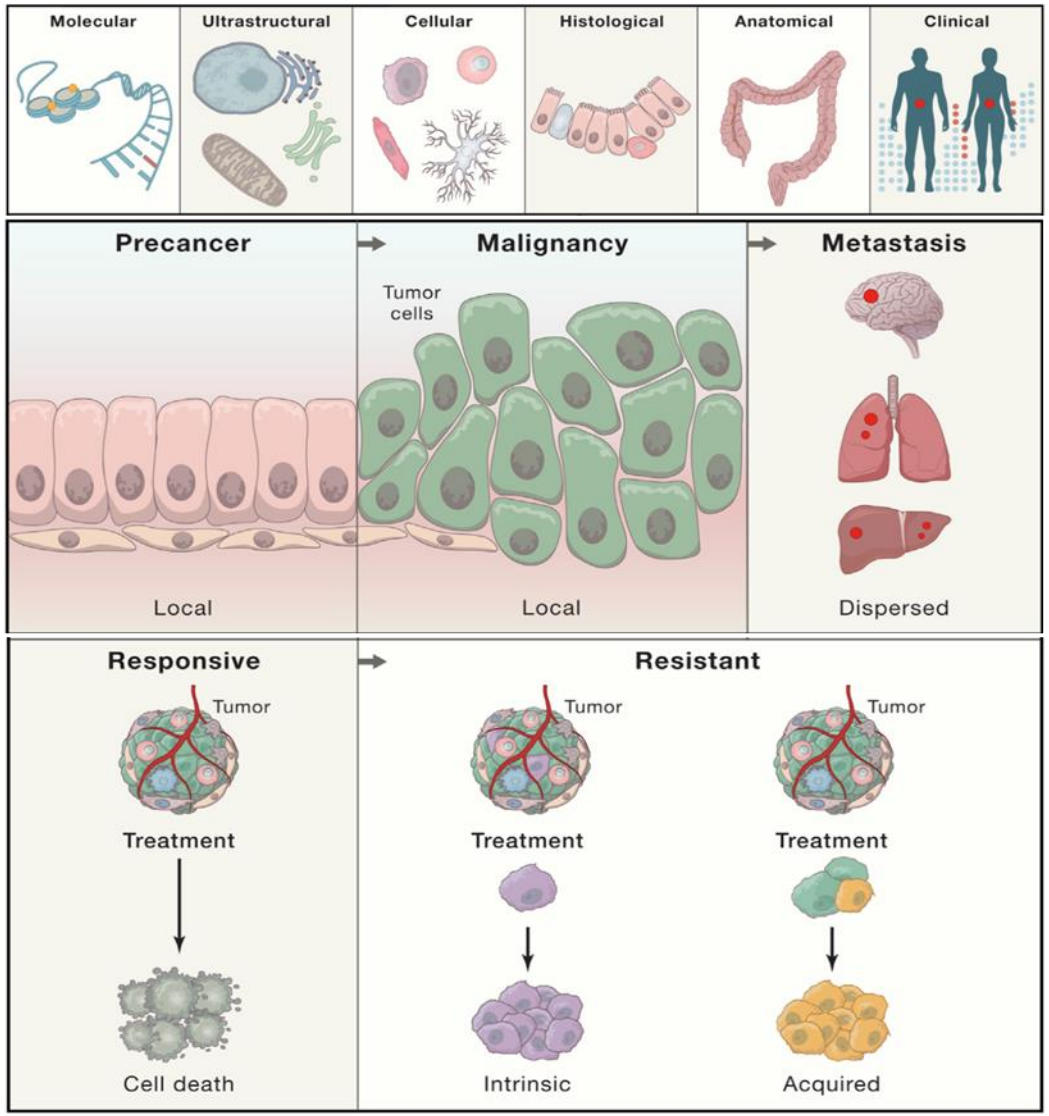
   NCI Program Officers: Indu Kohaar (Molecular), Nick Hodges (Technology), Sidney Fu (Clinical), Richard Mazurchuk (Imaging), Sean Hanlon (DCC-Data) and Sudhir Srivastava (Overall Program)

6. Next Step and Follow-up: All

The NCI Human Tumor Atlas Network (HTAN)

Overarching program goal: Construct dynamic 3D atlases of human cancers

- ***Integrate*** molecular, cellular, and tumor tissue composition and architecture, including the microenvironment and immune milieu.
- Describe ***transitions during cancer****:* pre-malignant lesions to malignancy, locally invasive to metastatic cancer, response to therapy.
- Represent a ***diverse patient population***, including underrepresented and underserved patients.
- Enable ***predictive modeling*** to discover biomarkers, understand basic cancer mechanisms, (eventually) refine therapeutic choices for patients.



