The Human Tumor Atlas Network

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NIH NATIONAL CANCER INSTITUTE

The Cancer Moonshot
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**

Recommendation I:
Generation of Human Tumor Atlases

Create dynamic 3-dimensional maps of human tumor evolution to document the genetic lesions, molecular pathways and cellular interactions that guide tumor development from a precancerous 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)

Defining Tumor Atlas

What is a tumor atlas?

A comprehensive tumor atlas can be defined as a **multidimensional molecular, cellular, and morphological mapping** of human cancers, **complemented with critical spatial information** (at the molecular, cellular, and/or tissue level) that **facilitate visualization of the structure, composition, and multiscale interactions** within the tumor ecosystem.

A **comprehensive tumor atlas** will inform:

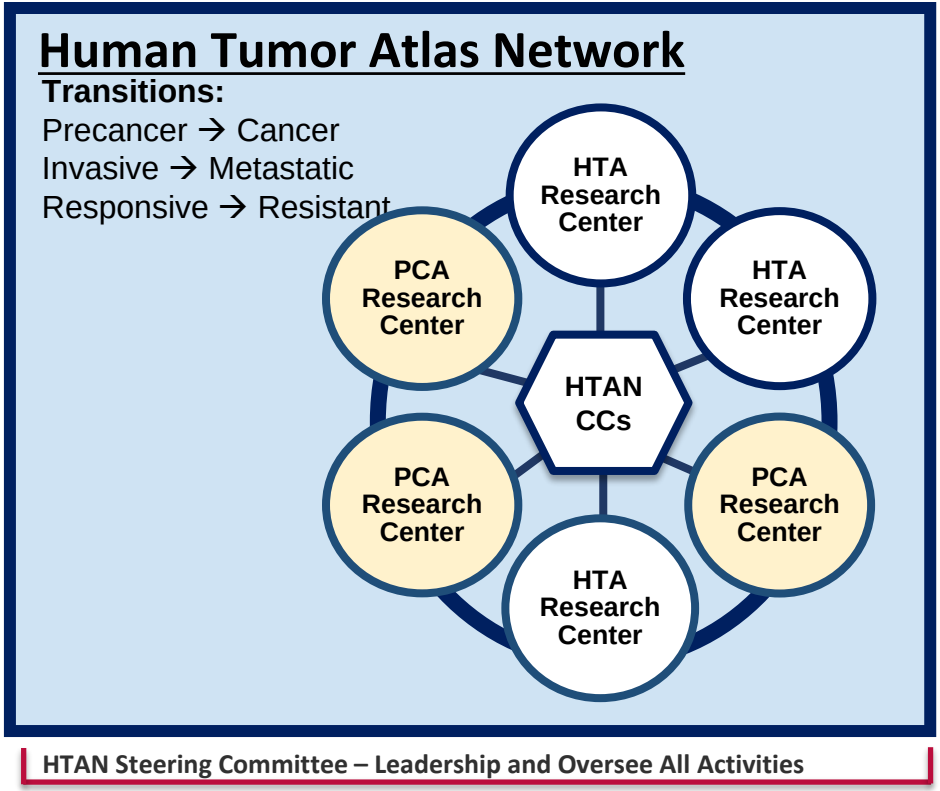
- Understanding of tumor heterogeneity and evolution
- Contribution of non-tumor components, such as stromal and immune cells, ECM
- Identification of markers of progression and drug resistance
- Development of early intervention strategies and robust therapies.

The Human Tumor Atlas Network (HTAN)

Goal: Construct pilot-scale human tumor atlases that facilitate basic and clinical scientific discovery regarding important transitions during tumorigenesis.

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. **PreCancer Atlas (PCA) Research Centers** (U2C) focused on construction of dynamic, multidimensional precancer 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 (HTA) Research Centers

RFA-CA-17-034 (U2C)

Tumor atlases supported under this FOA must focus on one of the following three important transitions in cancer:

