National Cancer Institute

National Human Genome Research Institute

Status Report:
The Cancer Genome Atlas Pilot Project

National Cancer Advisory Board Meeting

February 6, 2007

Anna D. Barker, Ph.D.
Deputy Director, National Cancer Institute

National Cancer Institute

National Human Genome Research Institute

TCGA: An NCI-NHGRI Collaboration in Medical Genomics

THE CANCER GENOME ATLAS

The Cancer Genome Atlas (TCGA)

is a three-year pilot project of the
National Cancer Institute and
the National Human Genome Research Institute
to increase our comprehensive understanding of the
genetic basis of cancer.

It is anticipated that TCGA's integrated database of molecular and clinical information will provide scientists unprecedented opportunities to discover and develop a new generation of targeted diagnostics, therapies, and preventives for cancer.

Enabling Rationale for TCGA

Achievements:

1. Human Genome Project
2. Gene families and pathways
3. Robust genomic analysis technologies
4. Sanger experience - sequenced known genes (e.g., kinases are druggable)
5. Number of early indications that somatic mutations are important potential targets

Overall Impact:

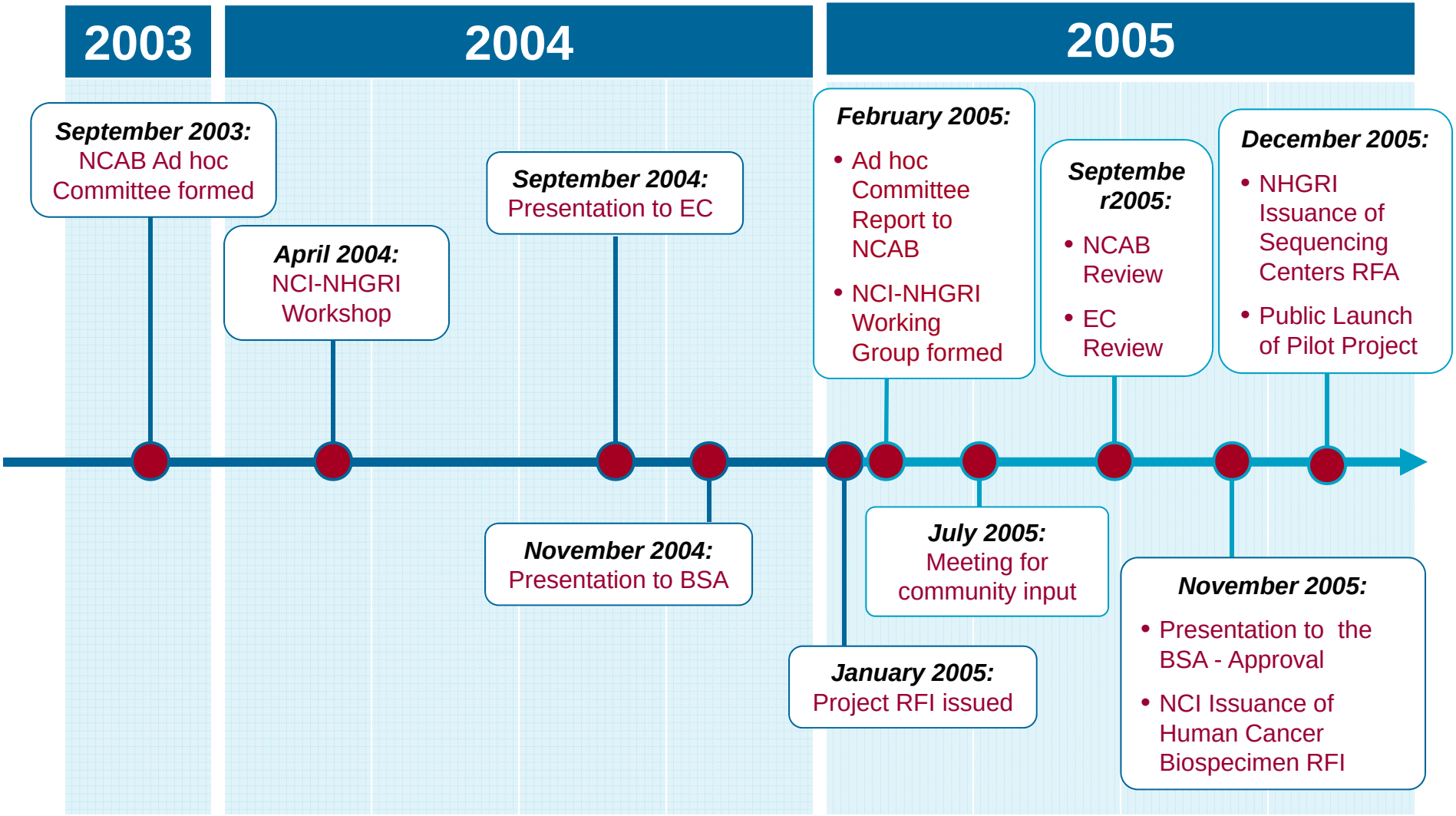
1. Known human sequence
2. Kinases, phosphatases, transcription factors, hormone responsiveness
3. Copy number changes, expression profiling, potentially epigenomic technologies
4. Survey of known genes that are abnormal *prior to sequencing - BRAF*
5. *BCR-ABL, EGFR1, ERBB2*

