The Cancer Genome Atlas
Pan-cancer analysis

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What is TCGA?

• **The Cancer Genome Atlas** is a large collaborative initiative to comprehensively study the molecular and genomic basis of 20+ types of cancer.

• Tumor tissues are collected from over 150 different source sites from around the world and collected over the past several decades
  – This makes a great dataset for an atlas or catalog of genomic alterations and less desirable for clinical associations
TCGA Research Groups
TCGA Pipeline for Comprehensive Characterization

Tissue Sample

Pathology QC

DNA & RNA Isolation, QC

Sequencing

Expression, CNA & LOH, Epigenetics

Data and Results Storage & QC

Analysis

Analysis

Integrative Analysis

GDAC

Comprehensive Characterization of a Cancer Genome

= Process

= Data

= Results

= BCR

= GSCs

= CGCCs

= DCC

= GDACs

http://cancergenome.nih.gov/
Publically Available Data
Multiplatform Analysis of 12 Cancer Types Reveals Molecular Classification within and across Tissues of Origin

Katherine A. Hoadley,1,2,20 Christina Yau,1,20 Denise M. Wolf,3,20 Andrew D. Cherniack,4,20 David Tamborero,5,6 Sam Ng,5 Max D.M. Leiserson,7 Beifang Niu,8 Michael D. McLellan,9 Vladislav Uzunangelov,6 Jiashan Zhang,5 Cyriac Kandoth,6 Rehan Akbani,10 Hu Shen,11,22 Larsson Omerb,12 Andy Chu,13,16 Adam A. Margolin,12,21 Laura J. van Veer,5 Nuria Lopez-Bigas,5,14 Peter W. Laird,11,22 Benjamin J. Raphael,7 Li Ding,8 A. Gordon Robertson,13 Lauren A. Byers,10 Gordon B. Mills,10 John N. Weinstein,10 Carter Van Waes,18 Zhong Chen,19 Eric A. Collisson,15 The Cancer Genome Atlas Research Network, Christopher C. Benz,2,* Charles M. Perou,1,16,17,* and Joshua M. Stuart6,*


Resource

Consortia Members

Pan-TCGA

Platforms

Exome seq
mRNA seq
miRNA seq

SNP Array
DNA Meth Array

RPPA

Reclassification of cancer types

Converged
diverged

LUAD-enriched
Lung adeno
Bladder

Squamous-like
Lung
Head neck
Bladder

BRCA/Luminal
Breast

BRCA/Basal
Breast

BLCA
Bladder

COAD/READ
Colon
Rectum

Same tissue origin

OV
Ovary

UCEC
Endometrium

KIRC
Kidney

GBM
Glioblastoma

LAML
Myelogenous leukemia

Hoadley et al., Cell, 2014. PMID:25109877
How do we compare five different classifications?

**Cluster of Cluster Assignments (COCA)**

- Turned each classification into a row per subtype of 0s and 1s.

- Allowed 1 missing data type per sample – 3,527 samples in the analysis.

- 5 classification schemes is now a matrix of 66 subtypes – 1 row for each subtype for each data type.

- All rows are equally weighted

- Consensus Cluster the matrix
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Consensus Clustering to define the number of groups/subtypes present within the 12 tumor types

At $K=13$, 11 main Cluster of Cluster Assignment (COCA) subtypes are observed.

Hoadley et al., Cell, 2014. PMID:25109877
12 Tissue of Origin Sites Translate into 11 COCA Subtypes

131/139 Basal-like are in this COCA group

Hoadley et al., Cell, 2014. PMID:25109877
HOW MANY ETIOLOGICAL SUBTYPES OF BREAST CANCER: TWO, THREE, OR MORE?

A: Female breast cancer
B: Estrogen receptor (ER)

A: Molecular subtypes
B: Basal vs. non Basal

n=2000
Clinical Associations

**Tumor Type**

**Cluster of Cluster Assignments**

- OS Probability
- Months

- Cancer types: AML, BLCA, BRCA, COAD, GBM, HNSC, KIRC, LUAD, LUSC, OV, READ, UCEC

- Cluster assignments:
  - 1 - LUAD enriched
  - 2 - Squamous-like
  - 3 - BRCA/Luminal
  - 4 - BRCA/Basal
  - 5 - KIRC
  - 6 - UCEC
  - 7 - COAD/READ
  - 8 - BLCA
  - 9 - OV
  - 10 - GBM
  - 13 - AML

Graphs showing survival probabilities over months for different tumor types and cluster assignments.
KIRC - Estrogen

Denise Wolf
## Mutations

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Cyriac Kandoth, Mike McLellan, Beifang Niu, Li Ding
Patient Outcomes According to Mutation and Tissue of Origin

TP53

- **TP53 Mutation**
  - mut n=1164
  - wt n=1666

PIK3CA

- **PIK3CA Mutation**
  - mut n=583
  - wt n=2247

Additional information for various tissues:

- BLCA n=48
- BRCA n=253
- COAD n=72
- GBM n=49
- HNSC n=215
- LAML n=14
- LUAD n=87
- LUSC n=147
- OV n=156
- READ n=44
- UCEC n=70

Log Rank p-values:

- TP53 Mutation: 1e-22
- PIK3CA Mutation: 5.67e-11
- Additional tissues with their respective p-values.
TP53 Mutation Spectrum

COCA2 - Squamous

COCA4 – BRCA / Basal-like

COCA9 - Ovarian

- Frame Shift Indel
- In Frame Indel
- Splice Site
- Nonsense Mutation
- Missense Mutation
- Silent
Copy Number

A

[Diagram showing copy number variations across different tumors]
Cluster Relationships

Gene Programs

DNA Copy Number
PanCan 12 Summary

• An analysis of 12 tumor types reveals 11 major groups, with some tumor types merging together (HNSCC, Lung Squamous, some Bladder) and others separating (breast luminal vs. Basal-like)

• We can start to separate cell-type of origin vs tissue-type of origin.