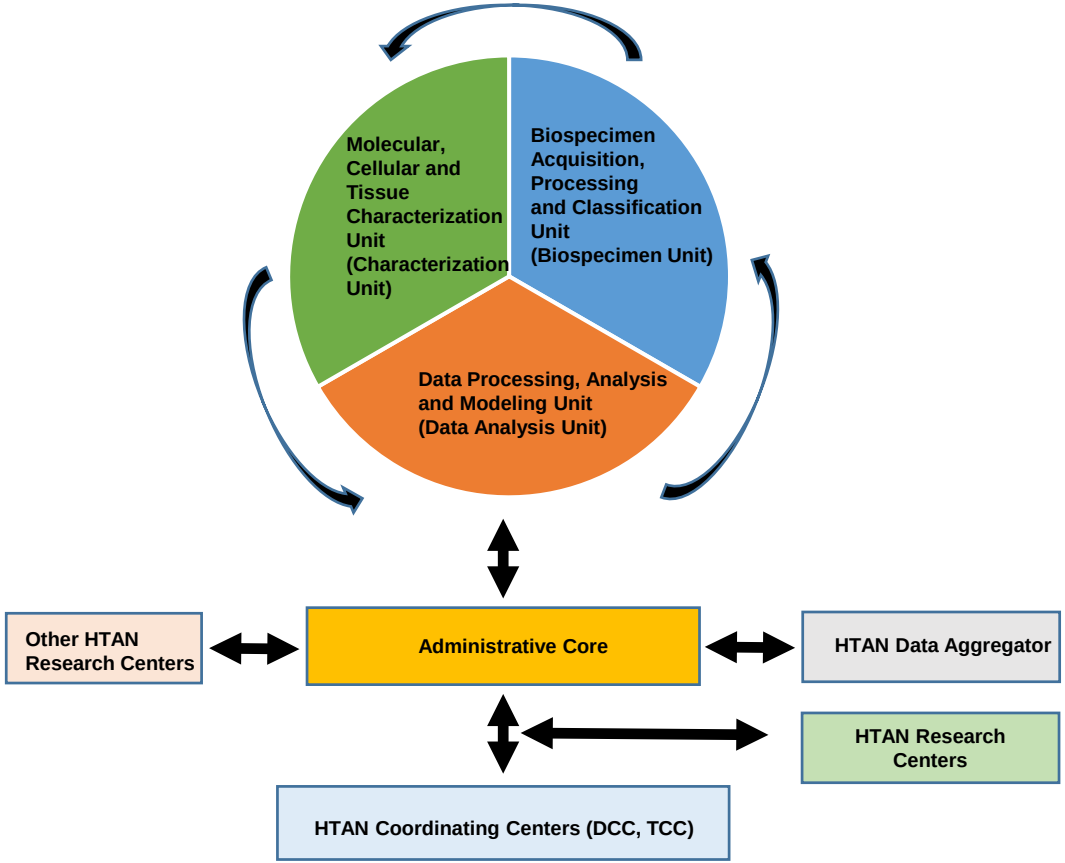
- ***The transition from locally invasive to metastatic cancer -*** atlases characterizing multiple metastatic sites, atlases describing the transition into or out of tumor dormancy, atlases capturing colonization of early disseminated tumor cells at distant sites.
- ***The dynamic response to therapy*** - atlases describing a positive response to traditional, targeted and/or immunotherapies, atlases that describe no response, incomplete response, or negative response to traditional, targeted and/or immunotherapies.
- ***The development of therapeutic resistance*** - atlases describing the transition from responsive to traditional, targeted, and/or immuno-therapy to resistant to that therapy.

The PreCancer Atlas (PCA)

RFA-CA-17-035 (U2C)

A human precancer atlas can be defined as a multidimensional cellular, morphological and molecular mapping of human premalignant 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.