Rozenblatt-Rosen et al., Cell 2020

Current HTAN Atlases

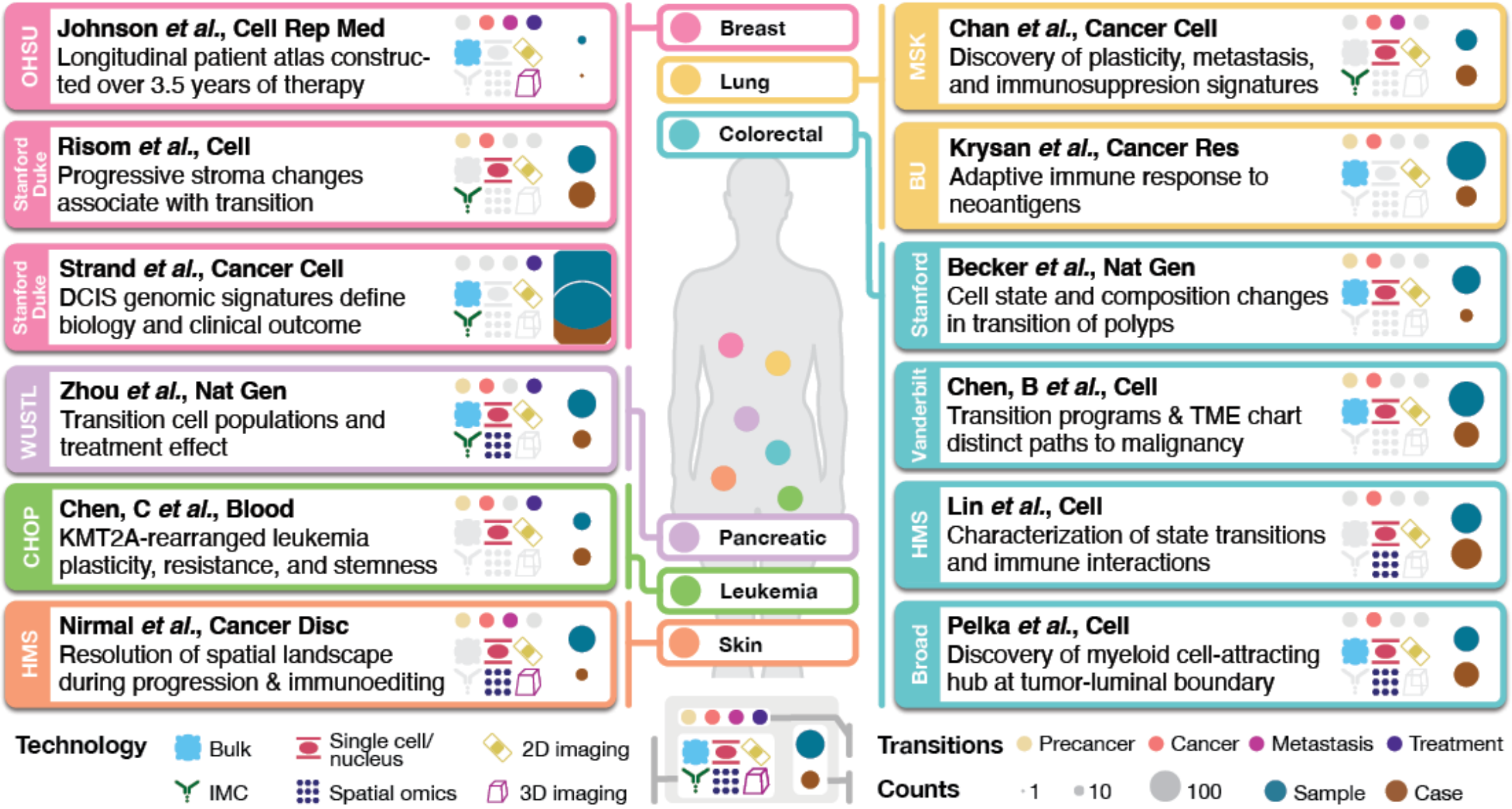
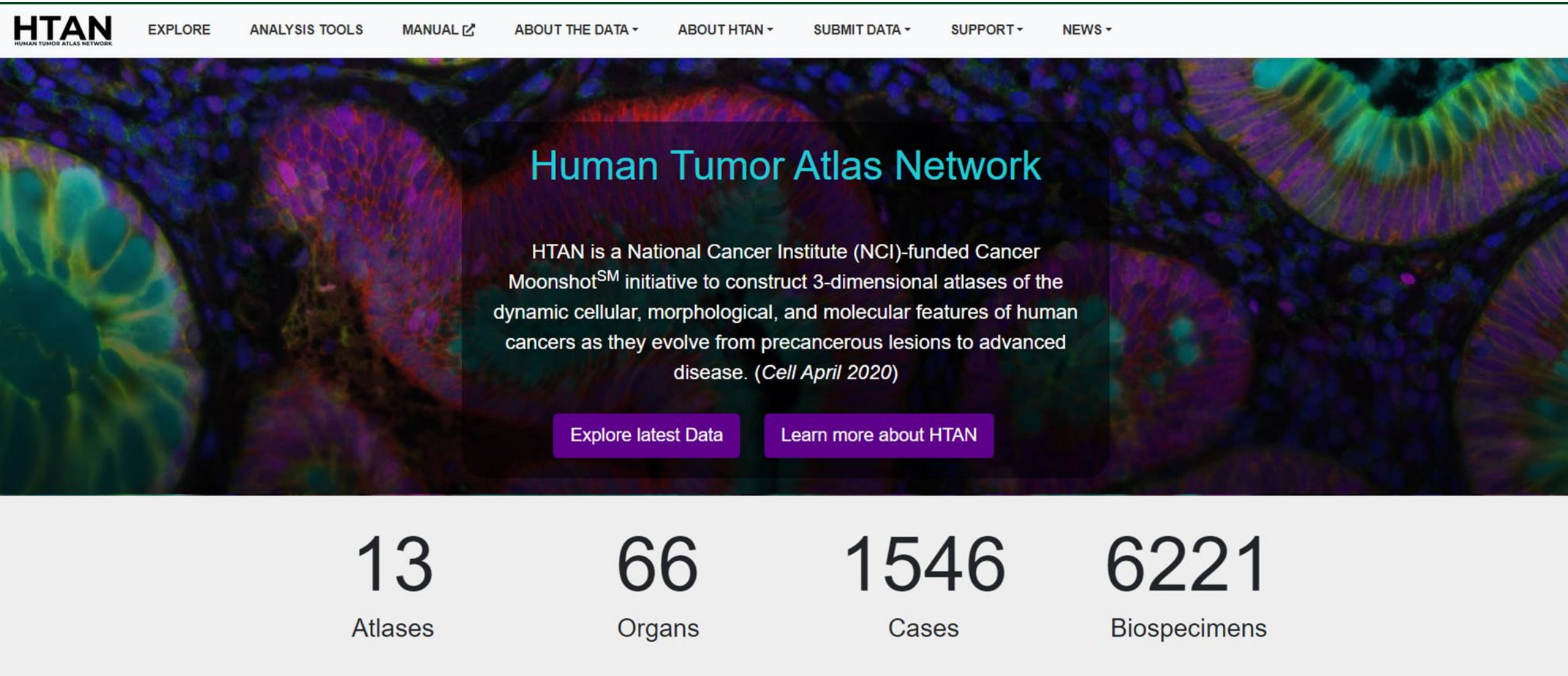