• Additional tumor types will soon be added to the next iteration of the pan-cancer analysis.
PanCancer Phase II

- Acute Myeloid Leukemia
- Adrenocortical carcinoma
- Bladder Urothelial Carcinoma
- Brain Lower Grade Glioma
- Breast invasive carcinoma
- Cervical squamous cell carcinoma and endocervical adenocarcinoma
- Cholangiocarcinoma
- Chronic Myelogenous Leukemia
- Colon adenocarcinoma
- Esophageal carcinoma
- Glioblastoma multiforme
- Head and Neck squamous cell carcinoma
- Kidney Chromophobe
- Kidney renal clear cell carcinoma
- Kidney renal papillary cell carcinoma
- Liver hepatocellular carcinoma
- Lung adenocarcinoma
- Lung squamous cell carcinoma
- Lymphoid Neoplasm Diffuse Large B-cell Lymphoma
- Mesothelioma
- Ovarian serous cystadenocarcinoma
- Pancreatic adenocarcinoma
- Pheochromocytoma and Paraganglioma
- Prostate adenocarcinoma
- Rectum adenocarcinoma
- Sarcoma
- Skin Cutaneous Melanoma
- Stomach adenocarcinoma
- Testicular Germ Cell Tumors
- Thymoma
- Thyroid carcinoma
- Uterine Carcinosarcoma
- Uterine Corpus Endometrial Carcinoma
- Uveal Melanoma
Potential Clinical Relevance of PanCancer Analyses

- HER2/ERBB2
- RAS/RAF
Activating HER2 Mutations in HER2 Gene Amplification Negative Breast Cancer
Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology

Jeffrey S. Damrauer, Katherine A. Hoadley, David D. Chism, Cheng Fan, Christopher J. Tiganelli, Sara E. Wobker, Jen Jen Yeh, Matthew J. Milowsky, Gopa Iyer, Joel S. Parker, and William Y. Kim

Department of Genetics, Department of Medicine, Division of Hematology/Oncology, Department of Surgery, Department of Pathology and Laboratory Medicine, and Department of Pharmacology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599; and Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10065

Edited by William G. Kaelin, Jr., Harvard Medical School, Boston, MA, and approved January 15, 2014 (received for review October 2, 2013)
CALGB 40601 (Alliance), a neoadjuvant phase III trial of weekly paclitaxel (T) and trastuzumab (H) with or without lapatinib (L) for HER2-positive breast cancer

Clinical stage II-III HER2+

Research tissue

R

wT+H+L x 16wks

wT+H x 16wks

wT+L x 16wks

SURGERY

Recommended: Dose-dense AC ➔ H x 34 wks

wT= weekly paclitaxel, H= trastuzumab, L= lapatinib
HER2/ERBB2 Mutations

8 mutations in 7 patients

- p.L755S
- p.V777L

- 2/8 HER2 mutations were detected at variant allele frequencies (VAF) greater than 10%
HER2/ERBB2 mutations

- **HER2-E with V777L**
  - THL Arm
  - *Preclinically predicted sensitive to Lapatinib*
  - Achieved pCR

- **Luminal A with L755S**
  - TL Arm
  - *Preclinically predicted resistant to Lapatinib*
  - No pCR

RAS/RAF Mutations

TCGA Melanoma, Cell in press

Integrated Genomic Characterization of Papillary Thyroid Carcinoma
Cell, Volume 159, Issue 3, 2014, 676 - 690
Integrated Genomic Characterization of Papillary Thyroid Carcinoma
Cell, Volume 159, Issue 3, 2014, 676 - 690
Predicting BRAF mutations

BRAF alterations

**BRAF/RAS Signature from THCA**
- Sens: 95.4%
- Spec: 86.0%
- PV+: 91.6%
- PV−: 92.1%

**BRAF/RAS Signature from SKCM**
- Sens: 14.1%
- Spec: 90.7%
- PV+: 70.8%
- PV−: 39.7%

**THCA**

AUC: 0.965

**SKCM**

AUC: 0.570

AUC: 0.816
Predicting RAS mutations

**THCA**

BRAF/RAS Signature from THCA

- Sensitivity: 98.1%
- Specificity: 80.8%
- PV+: 44.0%
- PV-: 99.6%
- AUC: 0.912

**SKCM**

BRAF/RAS Signature from SKCM

- Sensitivity: 66.3%
- Specificity: 85.9%
- PV+: 66.6%
- PV-: 96.3%
- AUC: 0.824

---

RAS mutations
TCGA Pan Cancer Analysis Working Group