Structure of the HTAN Research Centers

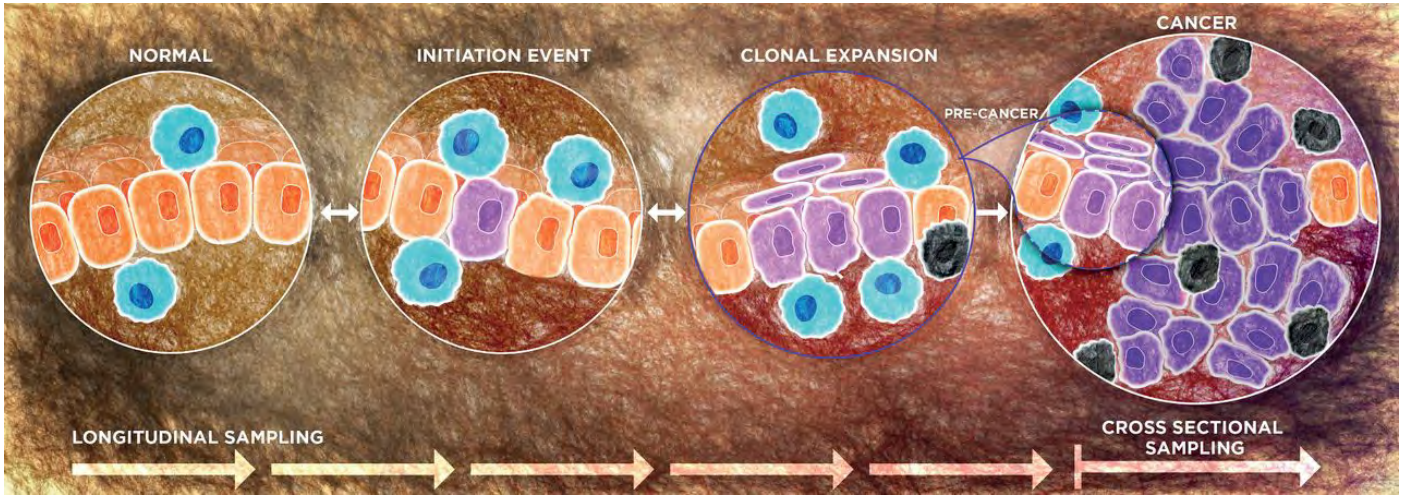


The HTAN Data Coordinating Center (DCC)

RFA-CA-17-036 (U24)

- The DCC will work closely with U2Cs.
- The HTAN-DCC will have **two major areas** of responsibility: (1) **Data Standards, Storage, Analysis, and Dissemination**(2) **Consortium Coordination**
- The HTAN-DCC will collect, **store, curate, and disseminate** all data, metadata, analysis and visualization tools, computational models, and **completed atlases** generated by the HTAN. Additionally, the DCC will **lead the development of** common data