Figure courtesy of L. Ding, WUSTL HTAN

HTAN Data and Resources for the Cancer Research Community

https://data.humantumoratlas.org



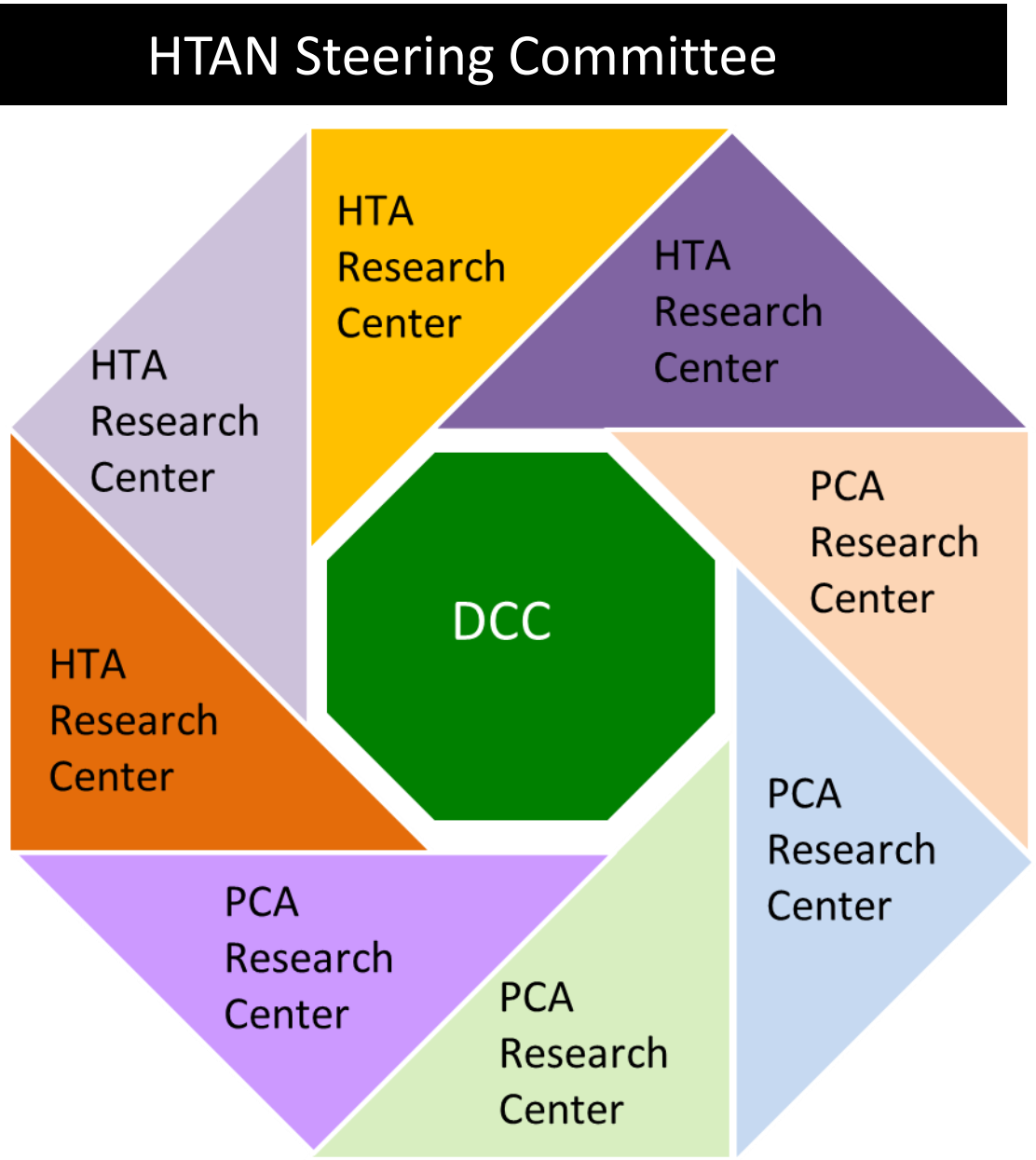
HTAN Organization

Components of the HTAN:

Human Tumor Atlas (HTA) Research Centers
RFA-CA-23-039 (U01)

Pre-Cancer Atlas (PCA) Research Centers
RFA-CA-23-040 (U01)

HTAN Data Coordinating Center (DCC)
RFA-CA-23-041 (U24)



The number of HTA and PCA Research Centers will depend on availability of NCI FY24 funding.

Human Tumor Atlas Network (HTAN)

PreCancer Cancer Atlas Application's Orientation Meeting

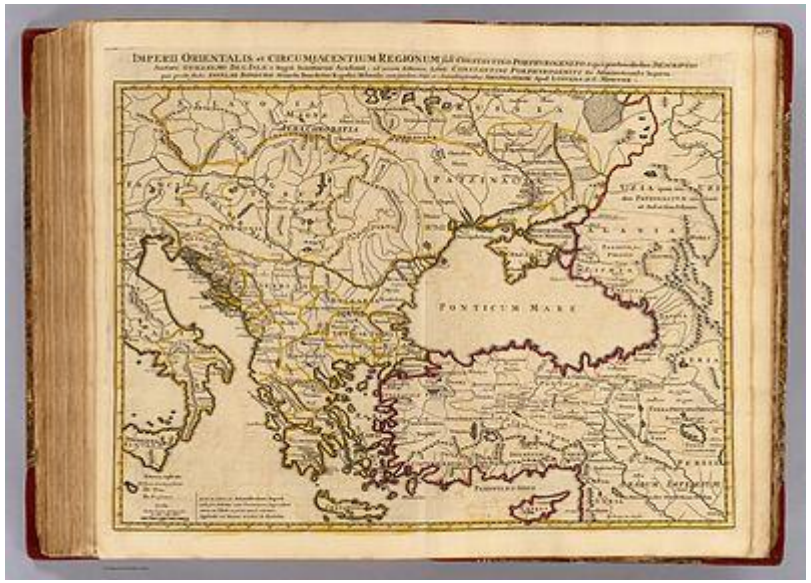
Sudhir Srivastava, PhD, MPH

Indu Kohaar, PhD

Nicholas Hodges, PhD

Sidney Fu, MD

Richard Mazurchuk, PhD



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

Purpose of Applicant's Orientation

Purpose of this orientation is to discuss Notice of Funding Opportunity (NOFO) that solicits applications for HTAN Precancer Atlas (PCA) Research Centers to construct temporal-spatial atlases that comprehensively characterize a pre-malignant lesion with an explicit focus on understanding the transition from a precancerous lesion to malignancy

Applicants must consult RFA-CA-23-040 for detailed information on the scope of this RFA, application procedures and requirements, and review criteria

What is a Cancer Atlas?

- In cancer, it is graphical representation of data in time and space.
- In cancer, the type of data may include, but are not limited to:
  - Omics data
  - Immune cells data
  - Imaging Data
  - Clinical Data

A PreCancer Atlas is a gateway to comprehensive knowledge of alterations in microenvironment, including histological, pathophysiological and omics profiles, e.g., genomic, proteomic epigenomic, immune cells, etc. and their interplay that drive cancer progression at its earliest stages. PreCancer Atlas envisages systematic efforts to longitudinally collect and perform molecular and cellular profiling of premalignant lesions in time and space as they progress towards frank malignancy

Why is Tumor Atlases Needed?

