# Multi-cancer mutual exclusivity analysis of genomic alterations

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Computational Biology - MSKCC
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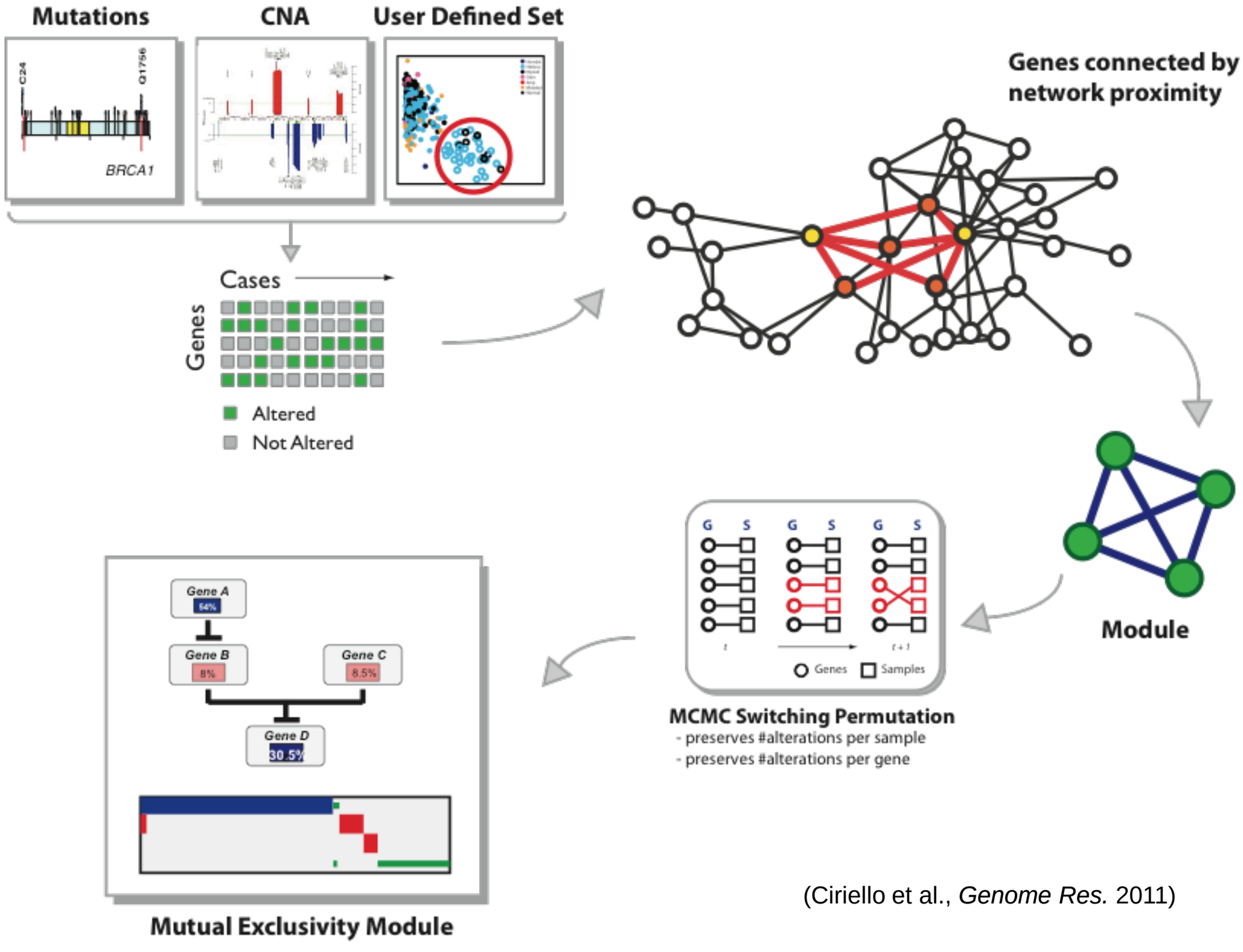
# Mutually exclusive alterations in Cancer

## Recurrent genomic alterations target specific pathways


## Functional alterations targeting the same pathway frequently occur in a mutually exclusive manner


(TCGA, Nature, 2011)

# MEMo: Mutual Exclusivity Modules




(Ciriello et al., *Genome Res.* 2011)

# MEMo results on TCGA Datasets

MEMo has been applied to the following TCGA projects:

- **Glioblastoma Multiforme (GBM)**
  - Phase 2 — 338 samples
- **Serous Ovarian Cancer (OVCA)**
  - Updated dataset — 384 samples
- **Colon and Rectum Adenocarcinoma (COAD)**
  - Non hyper-mutators — 151 samples
- **Uterine Corpus Endometriod Carcinoma (UCEC)**
  - Non serous / Non hyper-mutators — 144 samples
- **Invasive Breast Cancer (BRCA)**

  463 samples

Mutually exclusive patterns of alteration identified in several oncogenic pathways:

- Rb - signaling
- p53 - signaling
- DNA repair
- PI(3)K/Akt signaling

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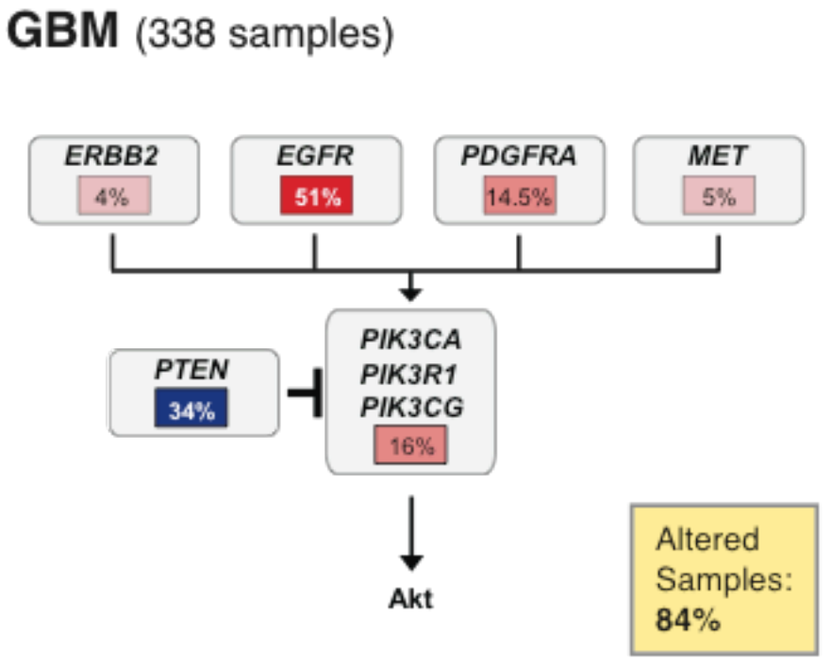
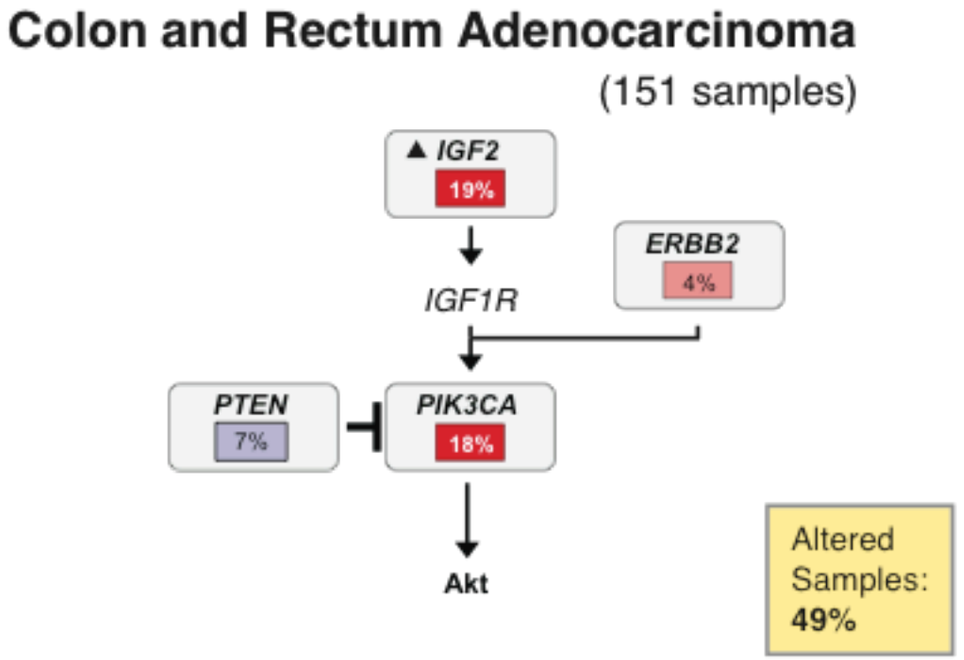
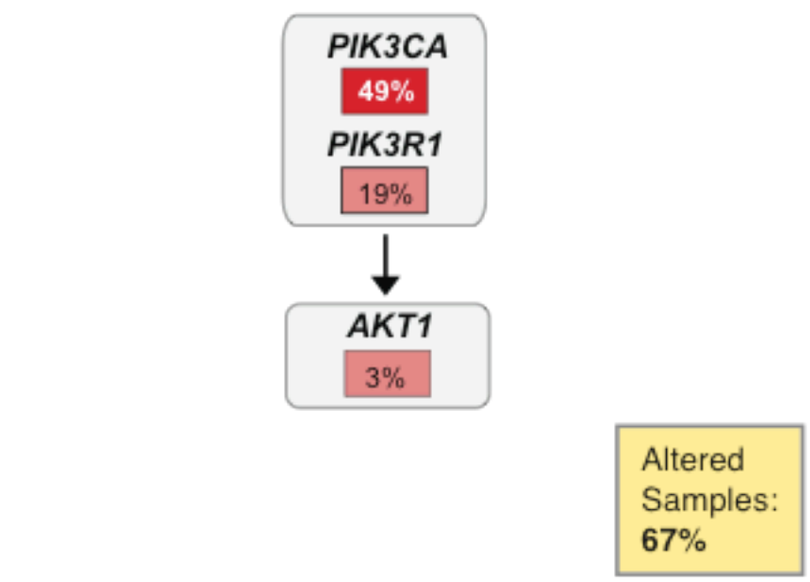
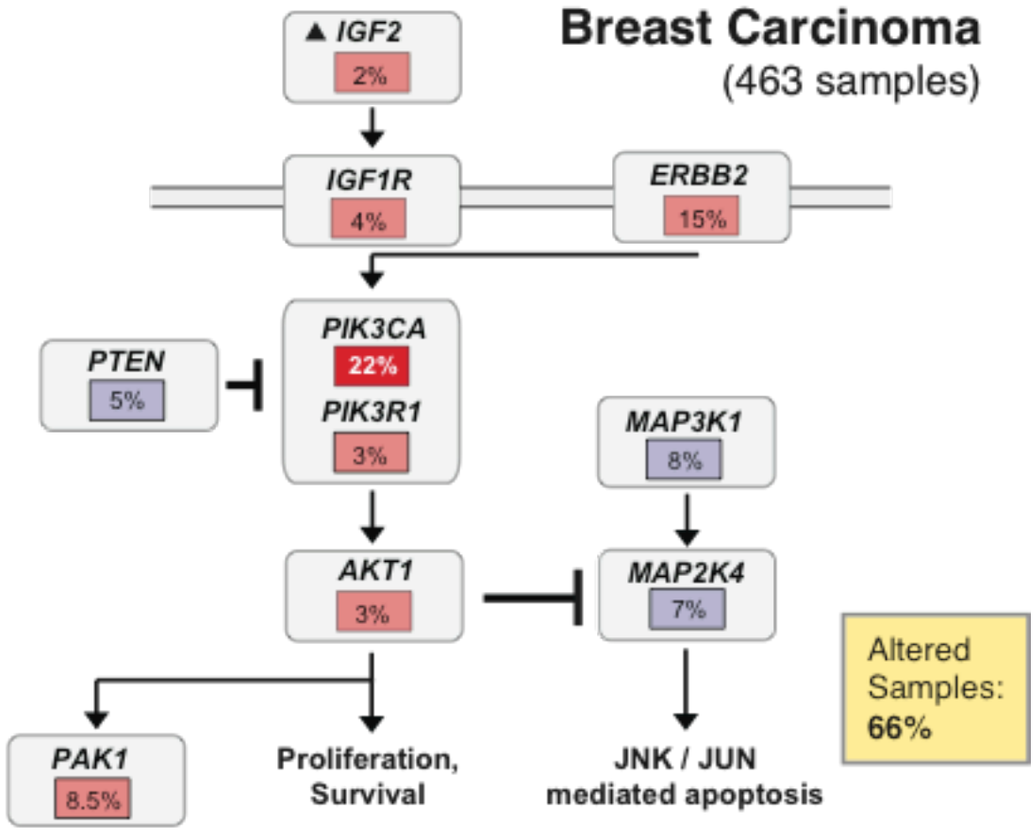
- **PI(3)K/Akt signaling**