National Cancer Institute

National Human Genome Research Institute

TCGA Development Milestones

THE CANCER GENOME ATLAS

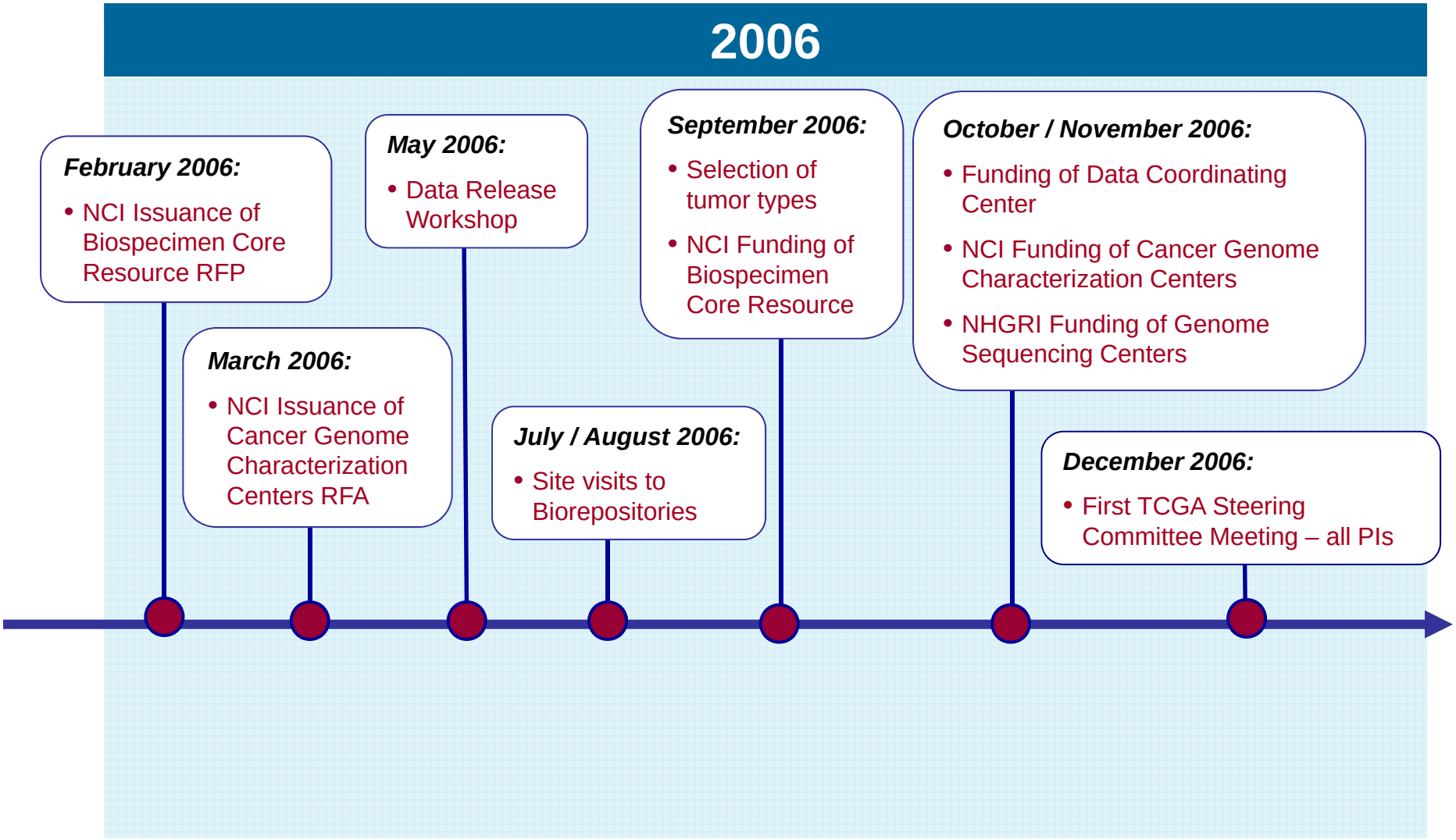


National Cancer Institute

National Human Genome Research Institute

TCGA Development Milestones

THE CANCER GENOME ATLAS



TCGA Development Milestones

THE CANCER GENOME ATLAS

2007

January / February 2007:

- TCGA Dry Run

March 2007:

- Biospecimen Core Resource distributes GBM, lung, and ovarian tumor biomolecules to GSCs and CGCCs

March / April 2007:

- GSCs and CGCCs perform sequencing and characterization of tumor biomolecules

May 2007:

- First set of TCGA data is deposited into public databases managed by DCC

TCGA: How it Works

National Human Genome Research Institute

TCGA Biospecimen Core Resource (BCR) Functions

Central to the Success of TCGA Pilot, the BCR is:

- Verifying all biologic and clinical data and performing the pathologic QC of qualified tumors from selected existing collections
- Performing central processing of specimens to provide uniform biomolecules and distributing to both genome characterization and sequencing centers
- Tracking and quality assuring all specimen-related operations (consent, acquisition, transport, processing, QC, distribution)
- Providing “standard” samples for technology platform comparisons
- Developing (with the Office of Biorepositories and Biospecimen Research) and monitor the SOPs for prospective specimen collection
- Serving as a member of TCGA’s Steering Committee

Cancer Genome Characterization Centers (CGCCs)

- **Technology platforms for high-throughput genome characterization:**
  - ✓ Expression profiling
  - ✓ Copy number changes
  - ✓ DNA methylation (epigenomics)
- **Improve existing technologies:**
  - ✓ Epigenomics to meet required throughput rate
  - ✓ Copy number detection and expression profiling for characterizing small amount of biological samples
- **Real-time data release into public database**

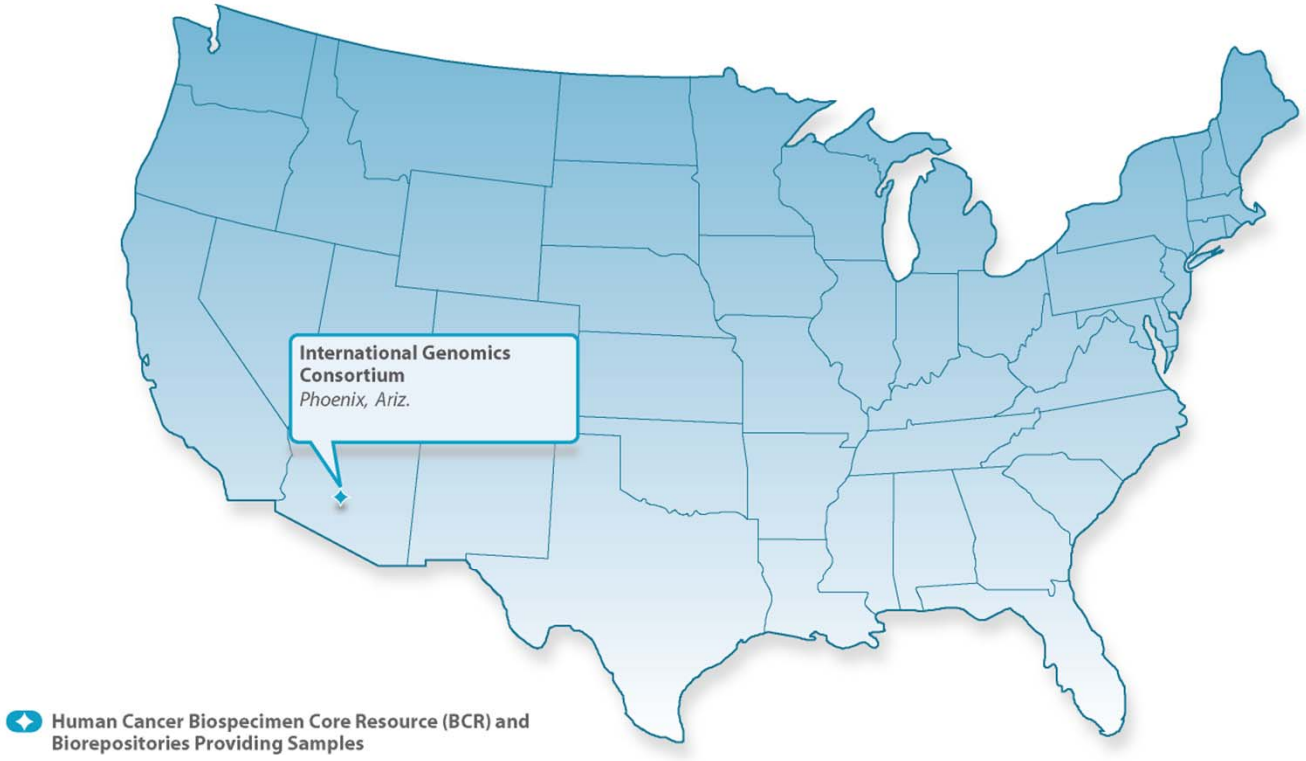
Genome Sequencing Centers

- **High-throughput Genome Sequencing Centers (NHGRI):**
  - ✓ Sequence large number of targets from three tumor types
  - ✓ Develop and integrate sequencing technologies