elements, data and metadata standards, clinical and epidemiological data requirements, and data processing pipelines. The DCC will also **coordinate HTAN activities** including in-person and virtual Network Steering Committee meetings and working groups.

PreCancer Atlas:
Charting Progression from PreCancer to Invasive Cancer

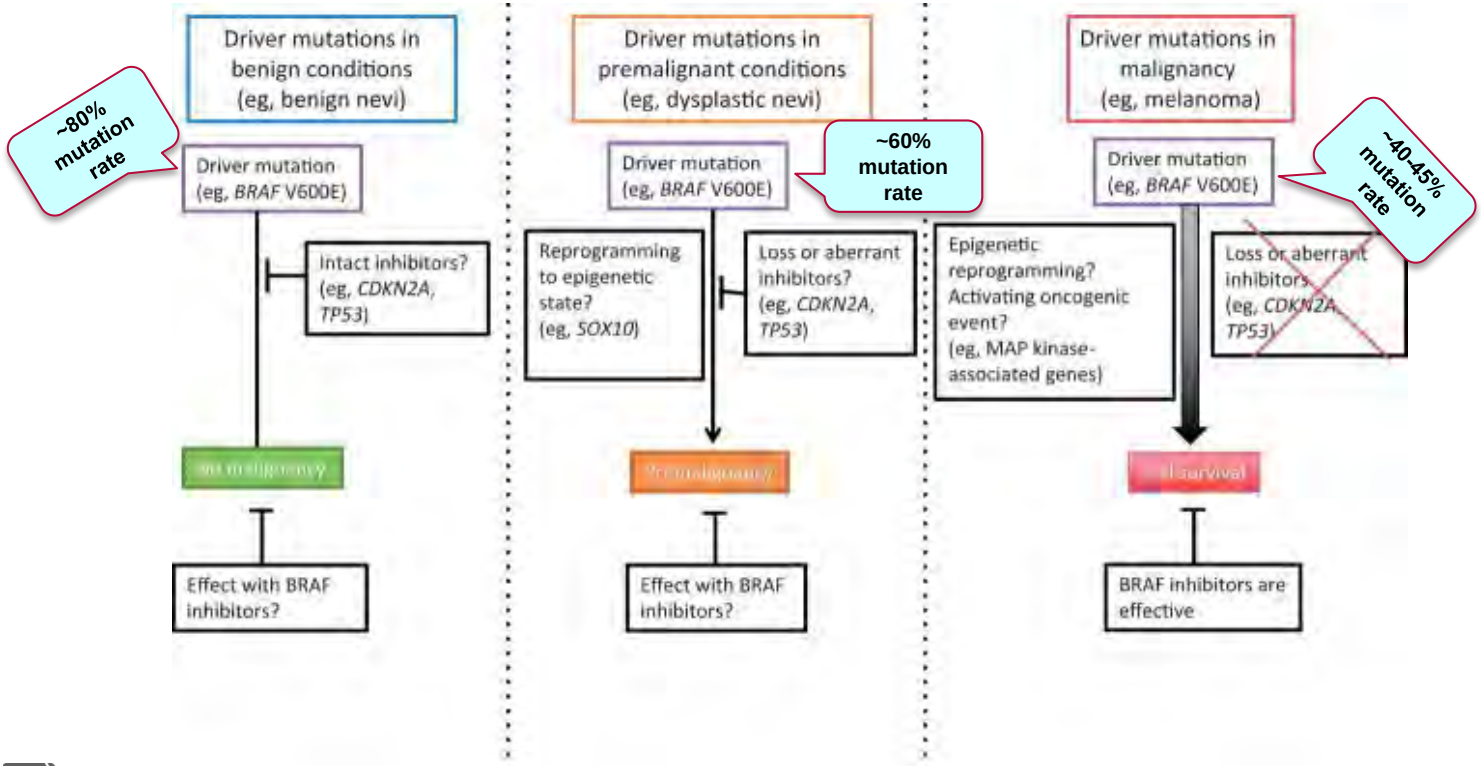


Comprehensive genomic profiling of longitudinally sampled premalignant lesions as they progress toward cancer will provide critical insights into the sequence of molecular events that drive progression to invasive cancer.