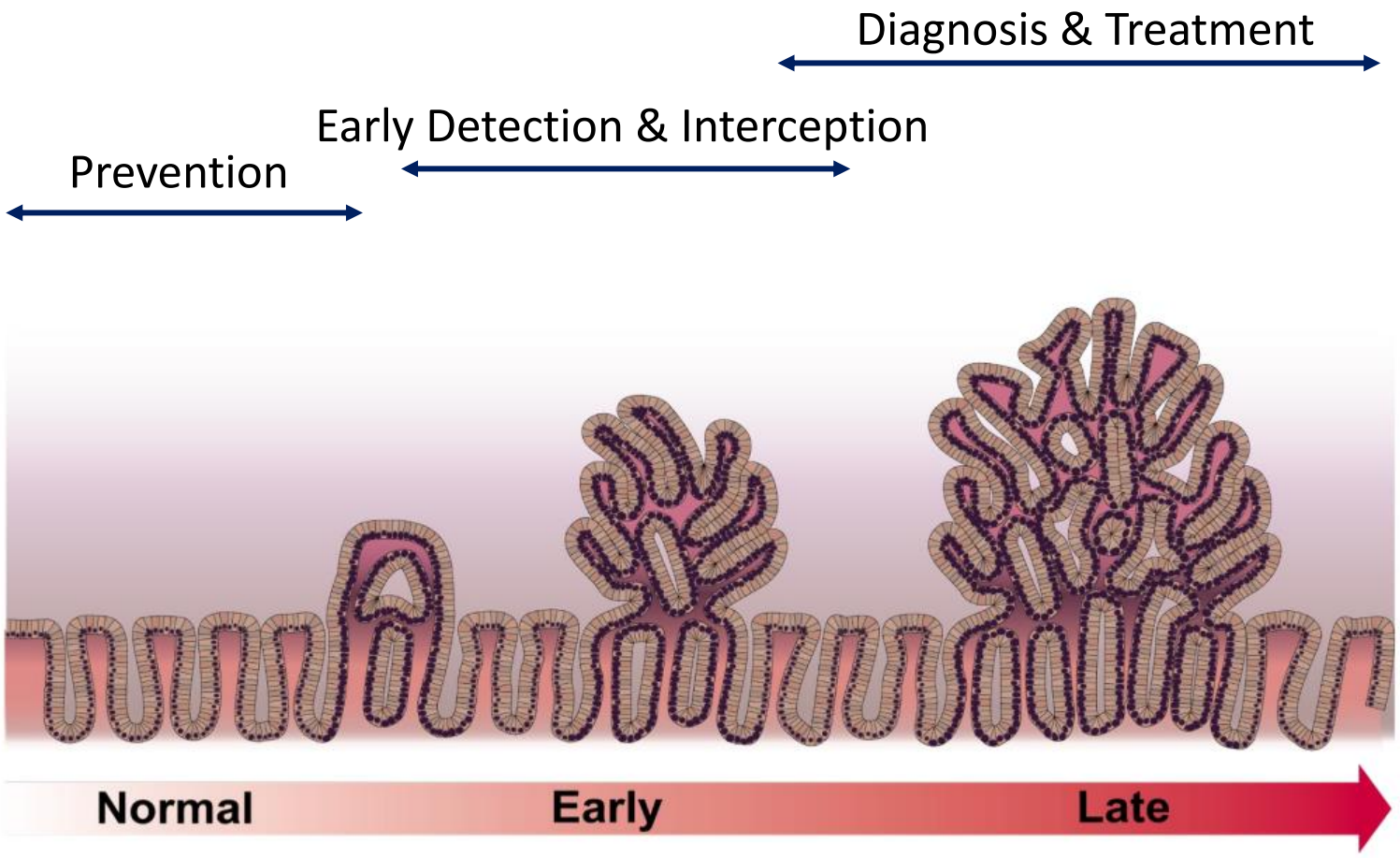


Figure modified from Ken Lau Lab, Vanderbilt University

Precancer Atlas Overview

- Atlas must address an important unmet clinical need
- Define the overall significance of the proposal with vision and goals for the center
- Describe the precancerous lesion atlas and how it will contribute to the understanding of the precancerous lesions and progression of precancerous lesions to invasive cancers.
- Provide background and rationale for the selection of tissue type and outline the significance and potential impact provided by the atlas
- Describe the planned final structure of the atlas, including Biospecimen, Molecular and Data functional units
- Briefly describe how the atlas might be employed by the scientific and clinical communities
- Provide one use case that illustrates how the proposed atlas datasets could be utilized to build a predictive model

Definition of Precancer

Precancerous lesions are regions of histologically and/or molecularly abnormal tissues that more often progress to invasive carcinoma than healthy or normal tissue.

Precancers can be defined as

- lesions that may or are likely to progress to invasive cancer
- lesions where there is clear evidence of an association with increased risk of invasive cancer
- lesions which are different from normal cells and share molecular and phenotypic features with invasive cancer

PCA Research Centers

- Undertake comprehensive characterization of human precancerous lesion/state and their surrounding microenvironment.
- Focus on deriving insights from the most informative measures from bulk or single cell molecular analysis.
- Collect at least two existing HTAN data types one must be a spatial assay. Additional data types that are appropriate and specific to the proposed research will be considered.
- Atlases that add significant value to current HTAN atlases
- Inclusion of diverse patient population (if possible)
- When possible, include longitudinally collected specimens from the same patients where outcome can be evaluated.

Required Resources and Capabilities of the PCA Research Center

- Access to high-quality, well-annotated premalignant biospecimens and reference controls
- Strong clinical and research environment
- Expertise and access to innovative technologies and instrumentation
- Expertise in data analysis and atlas building activities
- Demonstrated evidence for
  - understanding of the transition of precancerous lesions to invasive cancer,
  - generate testable hypotheses
  - potential to identify markers for risk, early detection and preventive intervention.

Proposed Research on Organ Site(s) Must Meet The Following

- Impact on Public Health*:* The proposed atlas should have the potential to have a substantial impact on clinical decision-making, as determined by public health burden, and high-risk populations.

- Access to Technologies and Biospecimens: The applicants must have access to state-of-the-art technologies and the resources to obtain well-characterized and well-annotated biospecimens (cross-sectional and longitudinal).