Data Coordinating Center

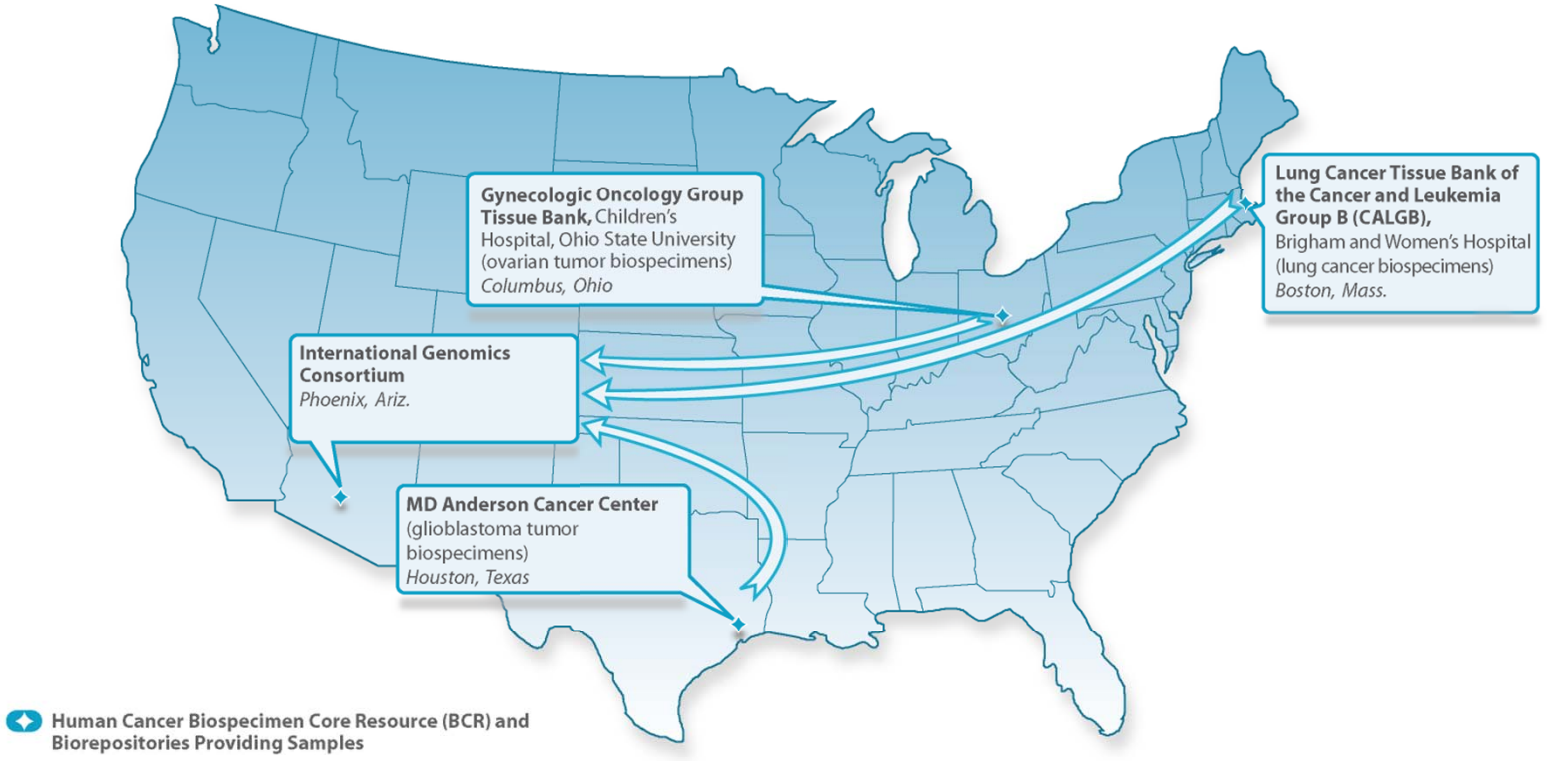
- **Platform for data collection and management**
  - ✓ Track data produced by components of TCGA
  - ✓ Ensure that data meets quality standards set for TCGA
  - ✓ Make TCGA data publicly accessible through databases supported by NCI's Cancer Biomedical Informatics Grid™ (caBIG™) and the National Library of Medicine's National Center for Biotechnology Information
  - ✓ Scientists will have access to TCGA data to generate new insights into causes and potential targets for interventions
  - ✓ Access to all TCGA data will be provided in a manner that meets the highest standards for protection and respect of the research participants

