

The NHGRI Extramural Program and Translational Research

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- NHGRI mission
- Nature of genomic research & relationship to translational research/clinical applications
- TCGA as an example
- (HMP)

Since the completion of the Human Genome Project, the NHGRI's mission has expanded to encompass a broad range of studies *aimed at understanding the structure and function of the human genome and its role in health and disease*

NHGRI-Sponsored Programs

- **Role is integrative, creating scientific infrastructure**
- **Data types of wide-spread utility across wide areas of biomedical research**
- **Community Resource Projects**

NHGRI-Sponsored Programs

- **Comprehensive catalogues, that can be produced**
 - **Efficiently**
 - **High data quality**
 - **Rapid, pre-publication data release**
- **Highly managed**
 - **Organized as Research Consortia**
 - **Funded as cooperative agreements**

NHGRI-Sponsored Programs

International Collaborations

- **Human Genome Project**
- **International HapMap Project**
- **International Cancer Genomics Consortium**
- **International Human Microbiome Consortium**
- **International Knockout Mouse Consortium**
- **1000 Genomes Project**
- **.....**

Disease with Genetic Component



Identify Genetic Risk Factors



Diagnostics



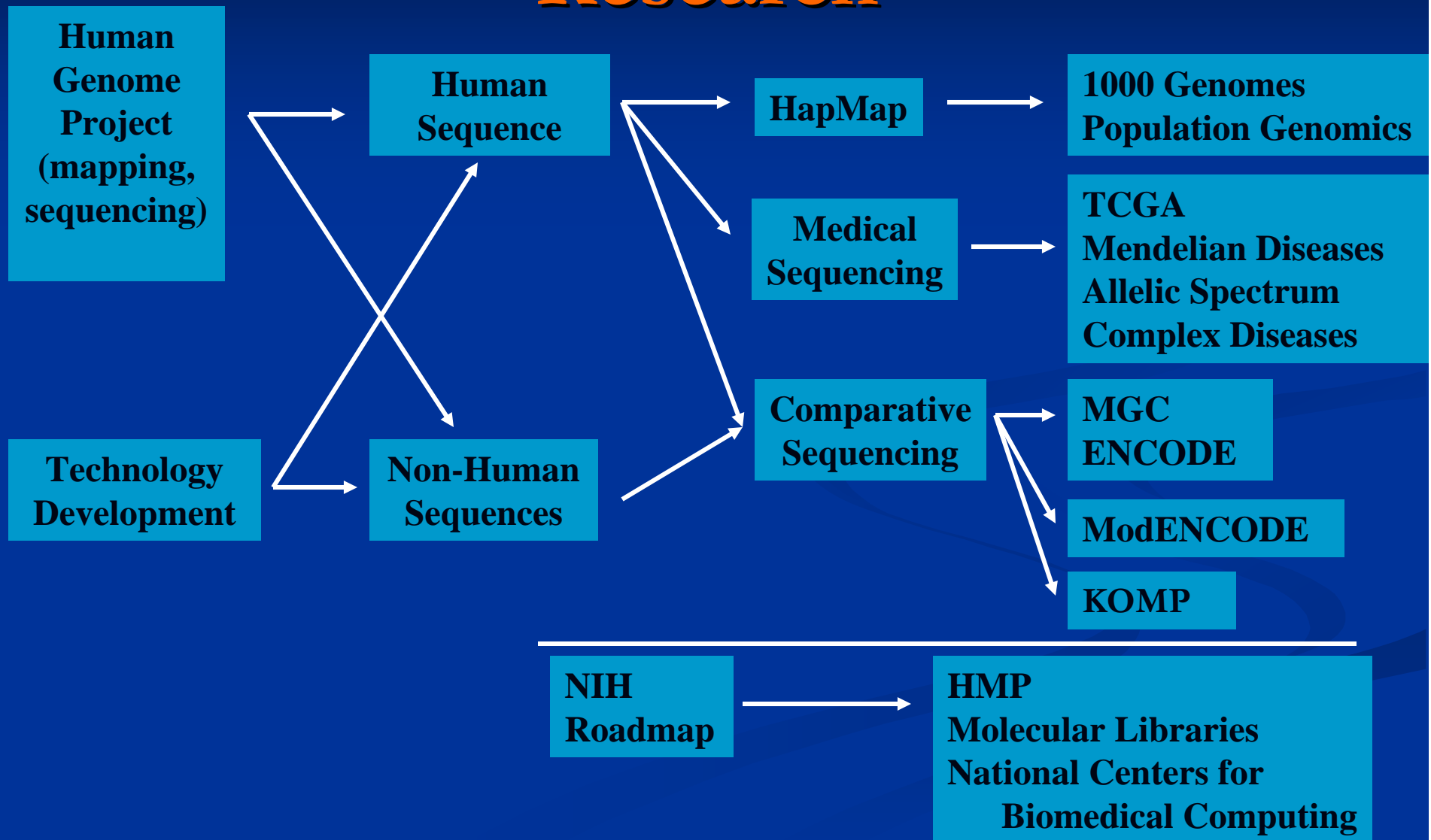
**Preventive
Medicine**

**Accelerated
by Human
Genome Project
and HapMap**

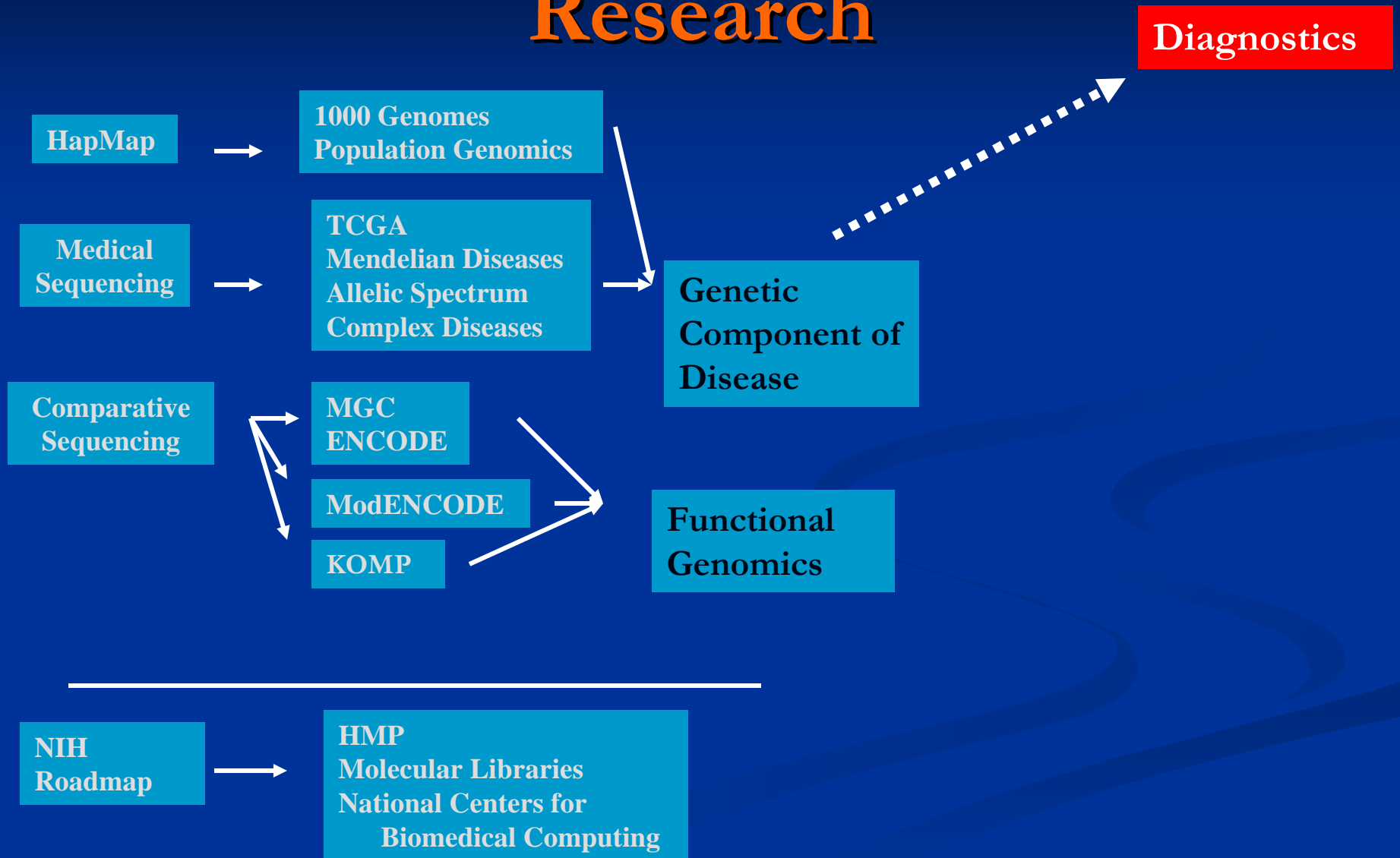
Time



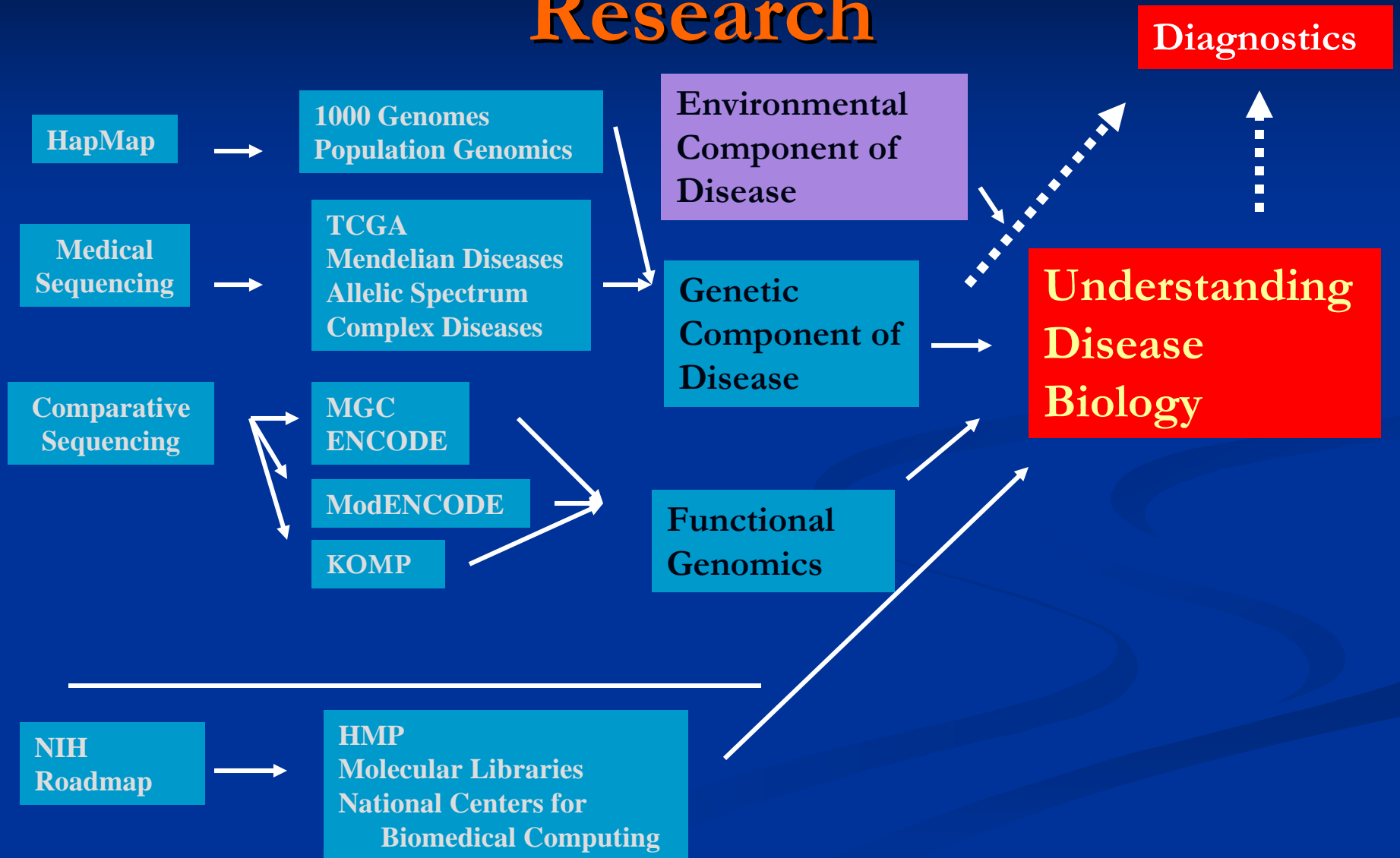
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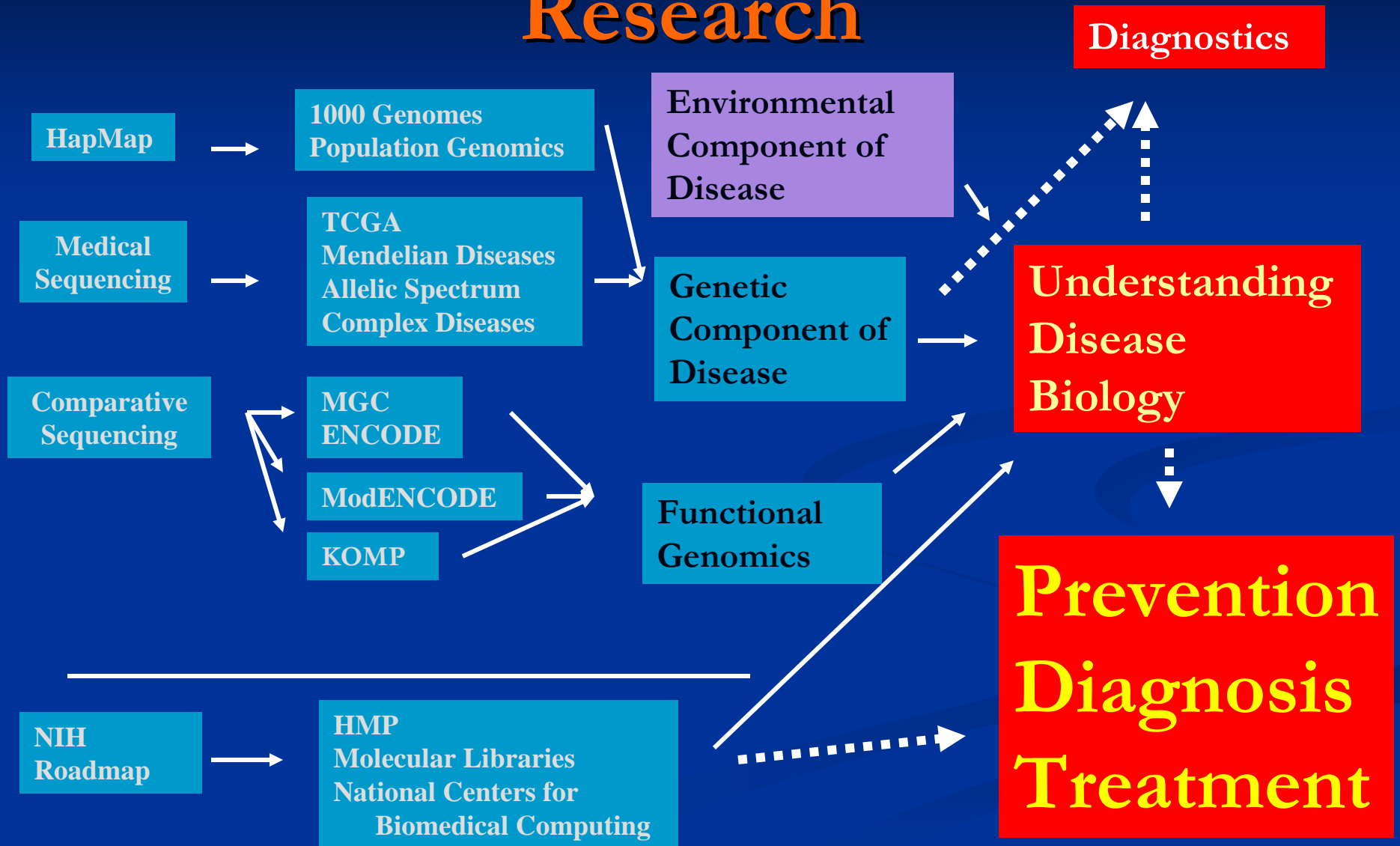
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RFAs and PAs Associated with Genomics in 2007-2008

AHRQ

1. **AHRQ Health Services Research (R01)**

NCCAM

1. **Omics and Variable Responses to CAM: Secondary Analysis of CAM Clinical Trials (R01) (R21)**