# Mutual exclusivity in PI(3)K/Akt



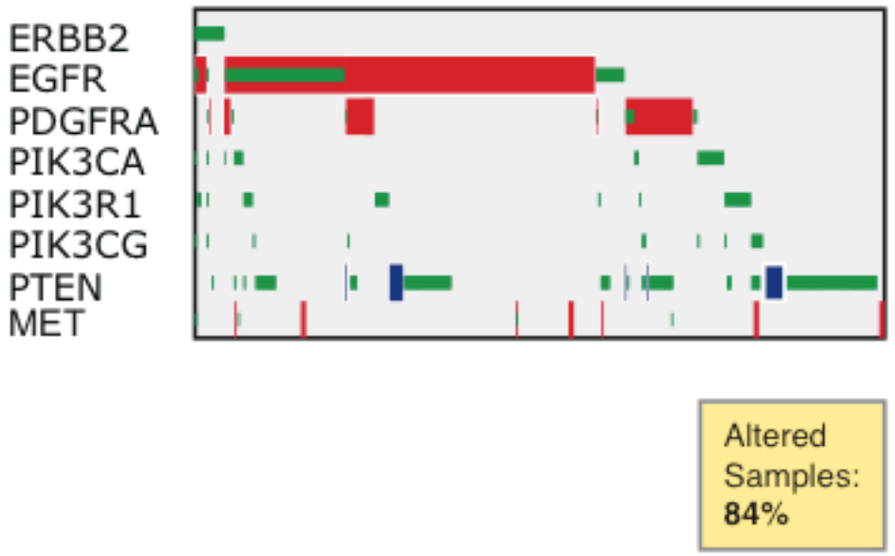



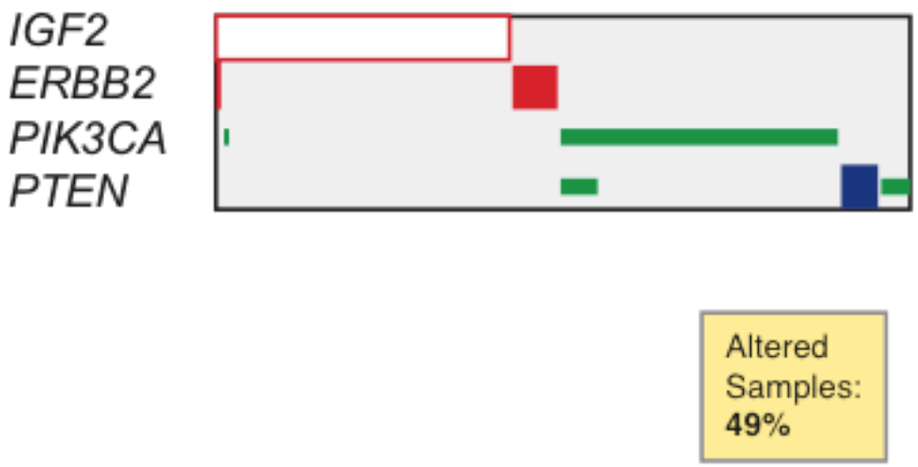



# Mutual exclusivity in PI(3)K/Akt

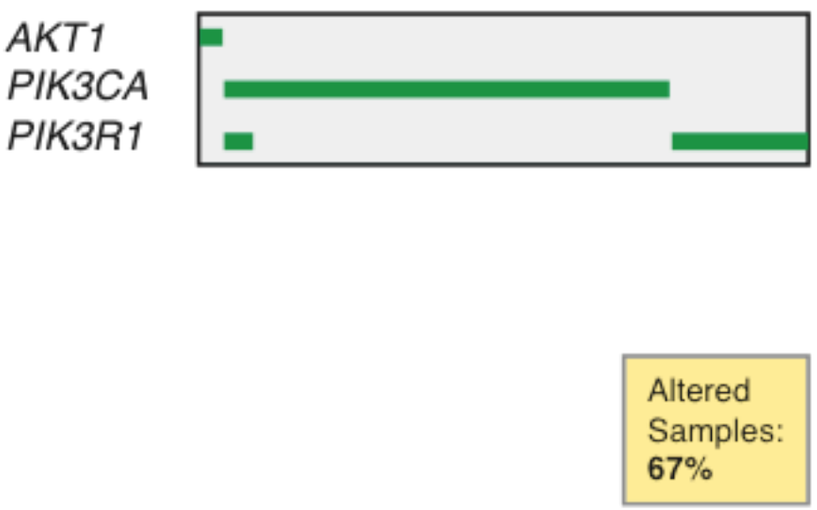
**GBM** (338 samples)