Courtesy: Campbell *et al*., *Cancer Prevention Research*, 2016, 9 (2)

The Enigma of Driver Mutations in Early Stage Cancer

Some driver mutations are more common in benign and premalignant conditions



Courtesy: Kato *et al.*, *J Natl Cancer Inst*, 2016, 108 (8)

Potential Players:
The Immune Microenvironment

- There is a need to characterize the complex interplay between the evolving mutations and the immune microenvironment (e.g., density of tumor-infiltrating lymphocytes [TIL], tumor associated macrophages, FoxP3+ regulatory T cells, other immune cell populations) as a premalignant lesion progresses to malignancy or regresses.

- Understanding how the immune microenvironment influences the tumor trajectory will not only help understand how tumors grow and evolve but also help develop intervention strategies.

What is an Atlas?

An **atlas** is a collection of **maps**; it is typically a **map** of earth or a region of earth, but there are atlases of other planets (and their satellites) in the solar system. Furthermore, atlases of anatomy exist, mapping out the human body or other organisms.

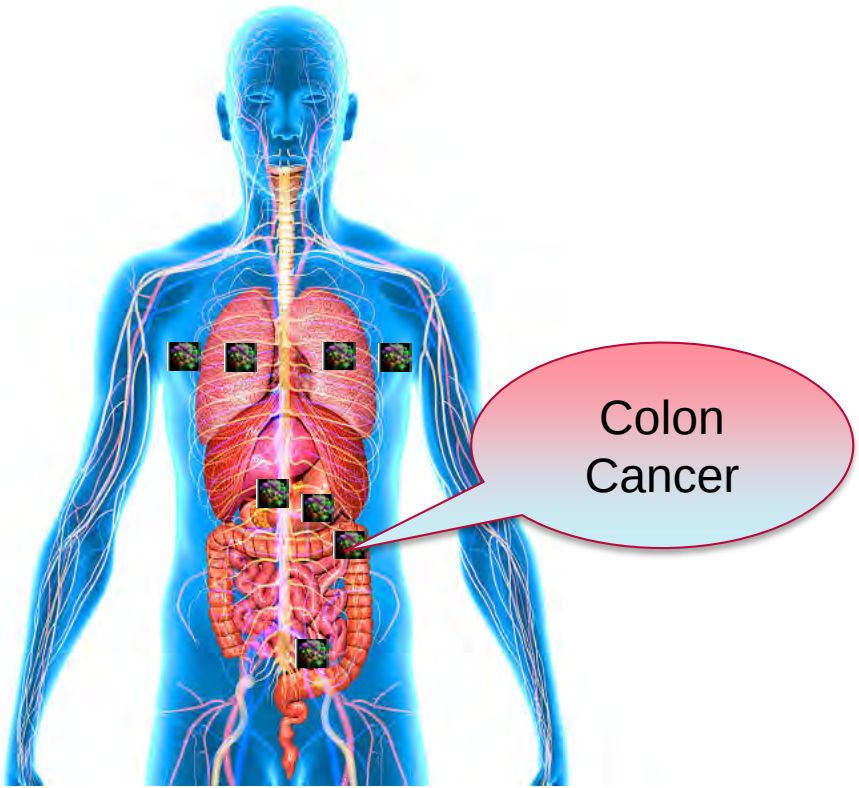
Developing a Framework for PreCancer Atlas

The National Cancer Institute's PreCancer Atlas Think Tank Meeting, June 15–16, 2017

Visualizing the PreCancer Atlas

Precision Detection

Clonality/
Heterogeneity
Breast
Pancreas
Prostate
Lung
Colorectal
Kidney
Stomach
Esophageal
Head & Neck
Hematologic