TCGA Components



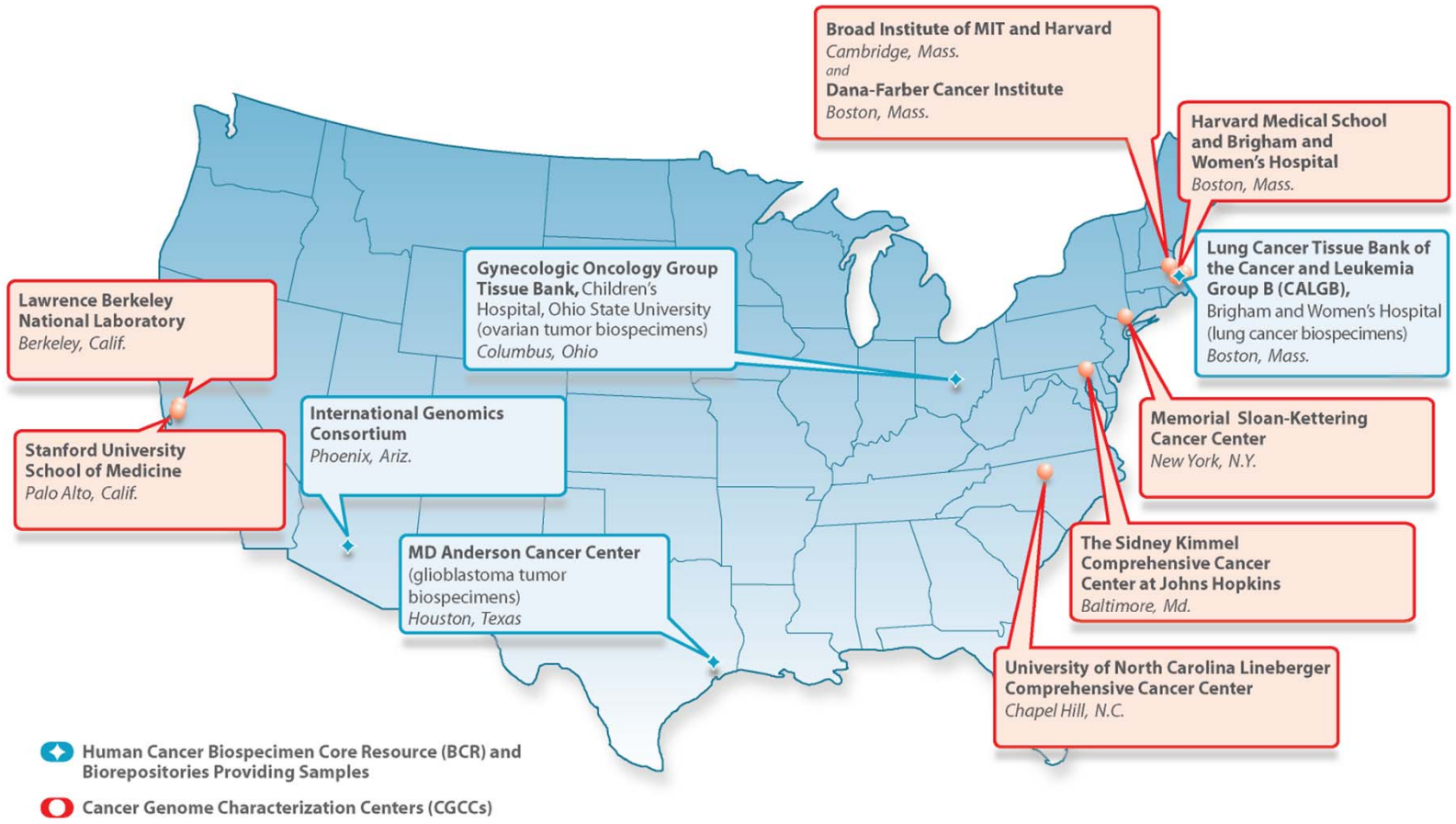
TCGA Components

THE CANCER GENOME ATLAS



TCGA Components

THE CANCER GENOME ATLAS

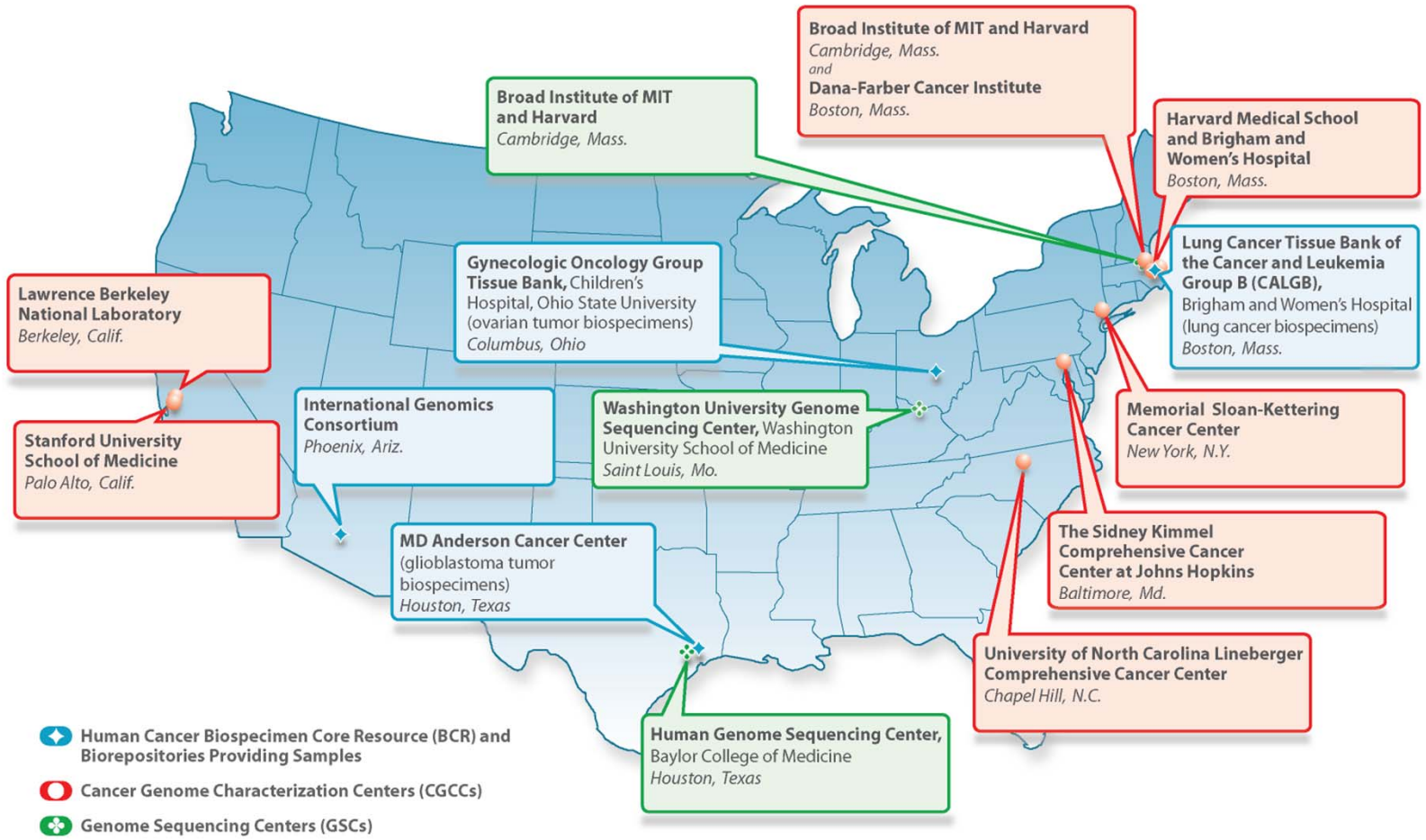


National Cancer Institute

National Human Genome Research Institute

TCGA Components

THE CANCER GENOME ATLAS

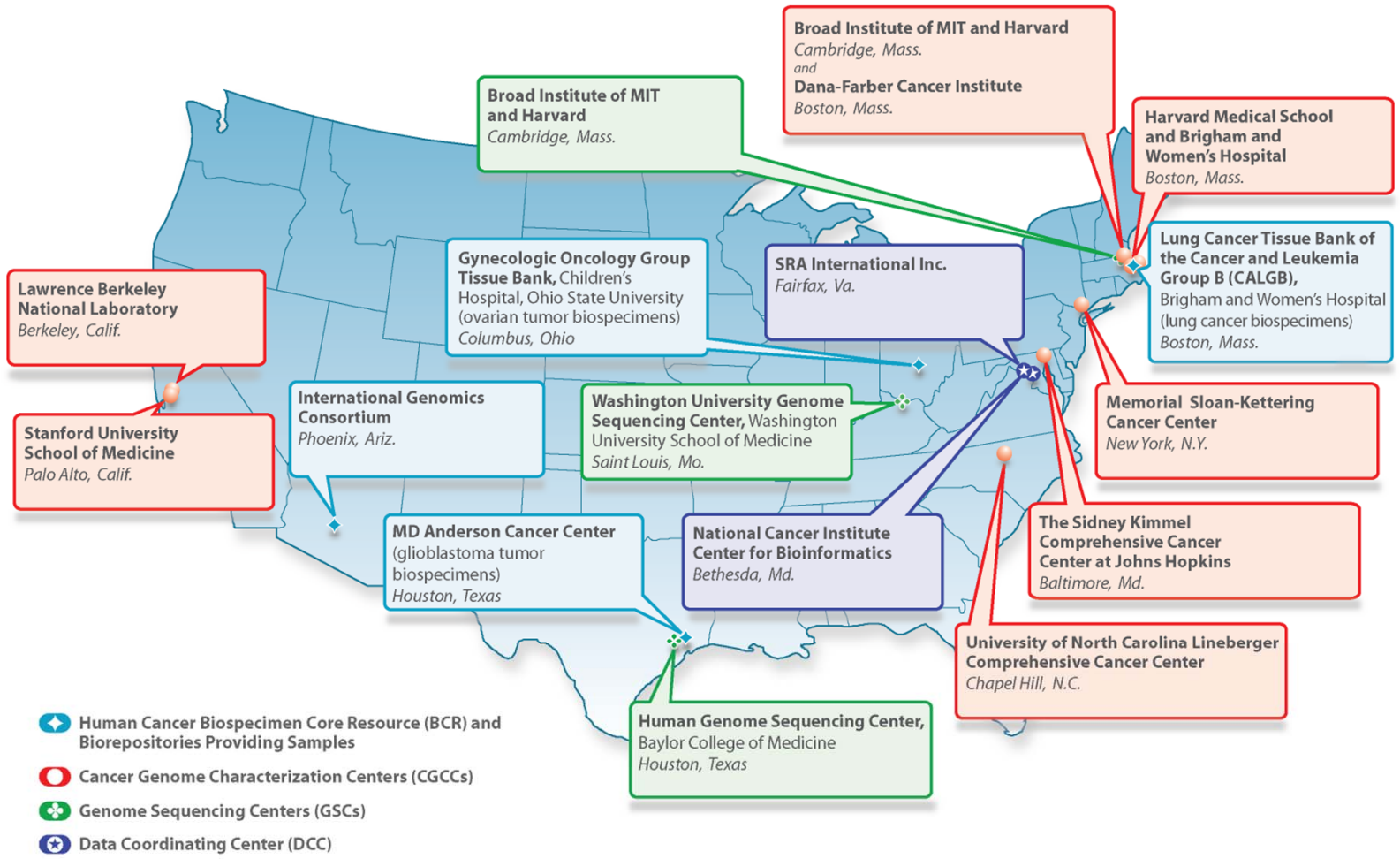


National Cancer Institute

National Human Genome Research Institute

TCGA Components

THE CANCER GENOME ATLAS



National Cancer Institute

National Human Genome Research Institute

TCGA Components – Procurement Process Completed in 2006

THE CANCER GENOME ATLAS

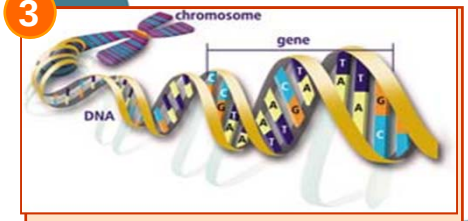
1

A patient donates tumor tissue for study.

2

Scientists study genetic material in the tumor tissue.

3

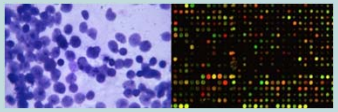


To find the genetic signatures for cancer, scientists study genetic material in many patients' tissues.

Data Management, Bioinformatics, and Computational Analysis

Genome Sequencing Centers

Cancer Genome Characterization Centers



4

Technology Development

Human Cancer Biospecimen Core Resource

5

Scientists analyze the data produced by TCGA, and develop a web-based information database.

6

Scientists use information in the database to speed research advances.

7

Research results are translated into new products to help patients.