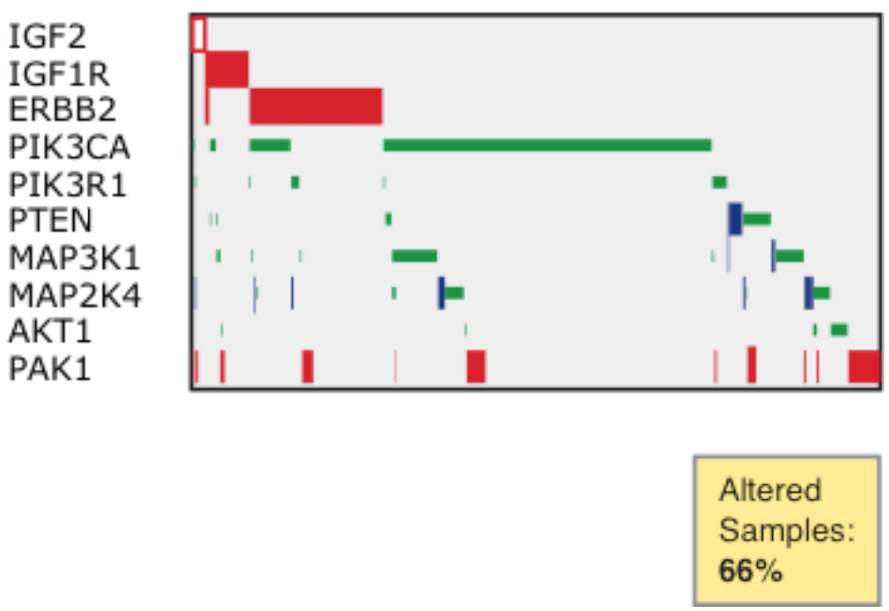

**Colon and Rectum Adenocarcinoma**
(151 samples)




**Endometriod Carcinoma** (144 samples)

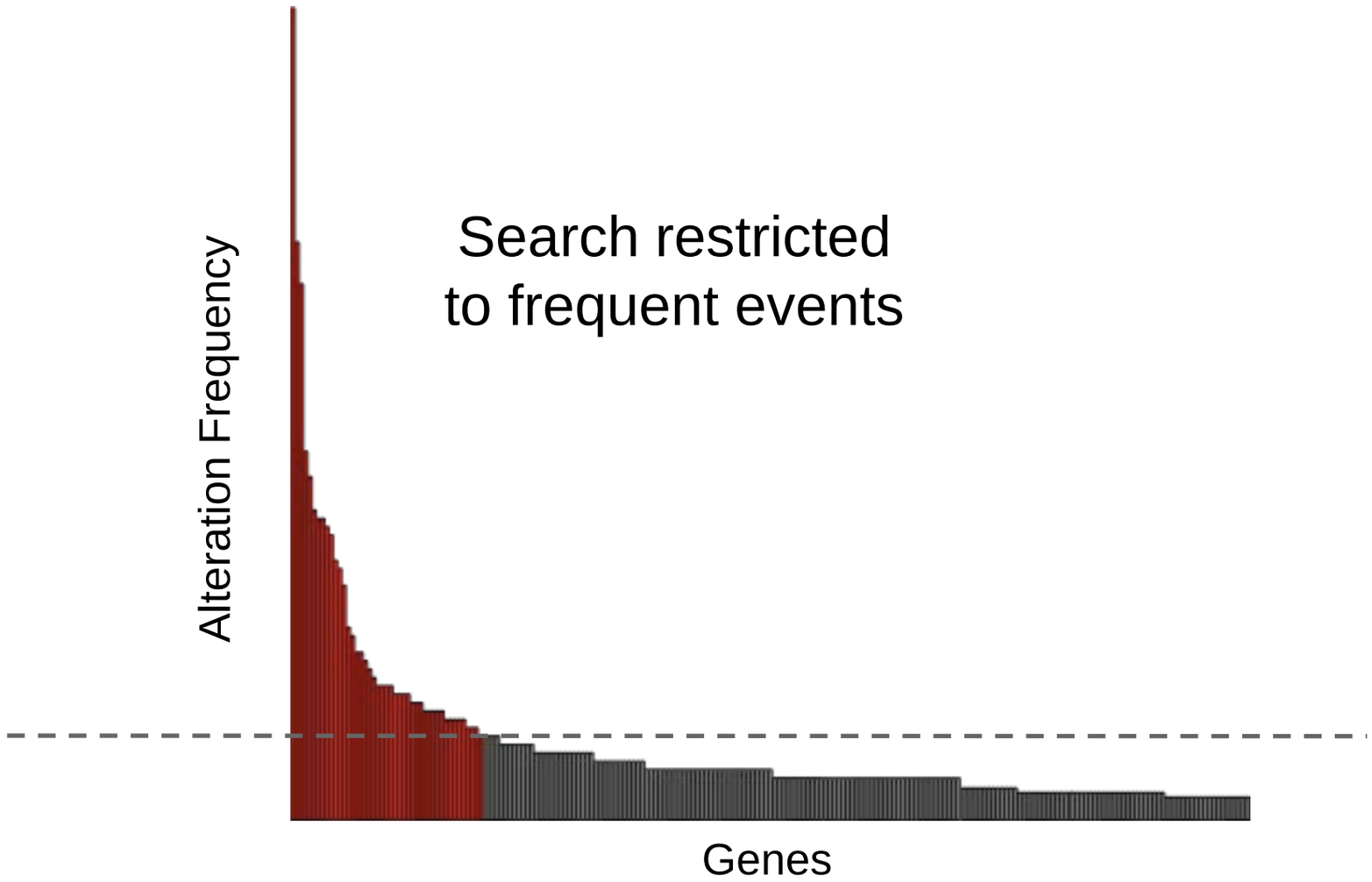



**Breast Carcinoma**
(463 samples)



# PI(3)K/Akt alterations in Ovarian Carcinoma

MEMo does not find PI(3)K/Akt modules



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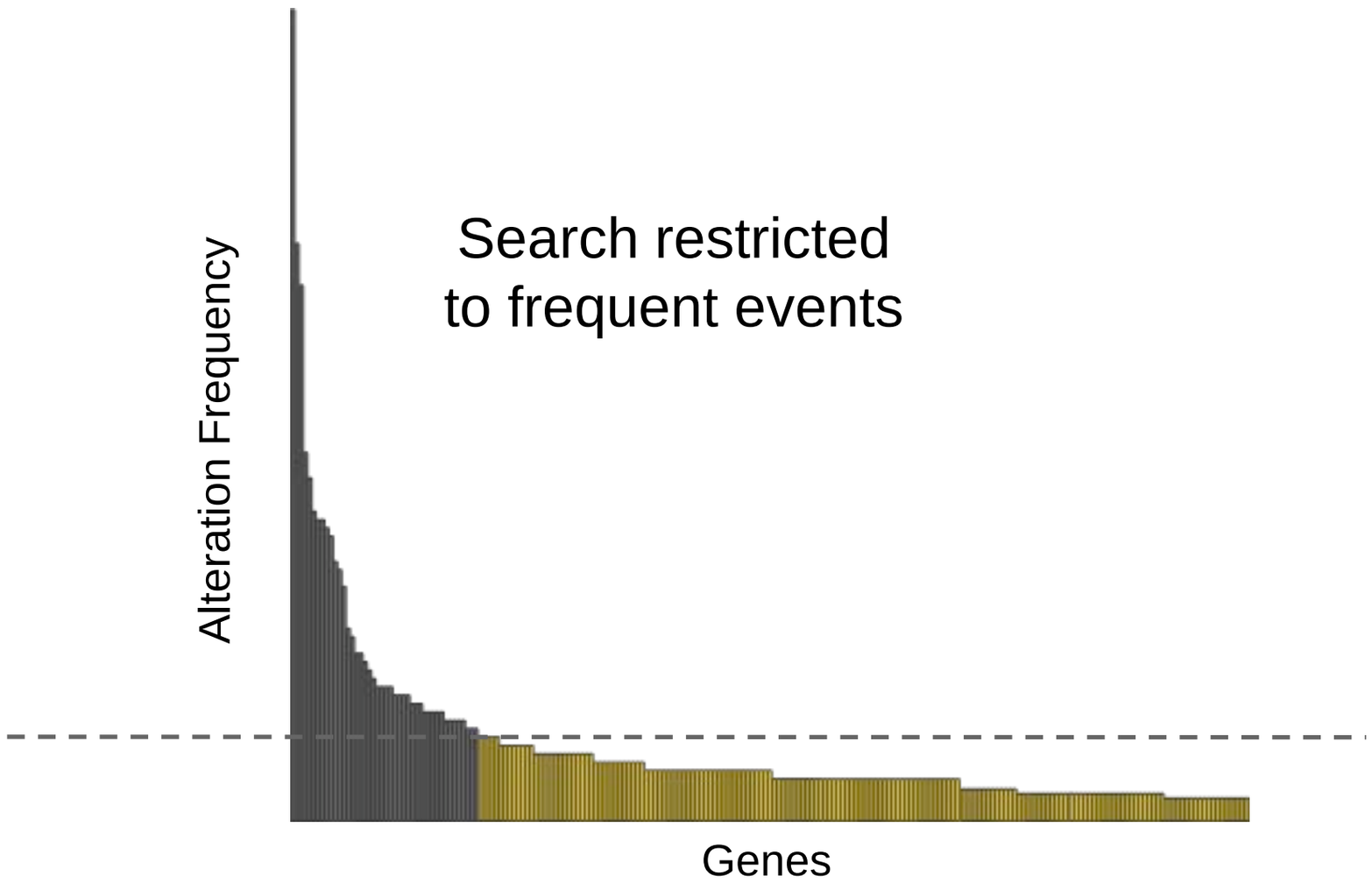
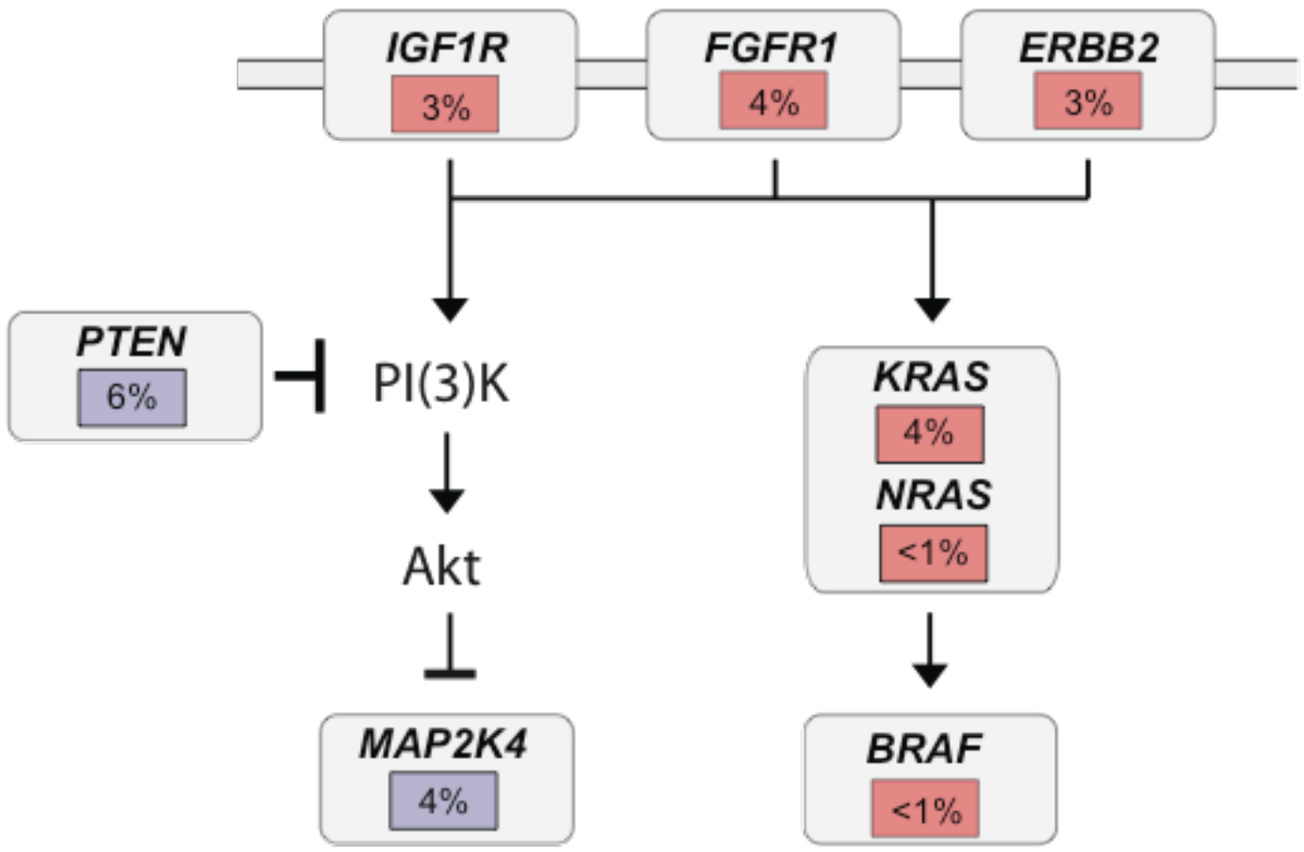
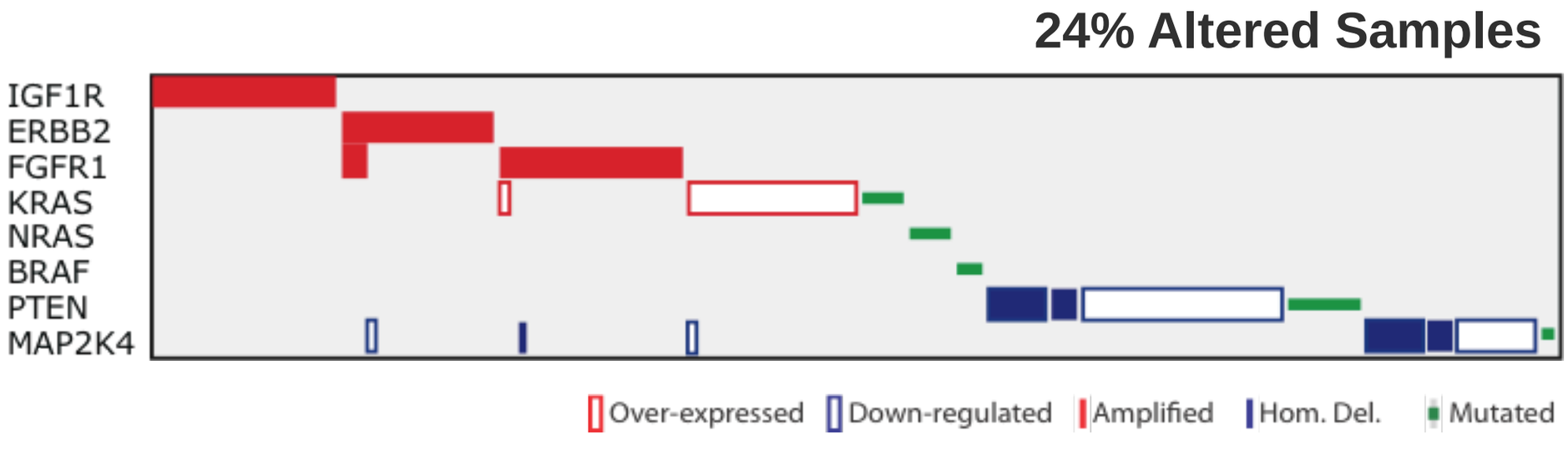