Molecular and Cellular Profile

Solid Tumors

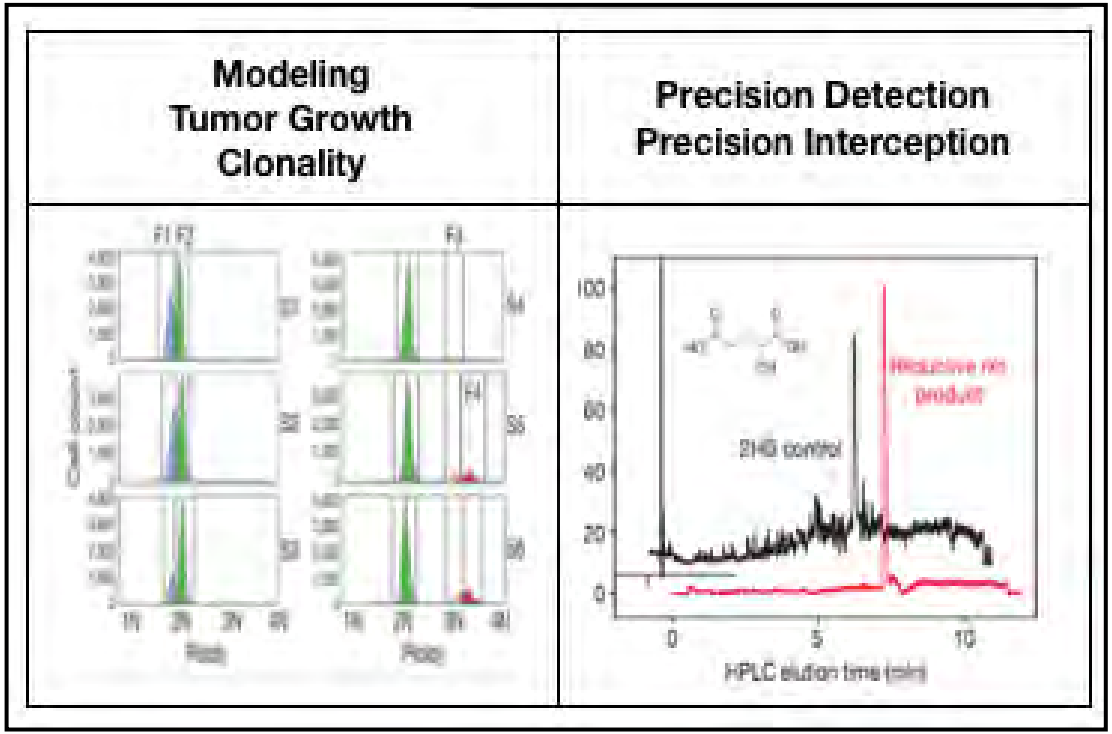
Genome (WGS, Exome)
Epigenome
Transcriptome
Proteome
Metabolome
Lipidome
Microbiome
Immune Milieu

Hematologic Malignancies

What Types of Data to Be Collected to support Atlas?

https://pre-cancer-atlas.jpl.nasa.gov/miscellaneous/pca.mp4/@@download/file/pca.mp4

Building Tumor Growth and Clonality Models



Computational Challenges for Tumor Atlases

- Development of algorithms to support the analysis of complex data sets arising from multiple biotechnologies for analyzing omic, imaging and another phenotypic features
- Need for supporting experimental methodologies, especially for precancerous lesions where the amount of sample available is limited.
- Need for algorithms for data capture, integration, and analysis with fewer false discovery and biases.
- How to visualize tumor atlases?

Methodological Challenges

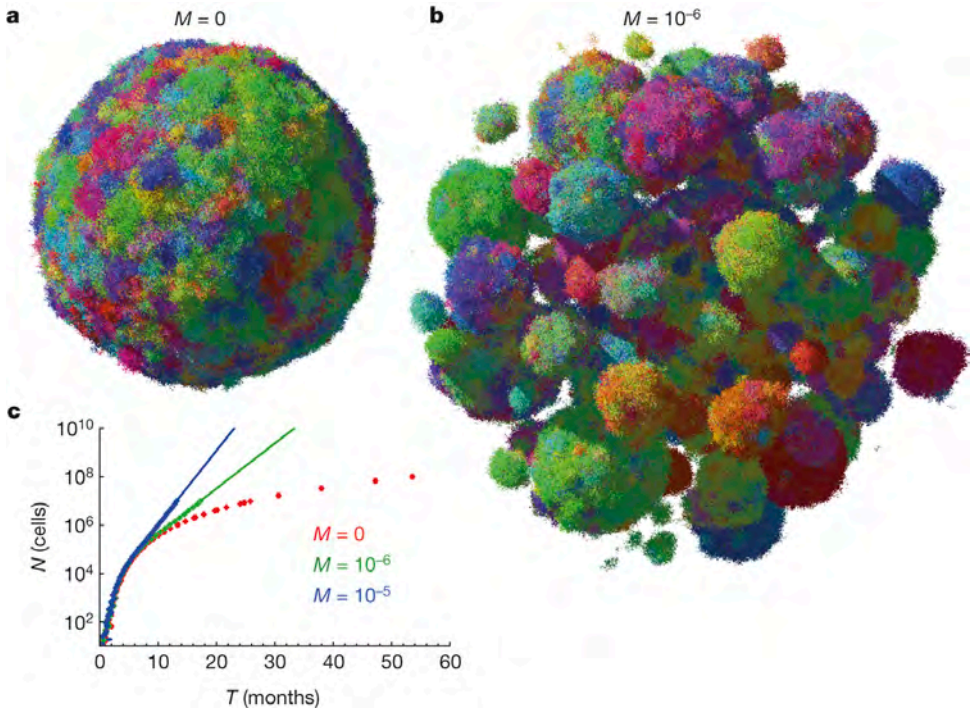
- How to characterize samples from a small amount of specimens, especially for precancer lesions?
- Single cell analyses for precancer lesions using paraffin-preserved specimens/slides in the absence of freshly frozen samples;
- How to optimize molecular, cellular and genomic characterization techniques for tiny amounts of specimens?
- Decision on bulk versus micro-dissected samples.