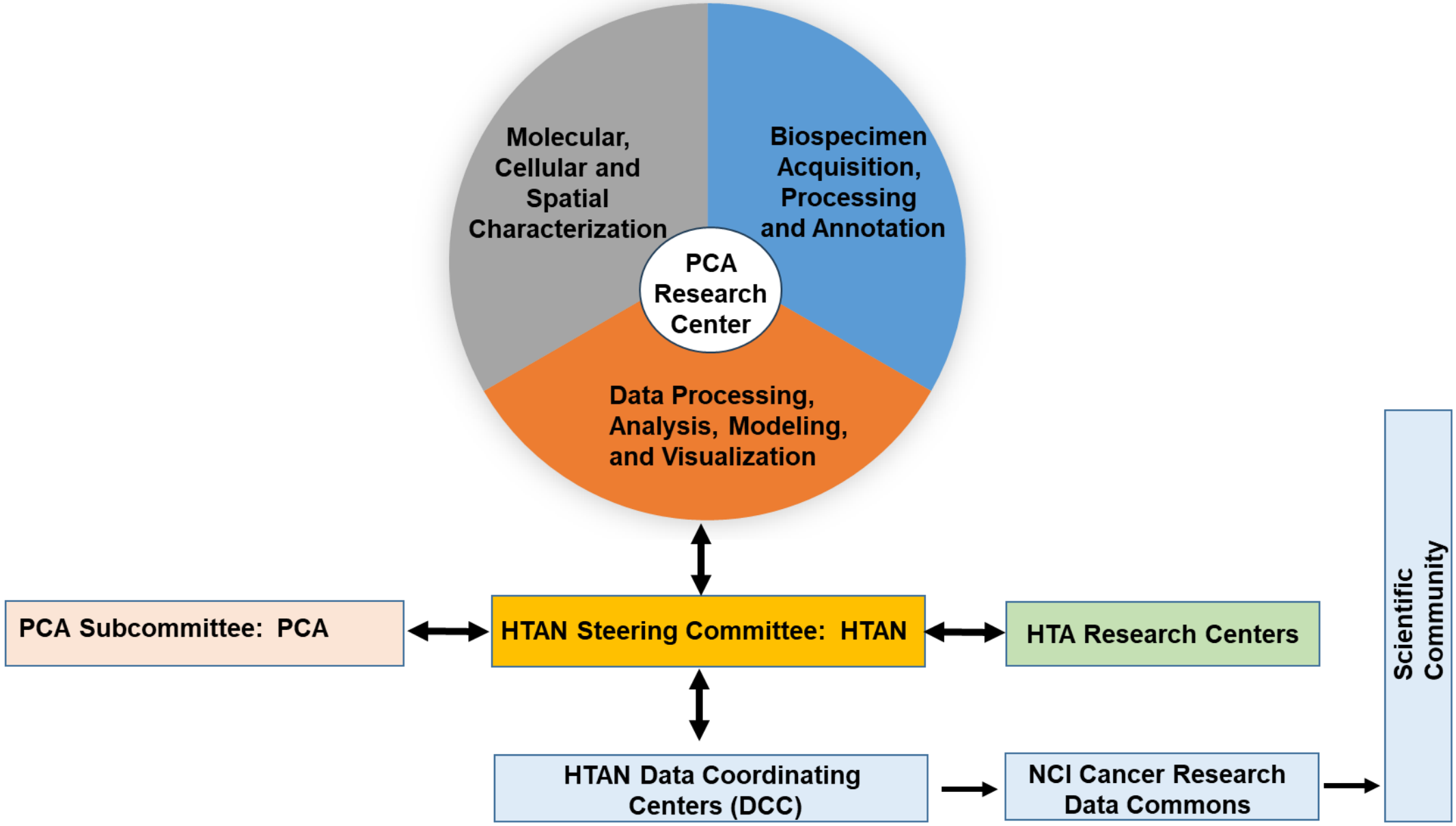
- Feasibility of Atlas Construction: The feasibility of atlas construction is based on the available cohorts, number of available biospecimens, rate of progression to cancer and available tools and technologies.

- Synergistic Partnerships for Maximizing Resources: The ability to partner with ongoing initiatives (federal, foundation, industry, etc.) is vital as this will increase access to cohorts, technologies, and other resources necessary for atlas construction.

Expected Outcomes of PCA Research Center

- Provide an improved understanding of disease initiation and 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 including somatic mutations; the interaction of germline mutations with somatic mutations, molecular changes that affect cellular fitness and immunity.
- Facilitate predictive modeling of pre-malignant to malignant transition

PCA Research Center Organization



Biospecimen Acquisition, Processing and Annotation

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

Describe the methods used for the identification, collection, preservation, labeling, and quality control of all biospecimens used to construct the proposed atlas.

- A biological and statistical justification for collection frequency, sample type, and volume of biospecimens to be acquired.
- Evidence of access to human biospecimens relevant to the proposed atlas.
- Information on quality assurance and quality control metrics employed to ensure high sample quality upon collection, after preservation, and upon pre-analytical processing.
- A short description of retrospective human samples, non-human tissues and/or alternative in vivo and/or ex vivo human models that maybe used in the conduct of the proposed research.
- Describe and, preferably, demonstrate through presentation of preliminary data strategies to minimize confounding variables during sample collection.