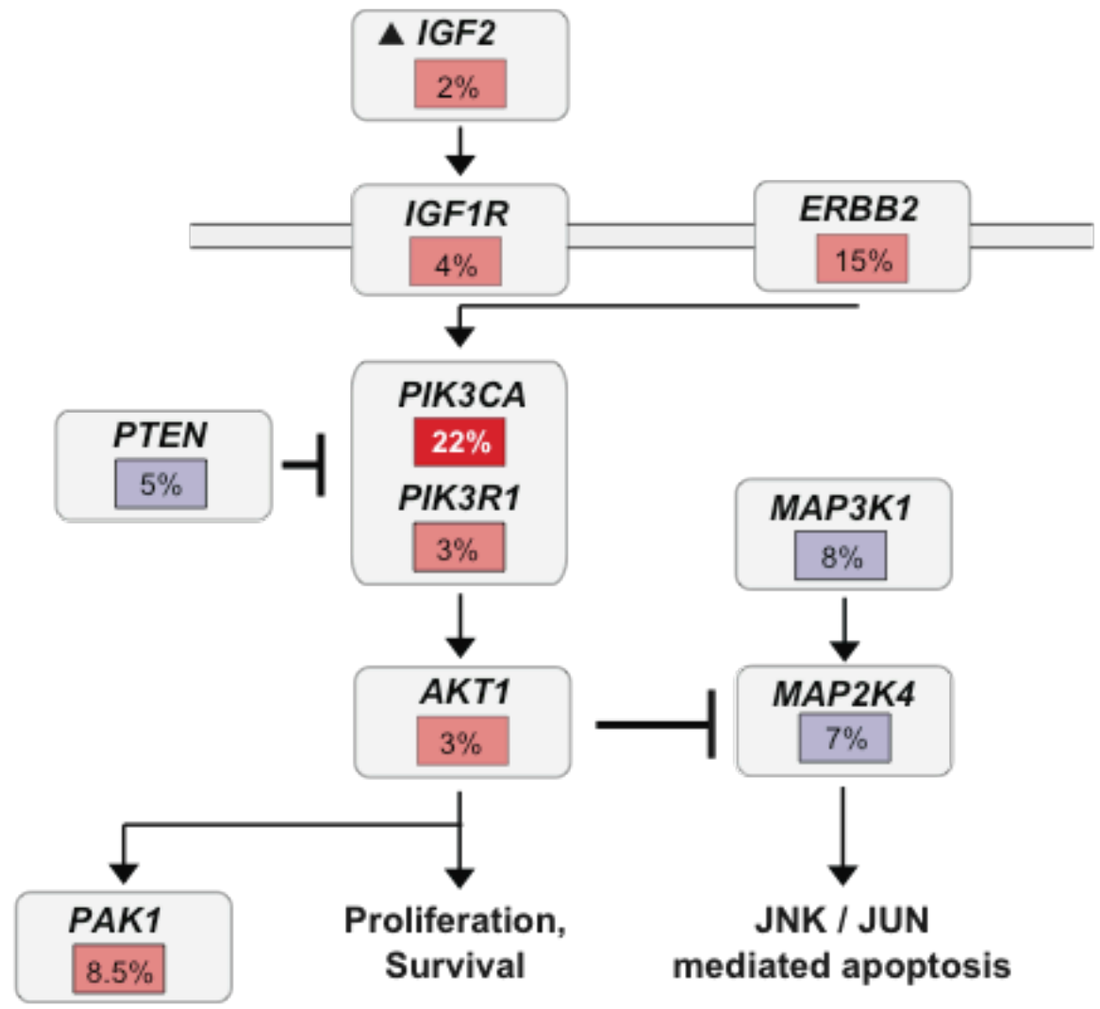

Are there low-frequency but functional events affecting this pathway?

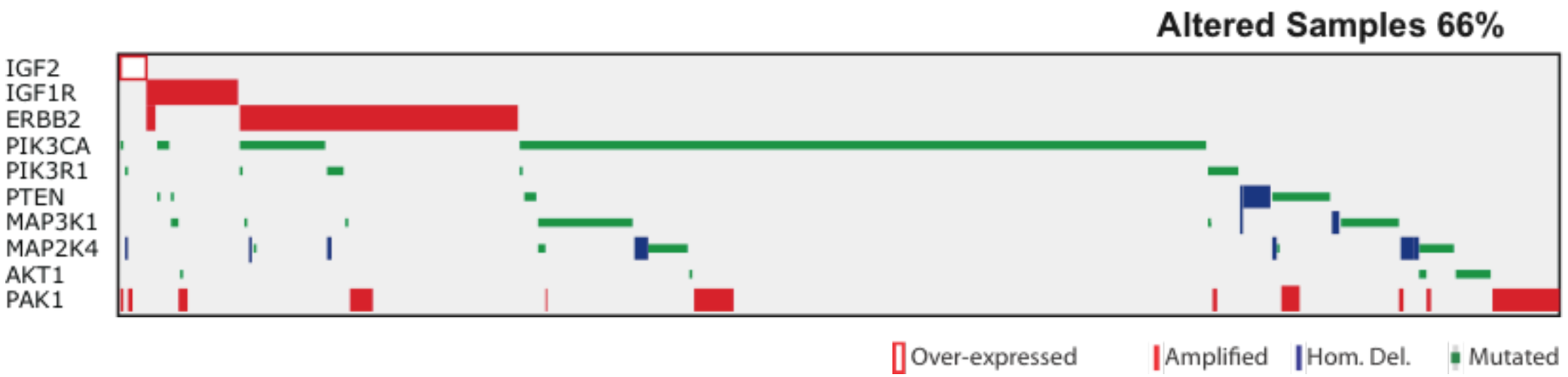
# Multiple Low-frequency events target PI(3)K pathway