Patient Community | TGCA Network | Research & Medical Communities

Tumors Selected for Study in the Pilot Project

- **Brain (glioblastoma)**
- **Lung**
- **Ovarian**

These three cancers collectively account for more than 210,000 cancer cases each year in the United States.

Glioblastoma is Ideal for TCGA Study

- A "homogenous" tumor – or about as good as it gets
  - Single grade (highest grade) of a single histological type of cancer
- Few other cell types, such as stromal cells or inflammatory cells, that might contribute extraneous, non-tumor DNA to the extracted biomolecules

Genetic Defects in Glioblastoma Suggest Therapeutic Interventions

THE CANCER GENOME ATLAS

- To date, glioblastomas seem to have the greatest number of genetic changes of all astrocyte-based cancers.
- A recent study systematically sequenced all tyrosine kinase genes in glioblastomas, confirming the presence of mutations in these and other genes involved in proliferation pathways.
- There are many proliferation pathway-targeted drugs in clinical trials, underlining the role of genetic complexity in glioblastoma.

Selected Small Molecule Targeted Agents Being Studied in Patients With Glioma

Class	Agent
Monoclonal antibodies	Cetuximab R3 EMD 55900
Toxin-linked conjugates	TGF-PE38 IL-13-PE38
EGFR tyrosine kinase inhibitors	Gefitinib (Iressa) Erlotinib (Tarceva) Imatinib mesylate (Gleevec)