Study Design Challenges

In the absence of serial and longitudinal samples for precancer, how would the study be designed to be informative in time and space;

- sample size
- multiplicity
- variability in laboratory measures
- how to define normal sample?
- How to reduce bias and chance

Visualization of Atlas Challenge:
Spatial Model for Tumor Atlas: Heterogeneity as an example



Waclaw *et al. Nature* 525, 261-264 (2015)

Summary

- The human tumor atlases will accelerate the progress in precision detection, prevention and treatment
- The precancer atlas(es) will provide molecular snapshots of events (genomic, proteomic, epigenomic, cellular, immune cells) in time and space
- Precancer atlases will help understand the biological underpinnings of progression or regression of premalignant lesions
- Precancer atlases will provide the opportunity to identify early detection markers and chemopreventive and immunopreventive targets for precision prevention of advanced cancers

The HTAN Team

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Thank You

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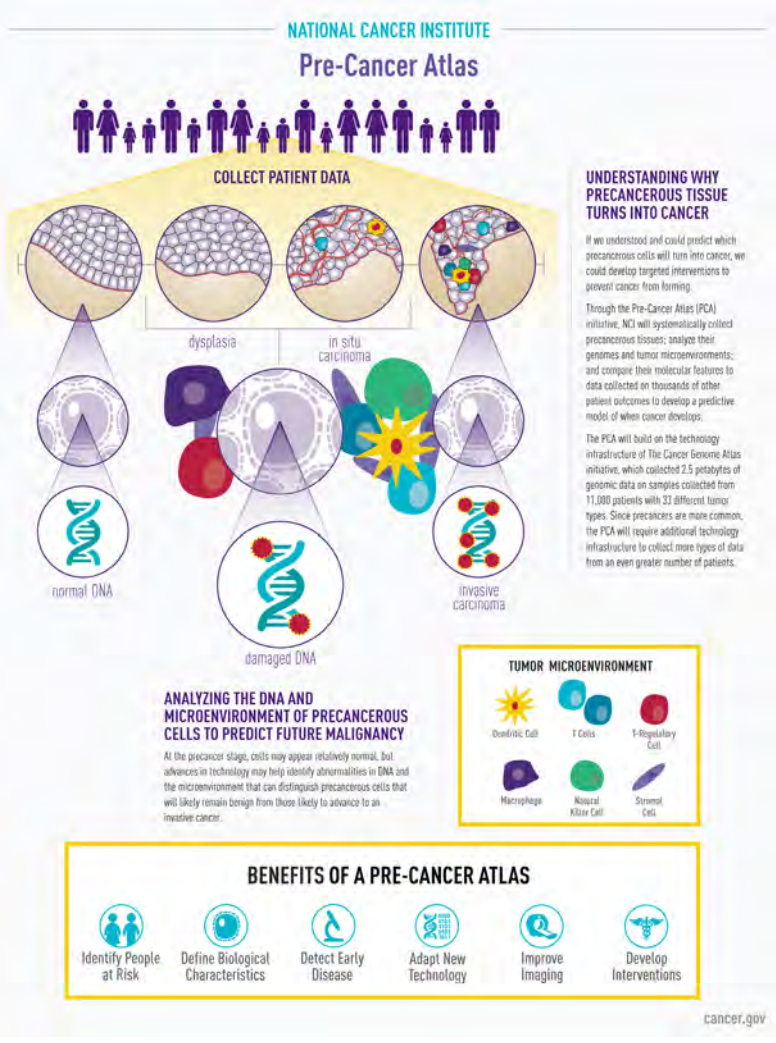
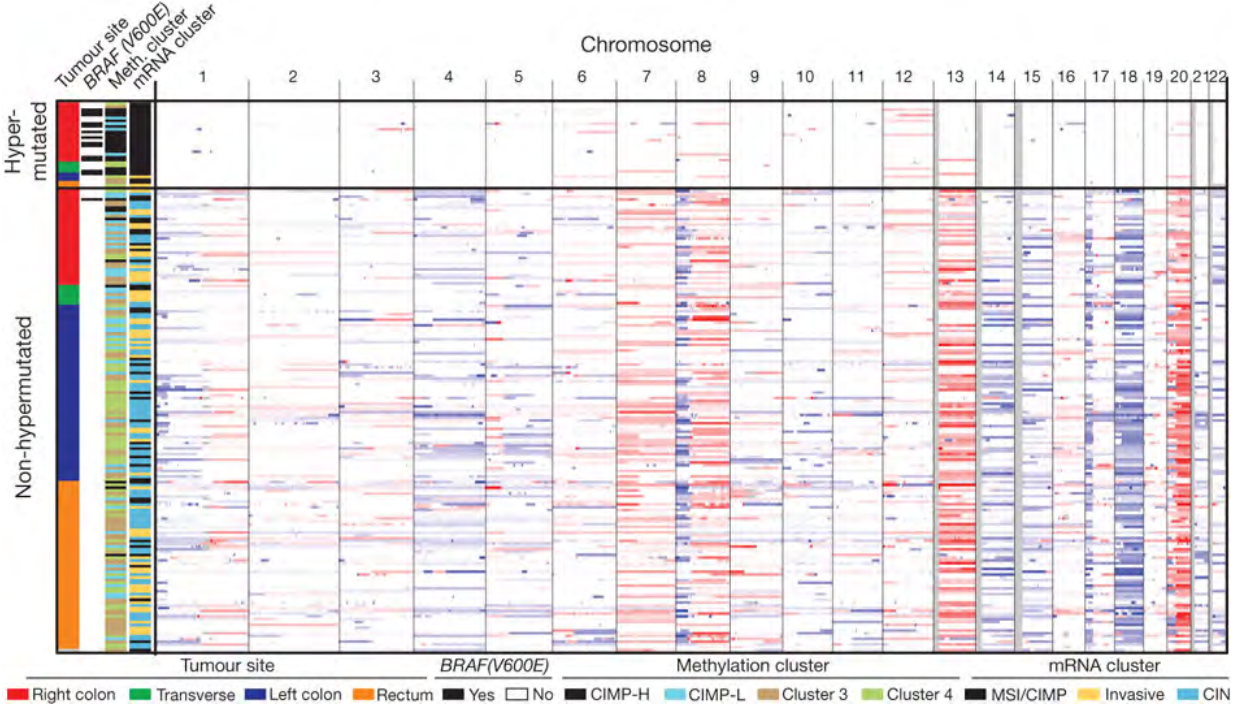
www.cancer.gov/espanol