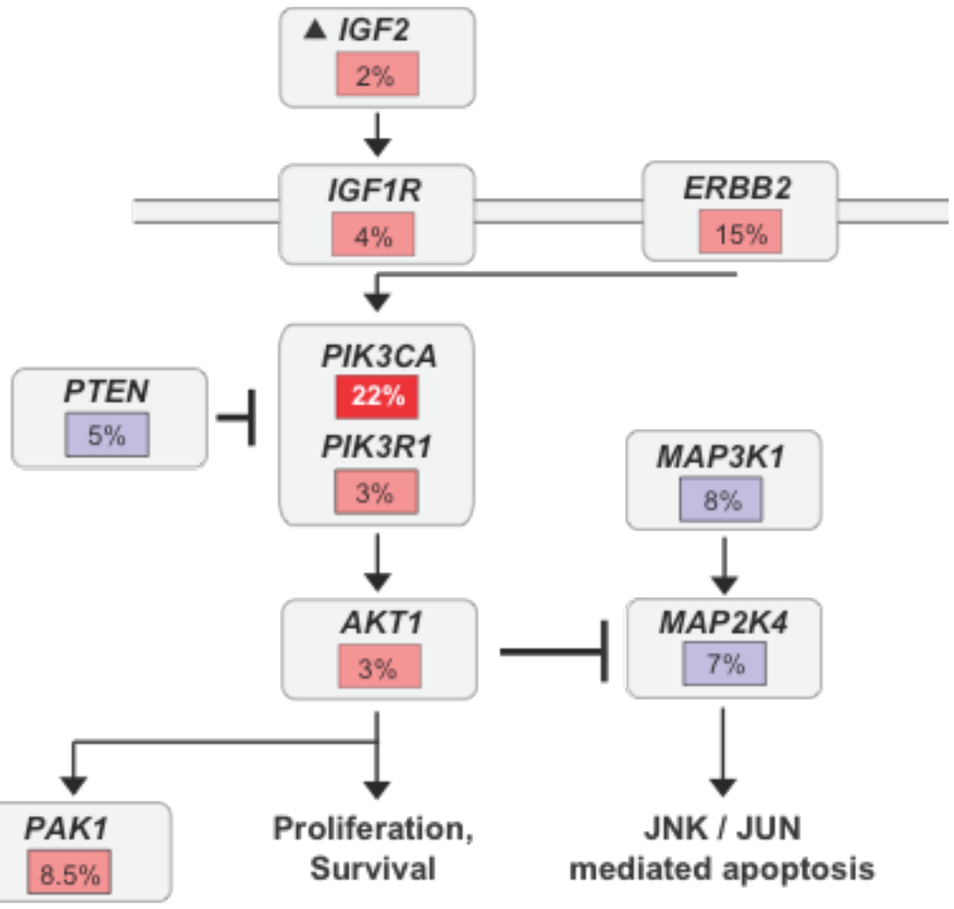



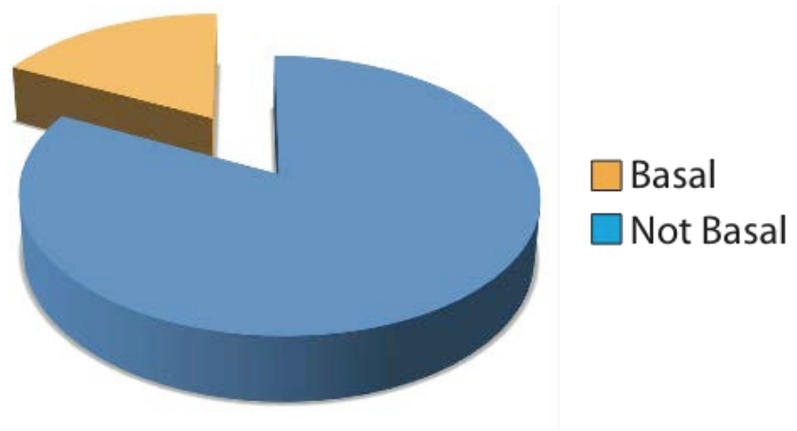
# Breast Cancer (463 samples)



# Basal vs. Not Basal



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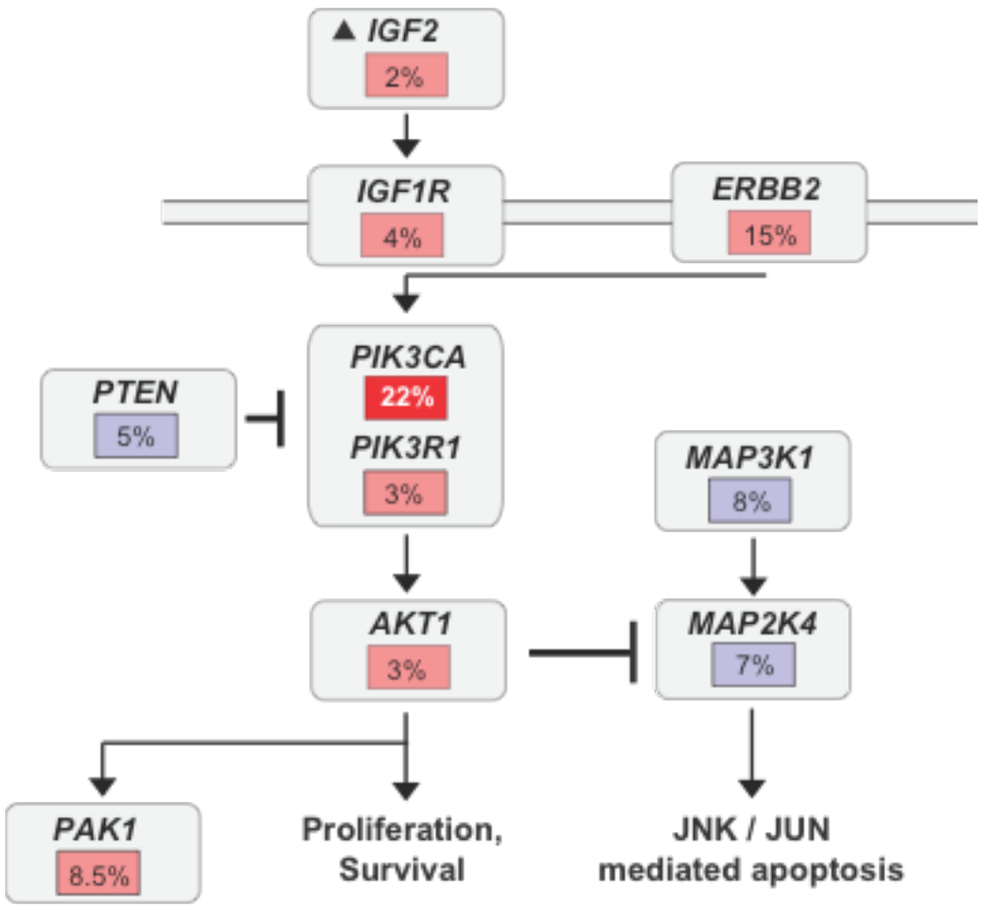
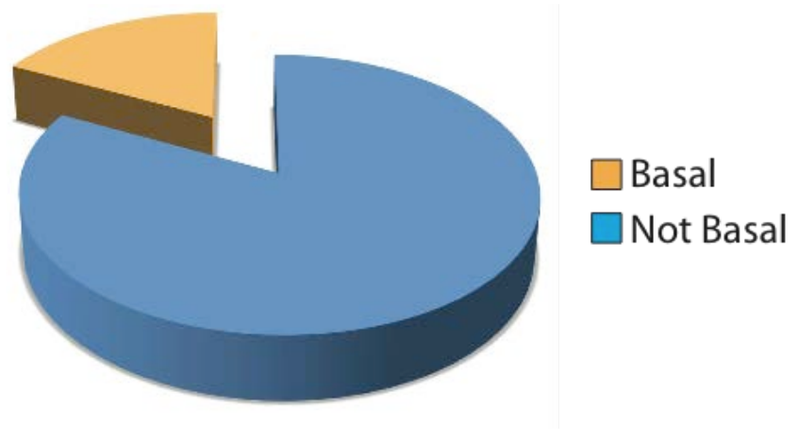
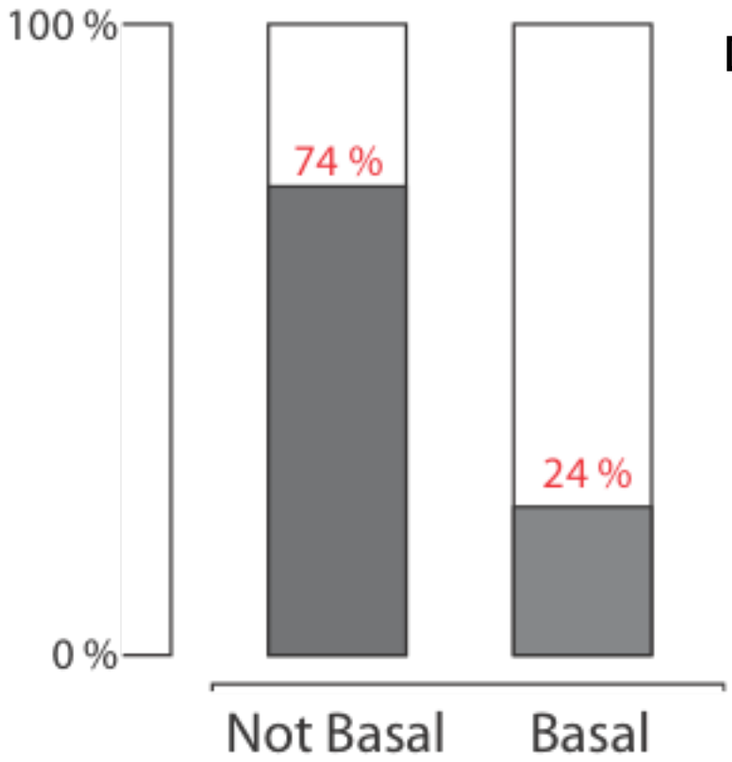