PI3K inhibitors	Wortmannin LY294002
Mammalian target of rapamycin inhibitors (mTORs)	Rapamycin CCI-779 RAD001
Farnesyltransferase inhibitors	R111577 SCH66336
Antiangiogenic agents	Thalidomide CC-5103 PTK787
Anti-invasive agents	Cilengitide Marimastat
Cell growth and migration inhibitor	Accutane

From Butowski and Chang (2005). Current Topics in Oncology

* Rand et al. (2005) *Proc. Natl. Acad. Sci. U S A*. 102(40): 14344-14349

Target Selection

- Identification of known cancer genes
- Integration of all cancer gene data bases
- Selection of a small number of genes (~800-1,000) to begin sequencing in glioblastoma samples
- Meeting with GBM experts to discuss strategy for identification of new genes from TCGA the CGCCs
- Meeting with participants in NCI's other programs to begin data interrogation processes

TCGA and Informed Consent

Key Issues:

- How detailed should informed consent be – more information vs. less? TCGA's informed consent is lengthy and detailed
- Who should have access to data?
- How do we leverage and capitalize on potential for progress against disease and ensure privacy protection? TCGA will provide two levels of data access – one completely open; the other password controlled
- Solving the issues of data access vs. patient protection will likely required genetic privacy legislation