Envisioning Applications of PreCancer Atlas

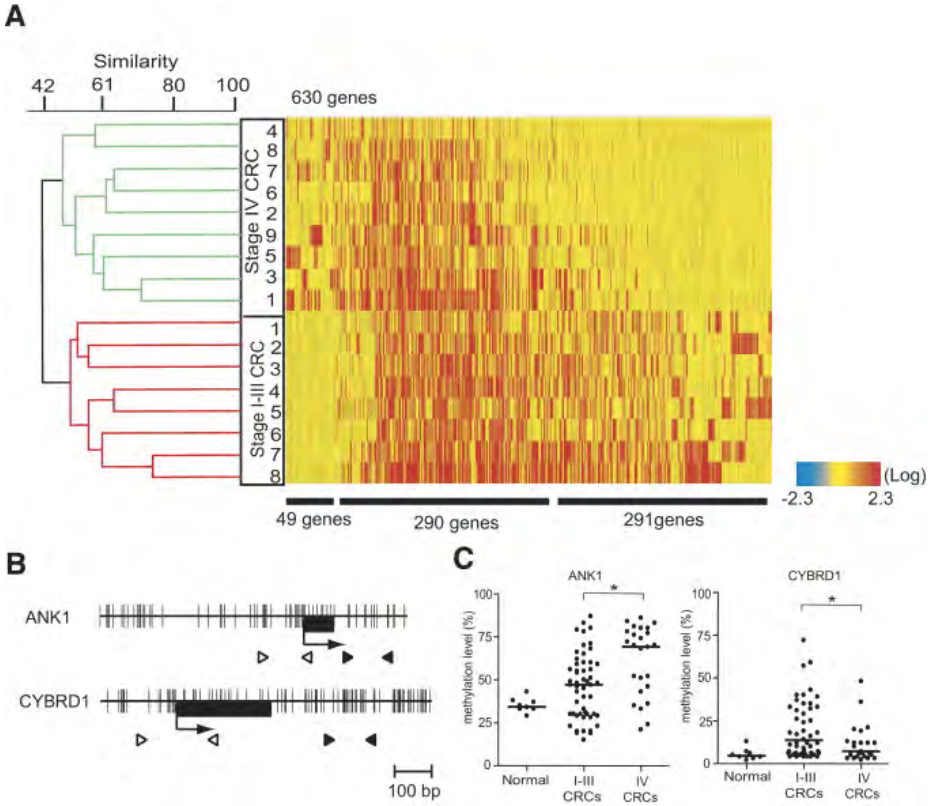


Integrative analysis of Genomic Changes in 195 Colorectal Cancers



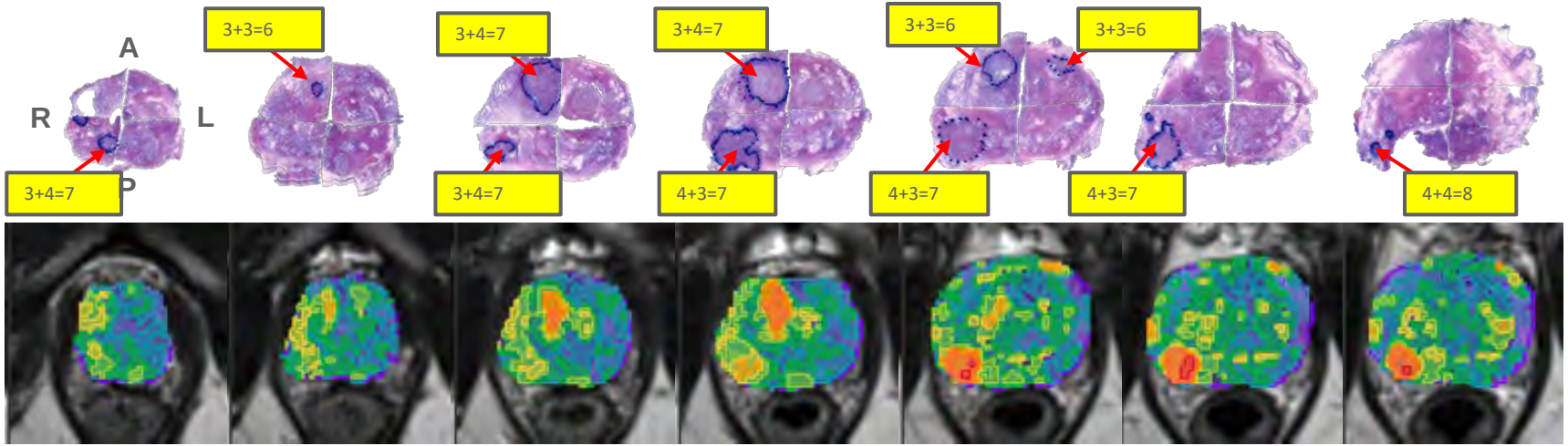
The Cancer Genome Atlas Network *Nature* **487**, 330-337 (2012) doi:10.1038/nature11252

Epigenetic Profile



The American Journal of Pathology, Vol. 178, No. 4, April 2011

Imaging Tumor Heterogeneity



Map of tumor habitats, based on ten-scale Habitat Risk Score (HRS). HRS is based on unique combination of analytic methods that extracts quantitative information from established MRI sequences for perfusion (Dynamic Contrast Enhanced (DCE-) MRI and diffusion (Diffusion Weighted Imaging (DWI)). An example of the excellent spatial concordance of these maps with histopathology is shown in the figure above. The hottest spots of the 3D heat-map depict higher microscopic tumor grade. (top panel) Pseudo-whole mount H&E-stained histopathology sections. The consecutive axial slices are displayed from apex (left) to base (right). Tumor nodules are labeled with the corresponding Gleason Score (GS). Note the heterogeneity of the right posterior nodule with increasing GS: 3+4=7, 4+3=7 and 4+4=8 (apex to base). The GS of the right anterior nodule changes from 3+3=6 to 3+4=7 and back to 3+3=6. (bottom panel) Corresponding Habitat Risk Score (HRS) maps, displayed on axial T2w slices. Image data is resampled at the same spacing (0.3 to 0.4 cm) as the histopathology specimens. Note that the color intensities of the heat-map correlate with the higher microscopic tumor grade.
Abbreviations: A = anterior; L = left; P = posterior; R = right

Courtesy: Radka Stoyanova, U Miami