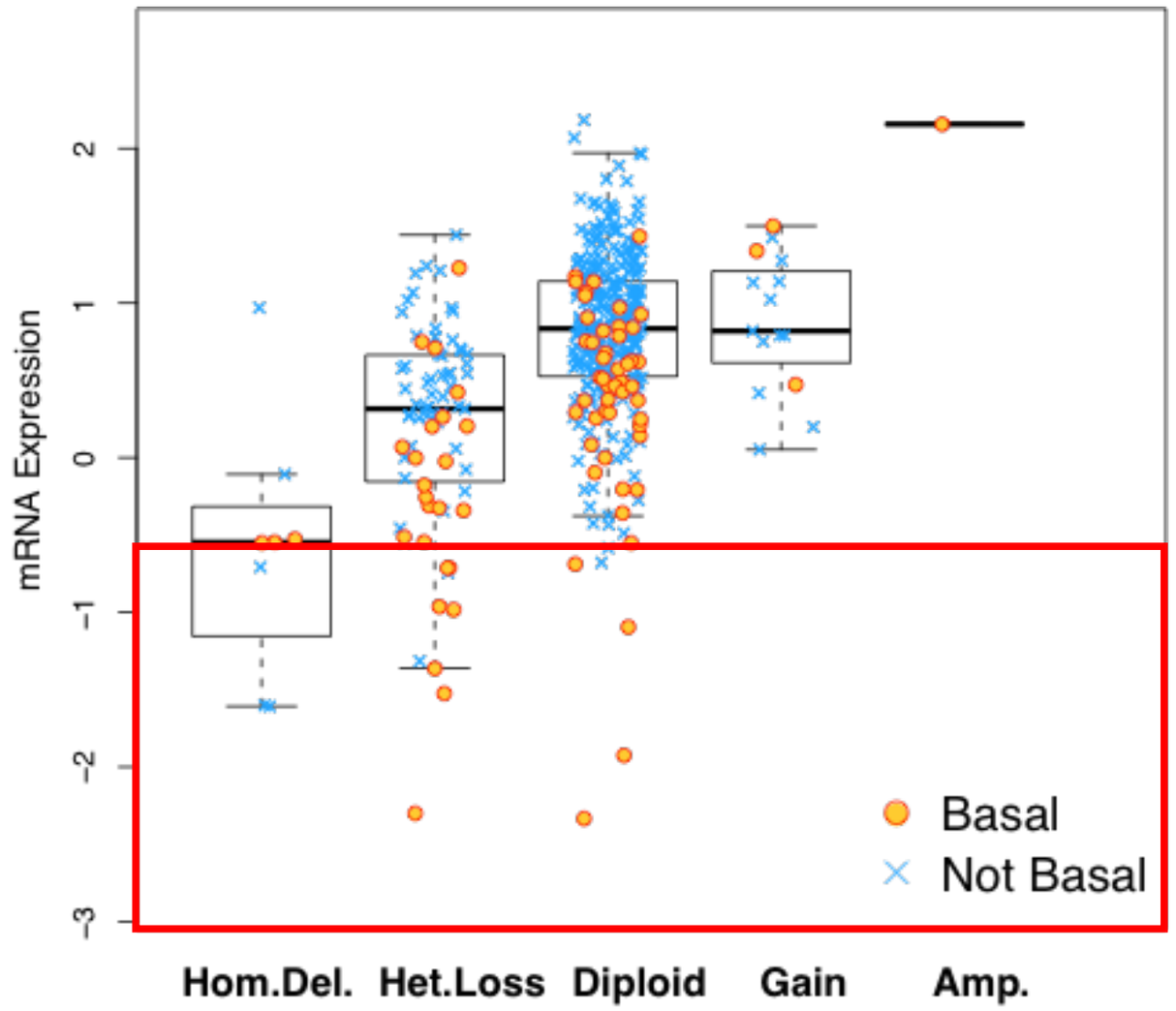




Is the PI(3)K pathway altered by other means in Basal tumors?