NCRR

1. **IDeA Networks of Biomedical Research Excellence (INBRE) [P20]**

NCI

1. **SBIR Phase II Bridge Awards to Accelerate the Development of New Cancer Therapies and Cancer Imaging Technologies Toward Commercialization (R44)**
2. **Enhancing Tumoricidal Activity of Natural Killer (NK) Cells by Dietary Components for Cancer Prevention (R01) (R21)**
3. **Exfoliated Cells, Bioactive Food Components, and Cancer (R21)**
4. **Research on Malignancies in the Context of HIV/AIDS (R21) (R01)**
5. **Feasibility Studies for Collaborative Interaction for Minority Institution/Cancer Center Partnership (P20)**
6. **Academic-Industrial Partnerships for Development and Validation of In Vivo Imaging Systems and Methods for Cancer Investigations (R01)**
7. **Understanding the Effects of Emerging Cellular, Molecular, and Genomic Technologies on Cancer Health Care Delivery(R01)**

NHLBI

- 1. Multidisciplinary Translational Research in Critical Care (R01)**
- 2. Integrating Lung Genetics and Genomics in Human Populations (R01)**
- 3. Sarcoidosis: Research into the Cause of Multi-organ Disease and Clinical Strategies for Therapy (R01)**
- 4. Protein Interactions Governing Membrane Transport in Pulmonary Health and Disease (R01)**

NIAAA

- 1. Mechanisms of Alcohol-Induced Tissue Injury (R01)**
- 2. Program for Extramural/Intramural Alcohol Research Collaborations (U01)**

NIAID

- 1. Novel HIV Therapies: Integrated Preclinical/Clinical Program (IPCP)(U19)**
- 2. Multicenter AIDS Cohort Study (MACS), Limited Competition (U01)**
- 3. Partnerships for Point of Care (POC) Diagnostic Technologies for Nontraditional Health Care Settings (U01)**
- 4. Cooperative Research Partnerships for Biodefense and Emerging Infectious Diseases (U01)**
- 5. Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCE) [U54]**

NICHD

- 1. Indo-US Program on Maternal and Child Health and Human Development Research (MCHDR) (R03)**
- 2. Genetic Susceptibility & Variability of Human Structural Birth Defects (R01)**
- 3. Developmental Mechanisms of Human Structural Birth Defects (P01)**
- 4. Developmental Pharmacology (R01)**

NIDA

- 1. Functional Characterization of Genetic Variants and Interactions: The Genes, Environment and Health Initiative (R21) (R03)**
- 2. Research Education Grants for Statistical Training in the Genetics of Addiction (R25)**
- 3. Neuroscience Research on Drug Abuse(R03)**
- 4. Neuroscience Research on Drug Abuse (R01) (R21)**
- 5. Functional Genetics And Genomics Of Drug Addiction (R01) (R21) (R03)**

NIDCR

- 1. Interdisciplinary Research on Oral Manifestations of HIV/AIDS in Vulnerable Populations (P01)**
- 2. Novel Approaches to Study Polymicrobial Diseases (R01) (R21)**
- 3. Metagenomic Analyses of the Oral Microbiome (R01)**
- 4. Nanoscience and Nanotechnology in Biology and Medicine (R01) (R21)**
- 5. Immunology of Biofilms (R01)**
- 6. Temporomandibular Joint and Muscle Disorders: Pathophysiological Mechanisms Linking Comorbid Conditions (R01)**

NIGMS

- 1. Large-Scale Collaborative Project Awards (R24/U54)**
- 2. Innovations in Biomedical Computational Science and Technology (R01)**