Molecular, Cellular, and Spatial Characterization

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

Describe methods to characterize the biospecimens that will be used to develop the precancer atlas.

- A biological and statistical justification for types and volumes of data to be acquired to construct the atlas.
- Assay methods and platforms to be employed, their reproducibility and preliminary data that demonstrate their use within the context of the proposed atlas construction.
- It is required that each atlas include at least two common HTAN data types (one must be a spatial data type) for which data and metadata standards have been developed.
- A strategy to monitor and ensure data quality, including action plans for when quality issues are discovered.
- The expected data collection workflow, QA/QC points, and potential challenges associated with the analysis of small or variable samples.

Data Processing, Analysis, Modeling, and Visualization

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

Describe methods that will be used for data processing, analysis, modeling, and visualization of atlas data.

- Existing or proposed data processing pipelines to be employed, specifically regarding imaging, spatial and omics data.
- State the degree to which the resulting processed data meets the qualifications for findability, accessibility, interoperability, and reusability (FAIR) data sharing standards.
- Plans for how the resulting human precancer atlas dataset can be utilized to build a predictive computational model of progression from a precancerous lesion to an invasive cancer.
- Describe the clinical or biological insight that can be gained from the modeling effort and steps required to test hypotheses derived from the modeling effort.
- Analytical flexibility and plans to aggregate and integrate data and metadata from the broad range of experimental and computational approaches.

Governance

- HTAN Steering Committee will provide oversight of HTAN collaborative activities, data sharing, data deposition to the HTAN-DCC.

- PCA Sub-Committee composed of all PCA Research Centers PIs will focus on scientific, programmatic, and administrative directions for PCA. The Sub-committee will integrate the efforts of all PCA Centers and will provide oversight of collaborative activities to be reported to HTAN Steering Committee.

Non-Responsive Applications

The following types of applications are outside the scope of this NOFO and will not be reviewed.

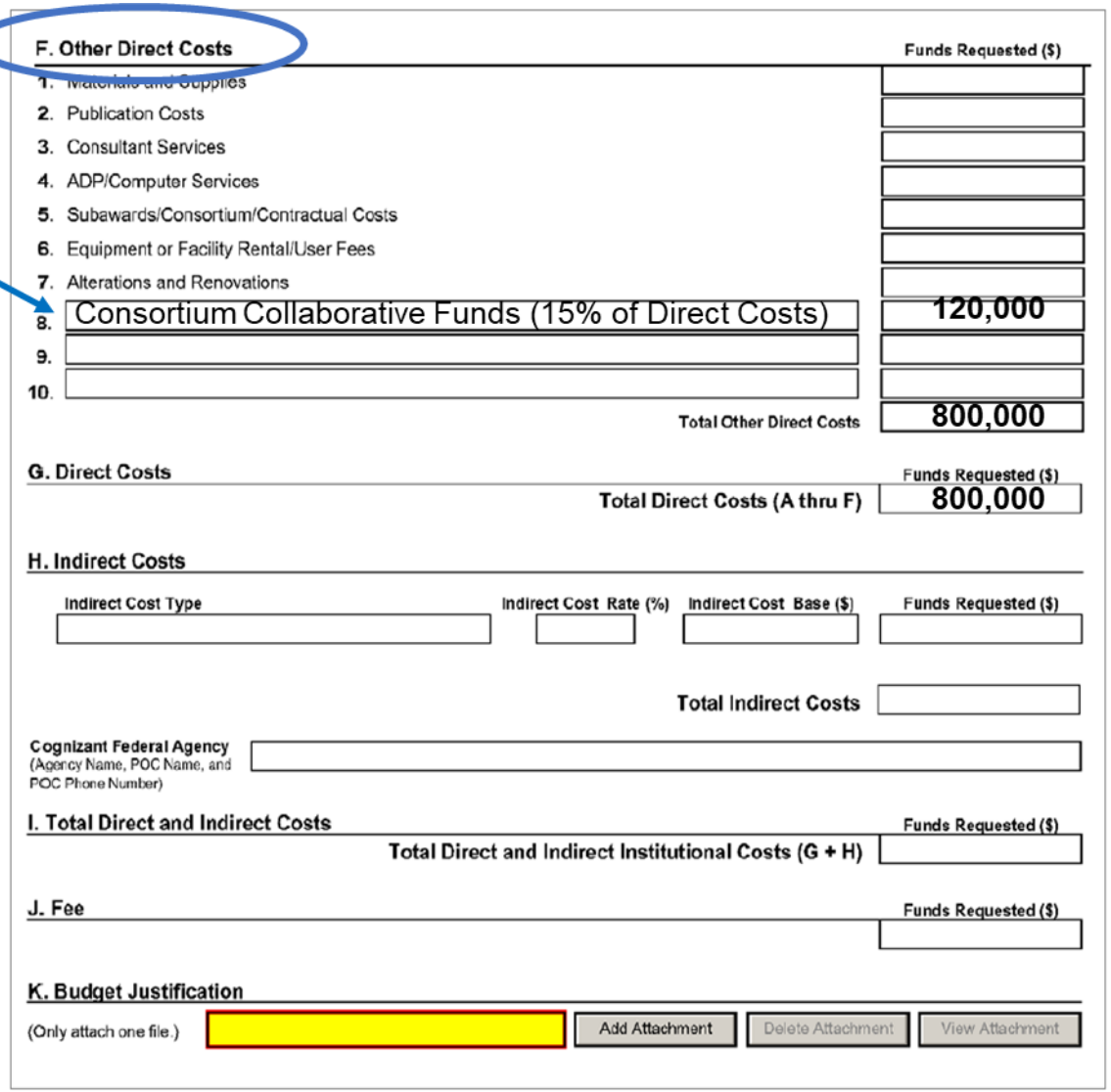
- Applications primarily focused on the pursuit of a biological mechanism through basic research that does not result in an atlas.
- Applications focused on the progression of invasive cancer to metastasis are not responsive to this NOFO but may be responsive to RFA-CA-23-039 , U01 for HTA Research Centers.
- Applications proposing atlases constructed through exclusive use of non-human biospecimens.
- Applications based upon one experimental measurement and do not propose methods that provide multidimensional data/information regarding the spatial distribution of cellular and/or non-cellular components of the tumor.
- Applications that propose to primarily study biofluids for identification of biomarkers without any attempt to reconstruct the multidimensional tumor ecosystem.
- Applications that do not propose to collect at least two existing HTAN data types (at least one must be a spatial assay) for which data and metadata standards and levels exist,
- Applications that are not able to satisfy current HTAN policies
- Applications that do not include biospecimens representative of patient diversity in the United States, as required by NIH policy.