TCGA's Informed Consent Approach

- Permission for detailed genomic research
- Permission for broad future research use of samples and health information
- Permission to place genomic and health information in widely accessible databases – with limitations
- Risks associated with loss of privacy
- Potential benefits for future cancer patients
- Issues related to withdrawal (data and samples)

Some Success Factors for TCGA

Three-Year Time Horizon

- Completion of genomic analysis of three tumors, hopefully leading to identification of new genes involved in these cancers
- Ability to find and identify specific genomic alterations in genes associated with cancer
- Ability to differentiate tumor subtypes based on genomic alterations
- Establishment of a genomics database that scientists can access – new questions – new research

TCGA's Potential Impact

- Identification of somatic changes in cancer genomes that could establish the molecular basis for each cancer – and inform and enable a new era of molecular oncology
- A molecular taxonomy of cancer
- New molecular targets for diagnostics, therapeutics, and preventives
- Improved ability to stratify patients for clinical trials

For More Information: Joint NCI-NHGRI TCGA Website

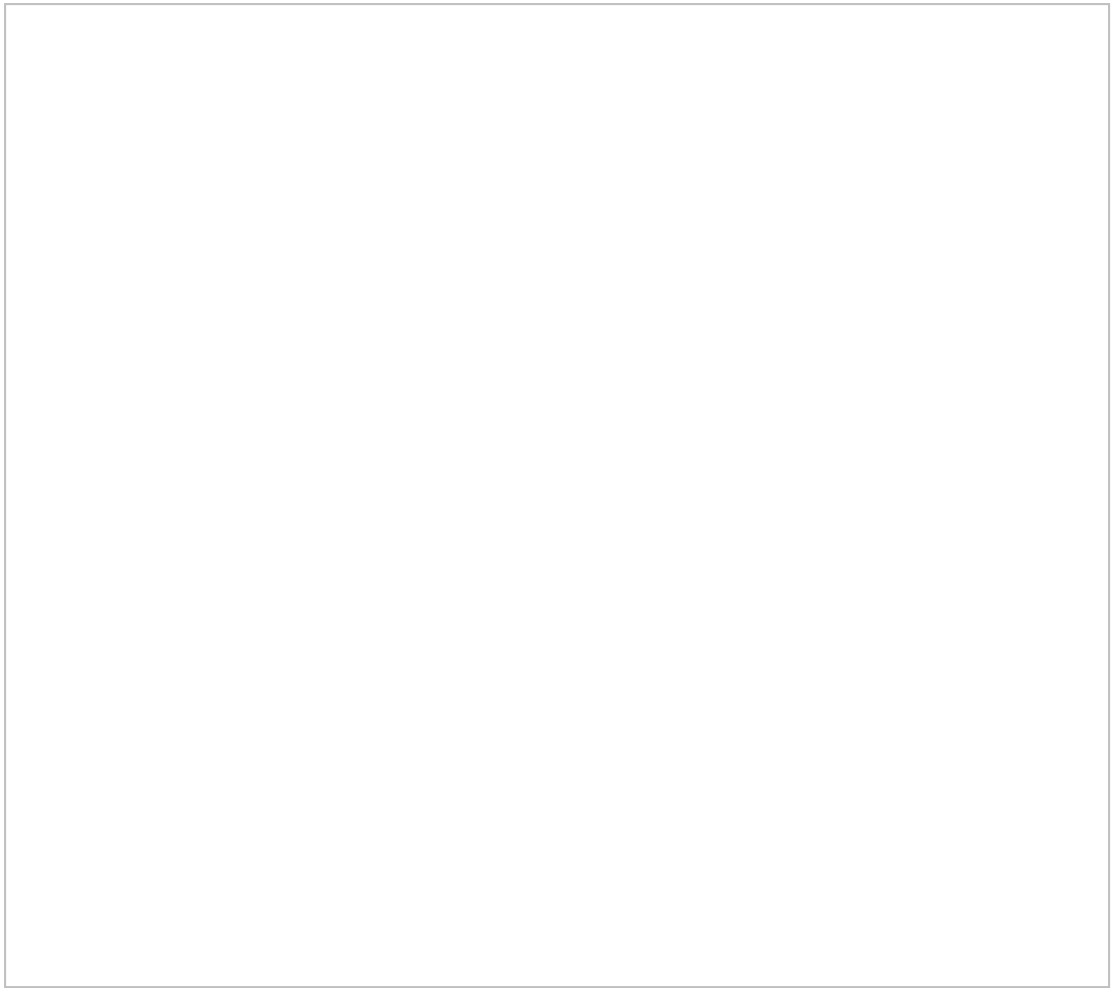
THE CANCER GENOME ATLAS

Updates on TCGA website:

- ✓ Information for patients, scientists, clinicians, policymakers, and the public

Coming Soon:

Sign up at the TCGA website to receive automatic updates and event news



http://cancergenome.nih.gov