NLM

- 1. NLM Express Research Grants in Biomedical Informatics (R01)**

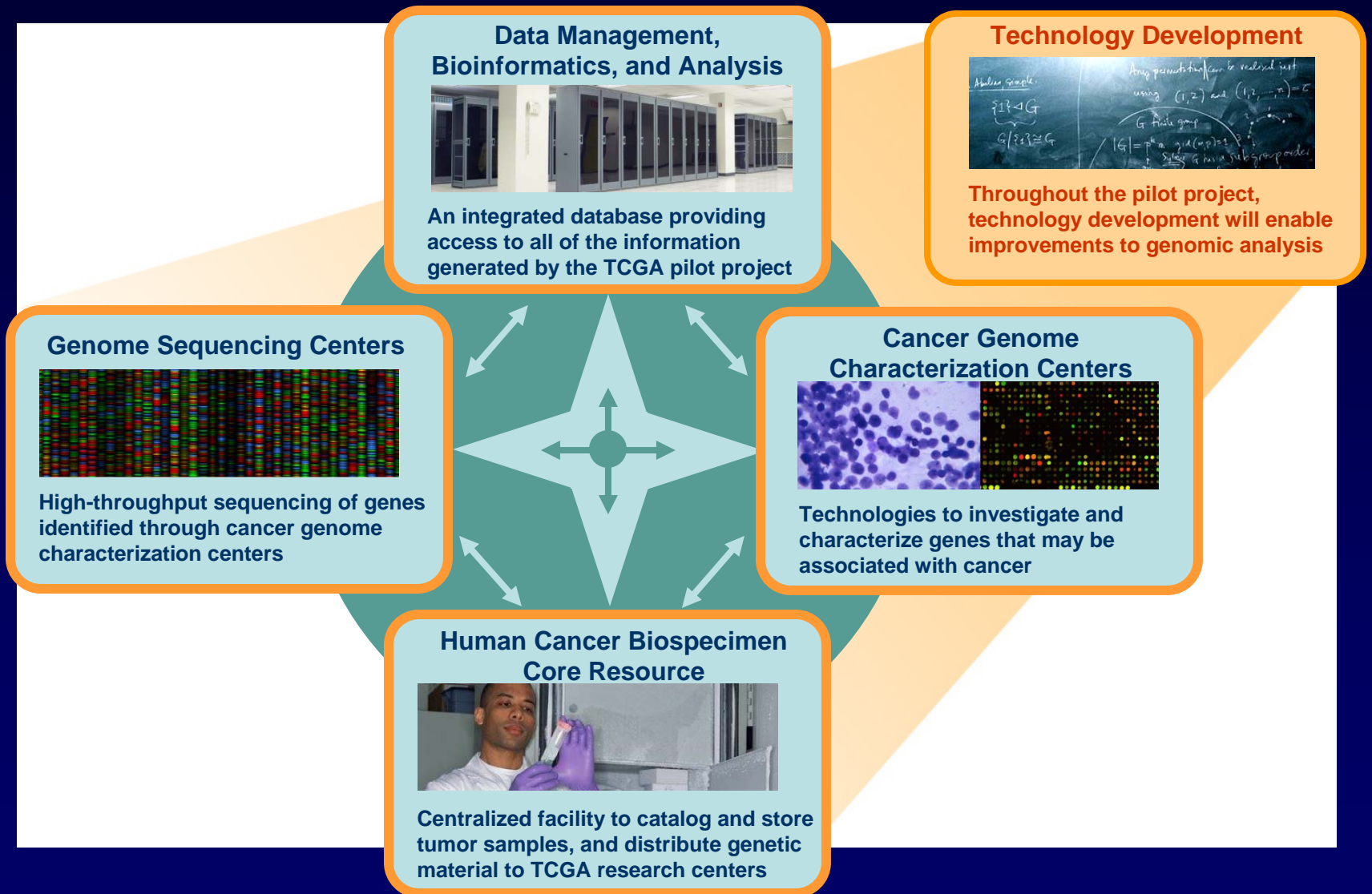
NIMH

- 1. Mouse Models Containing Human Alleles: Novel Tools to Study Brain Function (R21/R33)**
- 2. Innovative Approaches to Personalizing the Treatment of Depression (R01) (R34)**
- 3. Computational Tools for Research in Neuroscience, Behavioral Science and Mental Health: STTR [R41/R42], SBIR [R43/R44]**
- 4. Implicating Noncoding RNAs in the Genetics of Mental Disorders (Collaborative R01) (R01) (R21)**
- 5. Clinical Research on Mental Illnesses in Older Adults (R01)**

NINDS

- 1. Understanding and Preventing Brain Tumor Dispersal (R01) (R21)**
- 2. Human Pluripotent Stem Cell (hPSC) Research Using Non-Embryonic Sources (R01) (R21)**
- 3. Neurotechnology Research, Development, and Enhancement (SBIR [R43/R44]) (STTR [R41/R42])**
- 4. Collaborative Neurological Sciences (CNS) Award (S11)**

TCGA: Components of the Pilot Project



Development of TCGA program

- **Planning began in 2003 – Two large workshops - April, 2004; July 2005 – numerous presentations to NCI's Boards**
- **September 2003 – National Cancer Advisory Board (NCAB) study to determine areas of science/technology critical in accelerating progress against cancer**
- **NCAB recommended TCGA as a critical strategic project in February, 2005 (Hartwell-Lander Report)**
- **NCI-NHGRI Program work group -- February 2005**
- **Approach built on prior NHGRI/NCI experience with large scale initiatives**
- **RFAs and RFPs issued in 2005 – Awards made and TCGA launched in late 2006**
- **Three-year \$100 million dollar pilot**

Goals of the TCGA Pilot

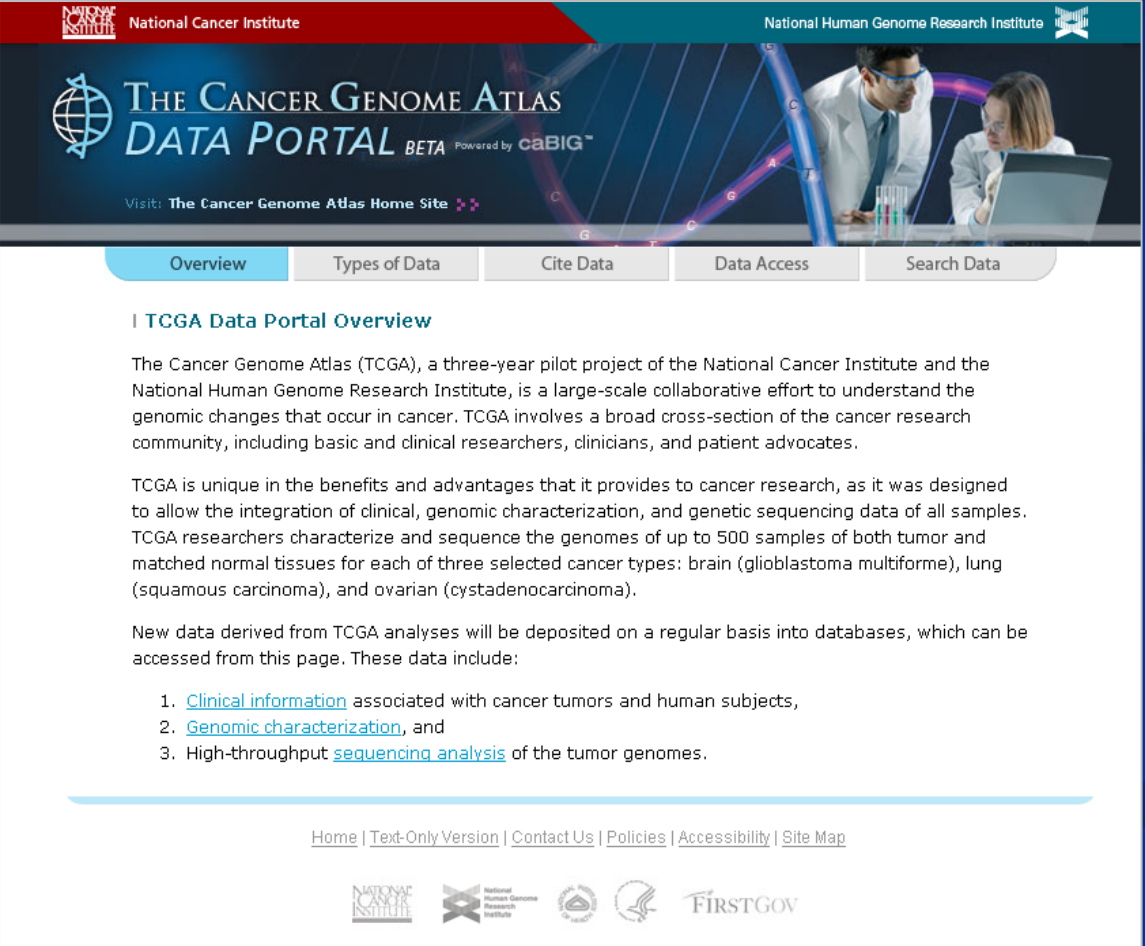
- To develop, deploy and connect a high quality biospecimen resource with genome characterization, sequencing and bioinformatics centers into a network with the combined capability to identify all relevant genomic changes in three tumor types
- To define all relevant genomic changes in three tumors through genome characterization and re-sequencing
- To create and deploy a pre-competitive, integrated public TCGA database of all of the various genome characterization, sequence and clinical data for the three tumors being studied