Award Information

- **Funding Mechanism:** Cooperative Agreement (U01)

- **Budget:**
  - should not exceed $800,000 per year in direct costs.
  - Commitment (minimum): Single PI applications: 1.8-person month per year; Multi-PD/PI applications: 1.2-person month per year to the award.
  - Set-Aside Funds for HTAN Pilot Projects and Trans-Network Projects (TNPs): Applicants must set aside 15% (Direct Cost) of their annual budget in Years 2-5 to facilitate the testing of hypotheses derived from atlas construction and to develop TNPs.
  - Support for Early-stage/Junior Investigators: The budget should include funds to enhance professional development of early-stage/junior investigators.
  - Travel Funds: Applicants must budget for travel and per diem expenses for biannual HTAN in-person meetings.

Where to Add the "Restricted Fund" Information in the Application



F. Other Direct Costs — Funds Requested ($)

1.	Materials and Supplies	
2.	Publication Costs	
3.	Consultant Services	
4.	ADP/Computer Services	
5.	Subawards/Consortium/Contractual Costs	
6.	Equipment or Facility Rental/User Fees	
7.	Alterations and Renovations	
8.	Consortium Collaborative Funds (15% of Direct Costs)	120,000
9.		
10.		
	Total Other Direct Costs	800,000

G. Direct Costs — Funds Requested ($)

Total Direct Costs (A thru F) 800,000

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)

Total Indirect Costs

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs — Funds Requested ($)

Total Direct and Indirect Institutional Costs (G + H)

J. Fee — Funds Requested ($)

K. Budget Justification

(Only attach one file.) Add Attachment | Delete Attachment | View Attachment

Do not include a description of pilot projects or TNPs within application

Research Strategy Section and Page Limitations

Applicants should use the following Research Strategy Subsections to present a concise plan for the proposed PCA Research Center.

All page limits described in the SF424 Application Guide must be followed, with an exception for the Research Strategy section. Research Strategy must not exceed 30 pages, but the program recommends (not required) the following page limits for each subsection:

- *Subsection A: Proposed Precancer Atlas Overview - 2 pages*
- *Subsection B: Research Team - 2 pages*
- *Subsection C: Integrated Functions of the PCA Research Center - 12 pages*
- *Subsection D: Addressing Cancer Health Disparities - 1 page*
- *Subsection E: Project Management Plan - 2 pages*

Helpful Tips for Application

- Please read the PCA RFA carefully to understand the requirements.
- Applicants must highlight the integrated functions 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 NOFO” section, to help you prepare a strong application.
- For any specific questions, contact Program Directors listed on the RFA for guidance on your application.
- Application due date: December 05, 2023
- Award start date (earliest): July 2024

Frequently Asked Questions

Is there a requirement for an ESI to act as Co-PI?

No, the ESI may hold the title of Postdoctoral Fellow, Staff Scientist, Research Associate, Instructor, Assistant Professor, or equivalent and should be within 6-8-years following completion of a professional degree or subsequent mentored academic or clinical training program.

Are HTAN data subtypes limited to previously data subtypes?

Any data subtype may be utilized that would support the application. Two previously established data subtypes within HTAN must be included and one must be spatial.

How many samples must be included?

The number of samples and timepoints in longitudinal samples is dependent on study design.

Can PIs be members of another application or leverage other consortiums/grants?

Yes; however, the contact PI may not be a contact PI for another application.

Are specific aims required to be organized according to the three integrated functions of the PCA Research Center?

No. The three integrated functions must be included in the research strategy but are not required to be divided into individual specific aims.

Thank you!

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www.cancer.gov/espanol