TCGA Data Access

New data derived from TCGA analyses will be deposited on a regular basis into databases, which will be accessible from a TCGA Data Portal.

All updates about the Pilot Project and Data Portal will be available at:

<http://cancergenome.nih.gov>



The screenshot displays the TCGA Data Portal website. At the top, it features the logos for the National Cancer Institute and the National Human Genome Research Institute. The main header reads "THE CANCER GENOME ATLAS DATA PORTAL BETA Powered by CaBIG™". Below the header is a navigation menu with options: Overview, Types of Data, Cite Data, Data Access, and Search Data. The "Overview" section is active, showing the title "TCGA Data Portal Overview" and a paragraph describing the project as a three-year pilot project of the National Cancer Institute and the National Human Genome Research Institute. It also includes a list of three data types: Clinical information, Genomic characterization, and High-throughput sequencing analysis. At the bottom, there is a footer with links for Home, Text-Only Version, Contact Us, Policies, Accessibility, and Site Map, along with logos for the National Cancer Institute, National Human Genome Research Institute, and FIRSTGOV.

National Cancer Institute National Human Genome Research Institute

THE CANCER GENOME ATLAS
DATA PORTAL BETA Powered by CaBIG™

Visit: [The Cancer Genome Atlas Home Site](#)

Overview Types of Data Cite Data Data Access Search Data

TCGA Data Portal Overview

The Cancer Genome Atlas (TCGA), a three-year pilot project of the National Cancer Institute and the National Human Genome Research Institute, is a large-scale collaborative effort to understand the genomic changes that occur in cancer. TCGA involves a broad cross-section of the cancer research community, including basic and clinical researchers, clinicians, and patient advocates.

TCGA is unique in the benefits and advantages that it provides to cancer research, as it was designed to allow the integration of clinical, genomic characterization, and genetic sequencing data of all samples. TCGA researchers characterize and sequence the genomes of up to 500 samples of both tumor and matched normal tissues for each of three selected cancer types: brain (glioblastoma multiforme), lung (squamous carcinoma), and ovarian (cystadenocarcinoma).

New data derived from TCGA analyses will be deposited on a regular basis into databases, which can be accessed from this page. These data include:

1. [Clinical information](#) associated with cancer tumors and human subjects,
2. [Genomic characterization](#), and
3. High-throughput [sequencing analysis](#) of the tumor genomes.

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NATIONAL CANCER INSTITUTE NATIONAL HUMAN GENOME RESEARCH INSTITUTE FIRSTGOV

Data are now available

- **TCGA Data Portal -**
<http://cancergenome.nih.gov/dataportal>
- **>130 gigabytes of genomic data available on a common set of glioblastoma samples**
- **Extensive clinical data**
- **Open access to all datasets except those in a controlled-access tier to protect patient privacy**
- **Controlled-access datasets available to qualified researchers**
- **Primary sequence data in NCBI Trace Archive**

Initial Conclusions

- **Samples with gene amplification also show high level of expression of that gene**
 - **Validation that sample process control is working well at both BCR and at CGCCs**
- **Genes with copy number changes and expression differences in some tumors also have point mutations in other tumors**
 - **Supports TCGA gene selection approach**
- **Activation of these oncogenes occurs via multiple mechanisms:**
 - **point mutation**
 - **gene amplification**
 - **high expression (with or without copy number gain)**
 - **and sometimes by all of the above**
- **Multiple platforms are required to fully characterize relevant genomic changes in cancer**

Initial Conclusions

- **NF1 is somatically altered in ~24% of GBM**
 - Mendelian disease and mouse data support the conclusion that loss of function of this tumor suppressor can lead to malignancy
- **ERBB2 has 7 candidate somatic mutations**
 - Validation is in progress
 - Extracellular domain point mutations are previously unreported in this gene, and are similar to localization of GBM mutations in EGFR
- *Both of these novel GBM genes have important therapeutic implications*

Overall Lessons Learned/ Perspectives from the First Year of TCGA

- **This is team science**
- **TCGA integrates two different cultures**
- **It isn't easy!**
- **Obtaining the highest quality samples is critical – based on stringent criteria**
- **The depth and breadth of analysis is unprecedented – analysis teams need to develop as the data integration proceeds**
- **TCGA will affect nearly every cancer researcher in some way – and everyone has an opinion!**

What Will Determine If TCGA Should Scale Up?

- Tumor biospecimen issues resolved
- New cancer genes discovered from the tumors studied – not based on current understanding
- Technology approaches achieved that improve the ability to differentiate meaningful biologic data from “noise”
- Cost-effectiveness demonstrated
- *Ability to differentiate tumor subtypes based on specific genomic alterations*
- *Clinical relevance*

International Cancer Genomics Consortium

- **Organizational meeting October 1 – 2, 2007 in Toronto**
- **Goal is to take advantage of worldwide interest in a comprehensive approach to all common types and subtypes of cancer**
- **Attendees agreed that shared policies will need to be established on comprehensiveness of analysis, data quality, data access, informed consent**
- **Interest expressed from US, UK, China, EU, Canada, India, Singapore, Australia, ?Japan**
- **Executive Committee established**
- **Scientific Planning Committee being established**

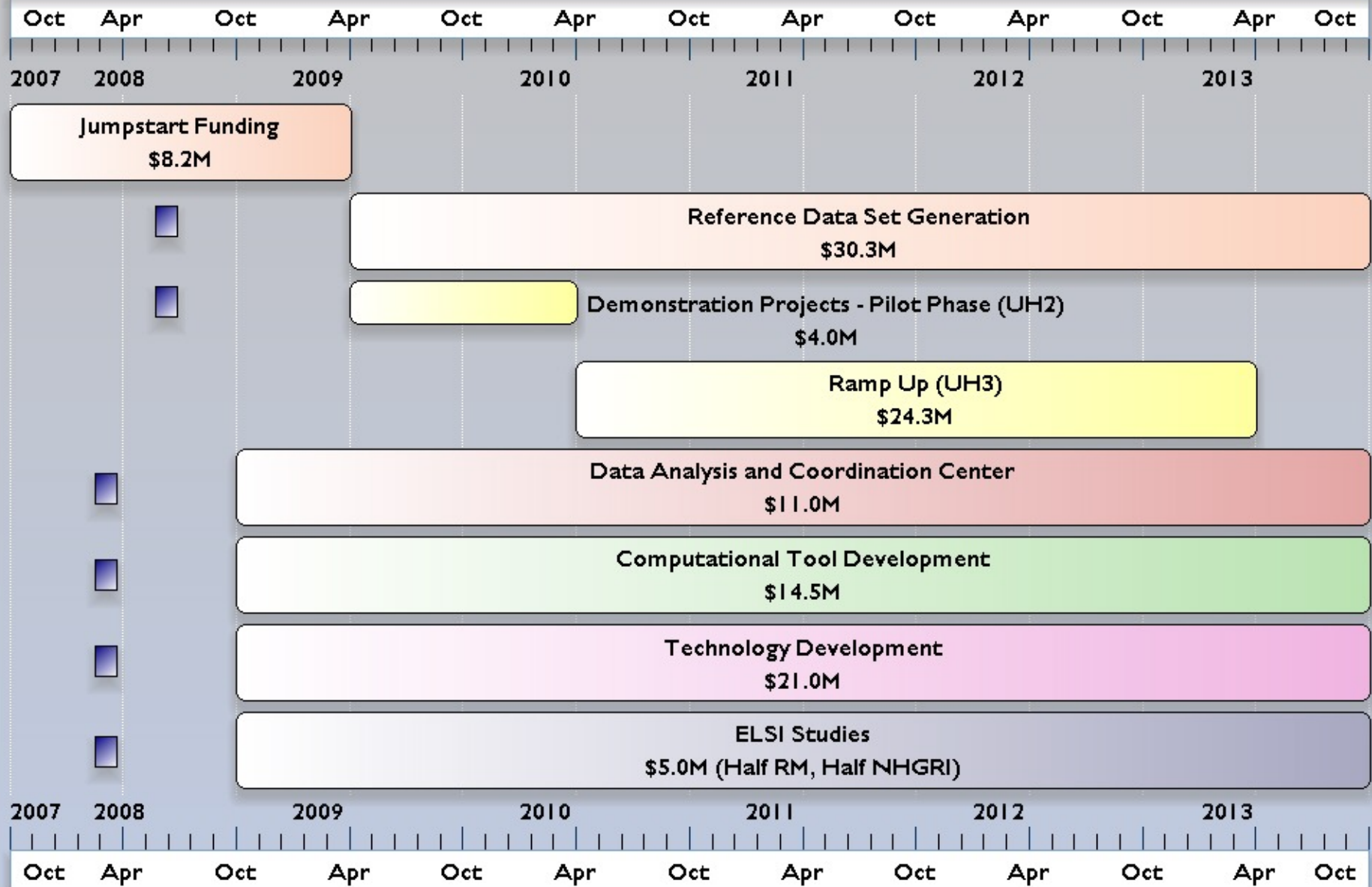


The Human Microbiome Project (HMP)

**An initiative of the NIH Roadmap for
Biomedical Research**

**The goal of the NIH Human Microbiome
Project is to characterize the microbes that
inhabit the human body and examine
whether changes in the microbiome can be
related to health and disease**

HMP Funding Opportunities



Legend:

■ Application Receipt Date

 Funding Period

The HMP

- **The HMP is:**
 - **Finite: A five-year project**
 - **Feasibility Study: designed to determine the value of microbial metagenomics to biomedical research**
- **The HMP is NOT:**
 - **the NIH's sole commitment to microbial metagenomics; Individual ICs currently support R01s in metagenomics**

The HMP

- **If the HMP is successful:**
 - **Individual ICs will incorporate metagenomic studies into their regular research programs**

International
HUMAN MICROBIOME
Consortium Meeting



December 9-10, 2007
Hilton Washington DC / Rockville
Executive Meeting Center
Rockville, MD



**The IHMC will be
launched in the
autumn of 2008**

**The EC & the US
are committed to be
members of the
IHMC.**

**Canada, China,
Singapore, Australia
and India are
considering
participation**

The International Human Microbiome Consortium (IHMC)

Goal: The goal of the IHMC is to work under a common set of principles and policies to study and understand the role of the human microbiome in the maintenance of health and causation of disease and to use that knowledge to improve the ability to prevent and treat disease.

The IHMC

The Consortium's efforts will be focused on generating a shared comprehensive data resource that will enable investigators to characterize the relationship between the composition of the human microbiome (or of parts of the human microbiome) and human health and disease.

The IHMC

Membership: The IHMC will be open, at any time to the funders and PIs of human microbiome research programs that have the capacity to mount a comprehensive analysis of the human microbiome in health and/or disease, and that agree to carry out their efforts according to a set of commonly agreed-upon IHMC policies.

The IHMC

Role: The role of the IHMC will be to coordinate the activities and policies of the international groups studying the human microbiome to promote the generation of a robust, data resource that is freely available to the scientific community and that can be analyzed across many groups.

The IHMC

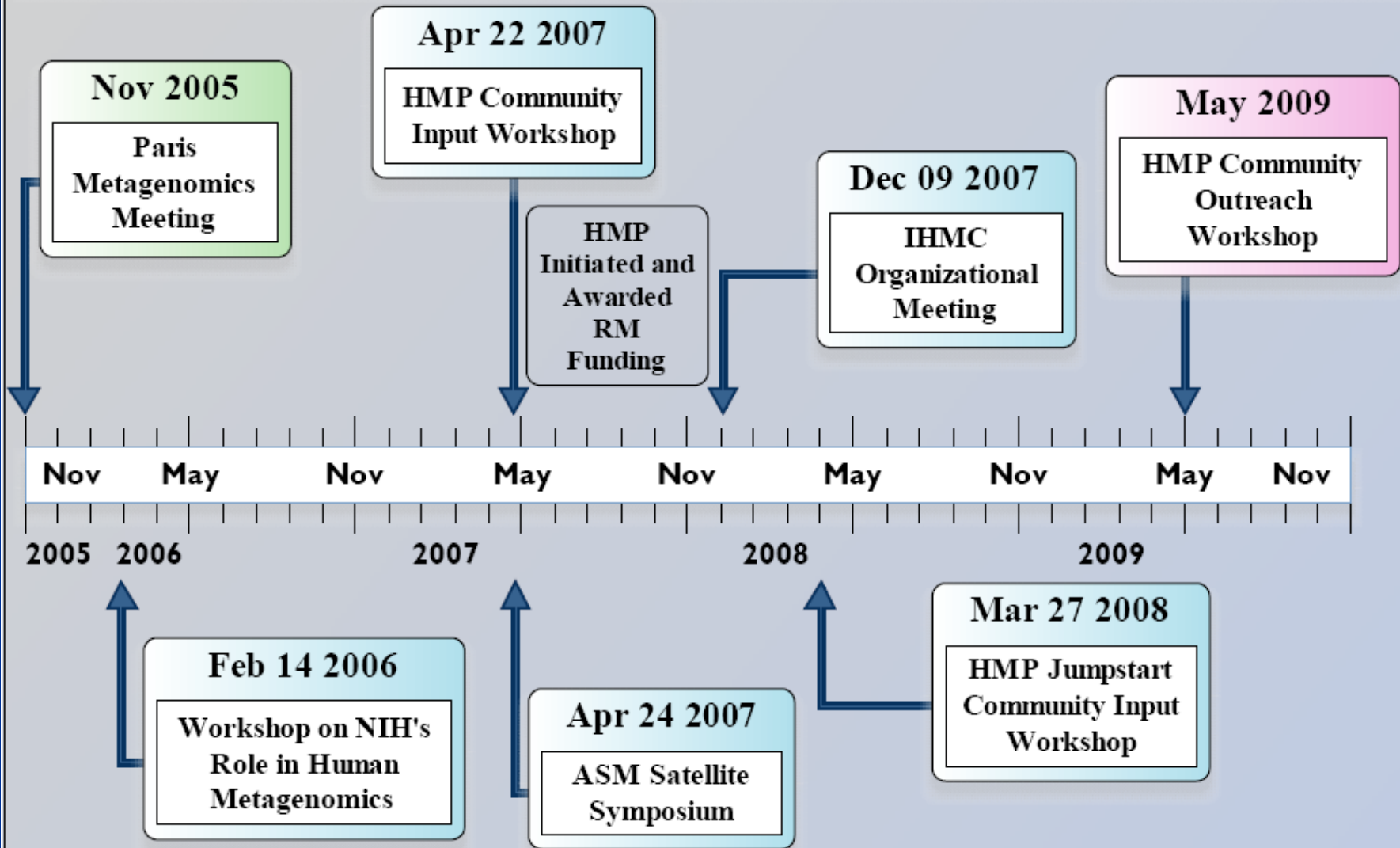
Principles for membership in the IHMC

- **Data release**
- **Intellectual Property**
- **Publication**
- **Quality assessment**
- **Standards for consent of participants**

Goals for The Cancer Genome Atlas Pilot Project

- Overall Goal: To describe the genomic changes in the three tumors being studied in the TCGA pilot project
- ┌ Secondary Goal: To determine the feasibility of undertaking a *full-scale* project to develop an “atlas” of all common genomic alterations involved in all common cancers

HMP-Related Meetings



Legend:



Community Workshop



NIH-Led Workshop



Planned Meeting