# PTEN is down-regulated in Basal Breast Cancer

- PTEN is down-regulated in Basal tumors

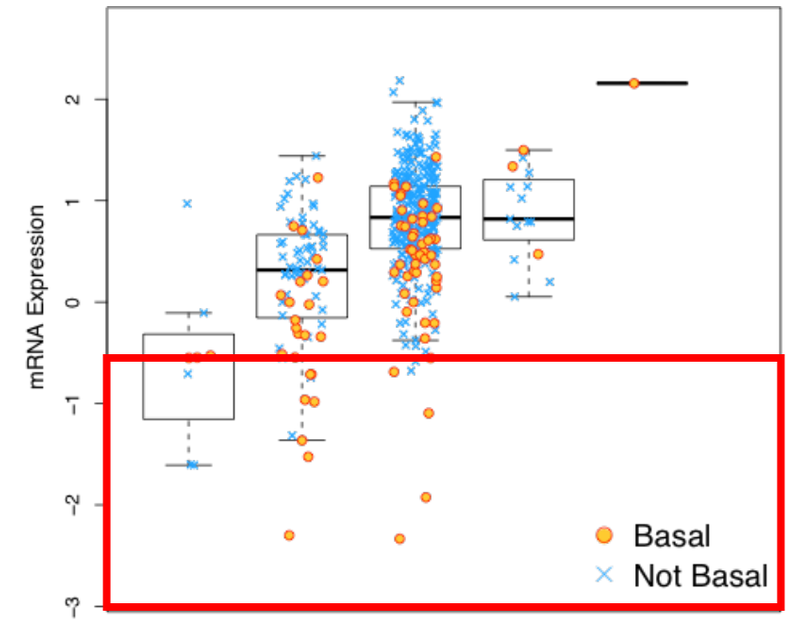
**10% of Basal Tumors**

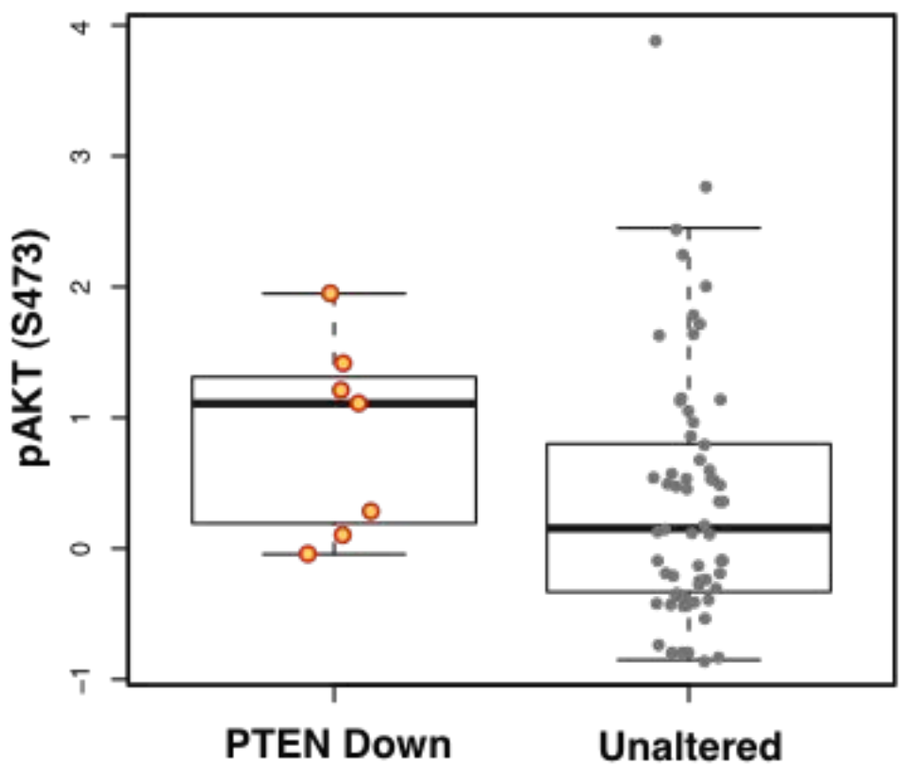


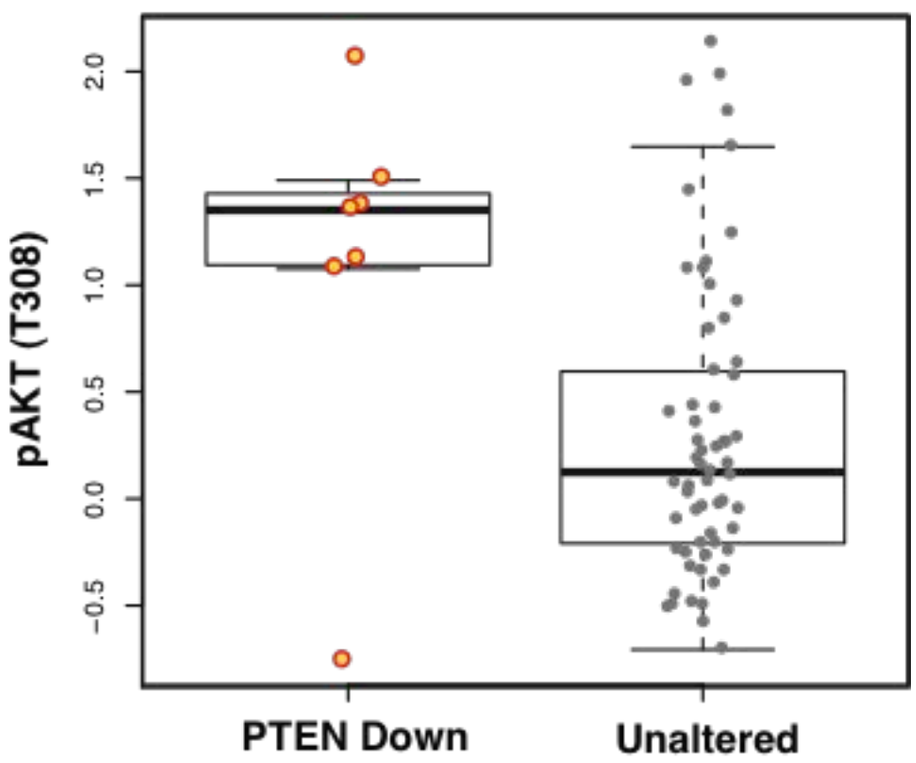
# PTEN down-regulation activates Akt

- PTEN is down-regulated in Basal tumors
- Down-regulated samples show higher Akt phosphorylation

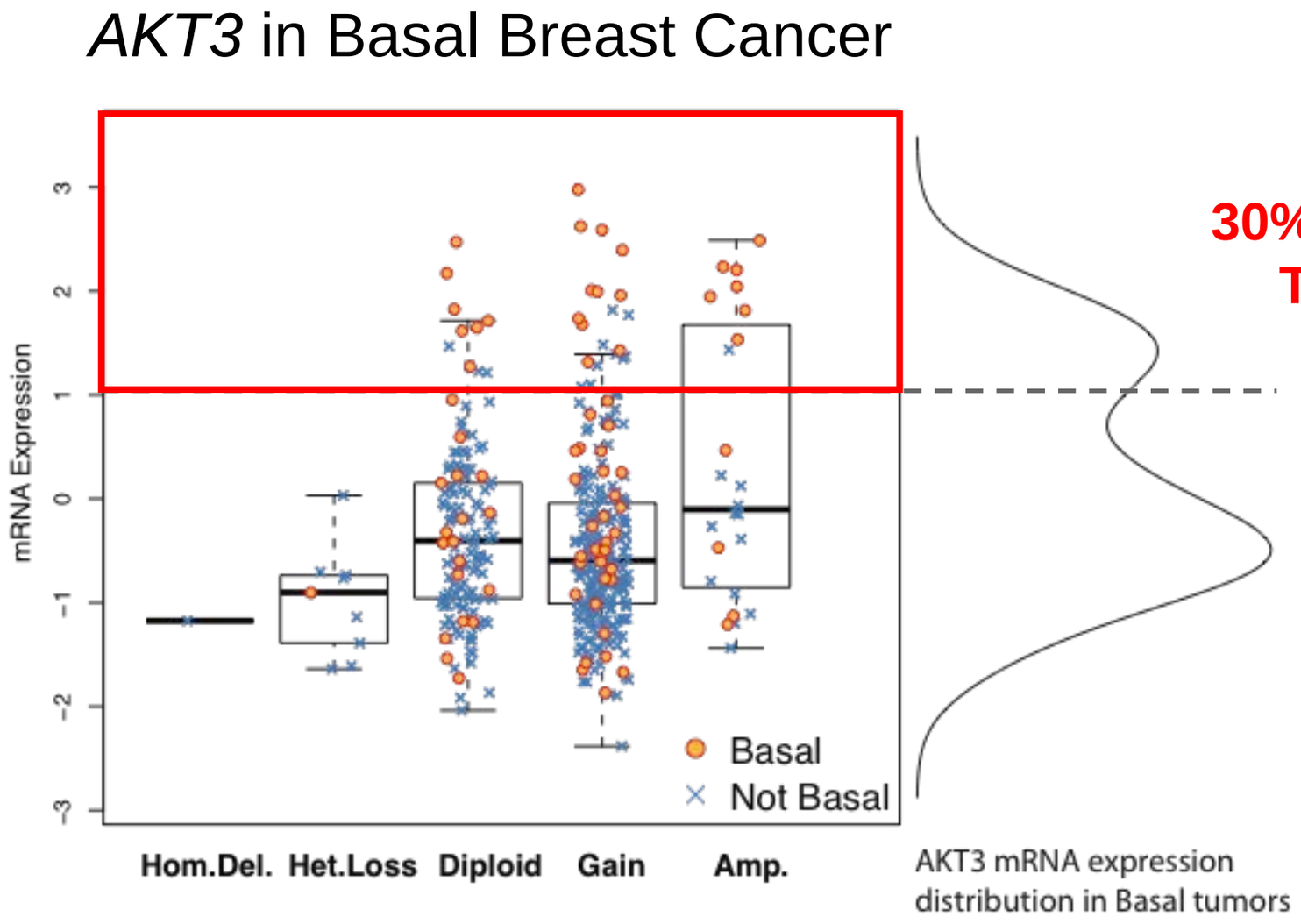
**10% of Basal Tumors**

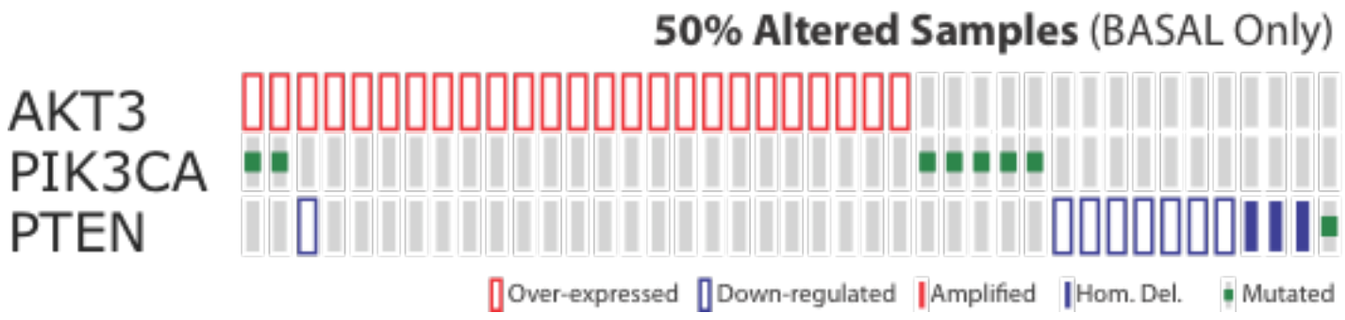


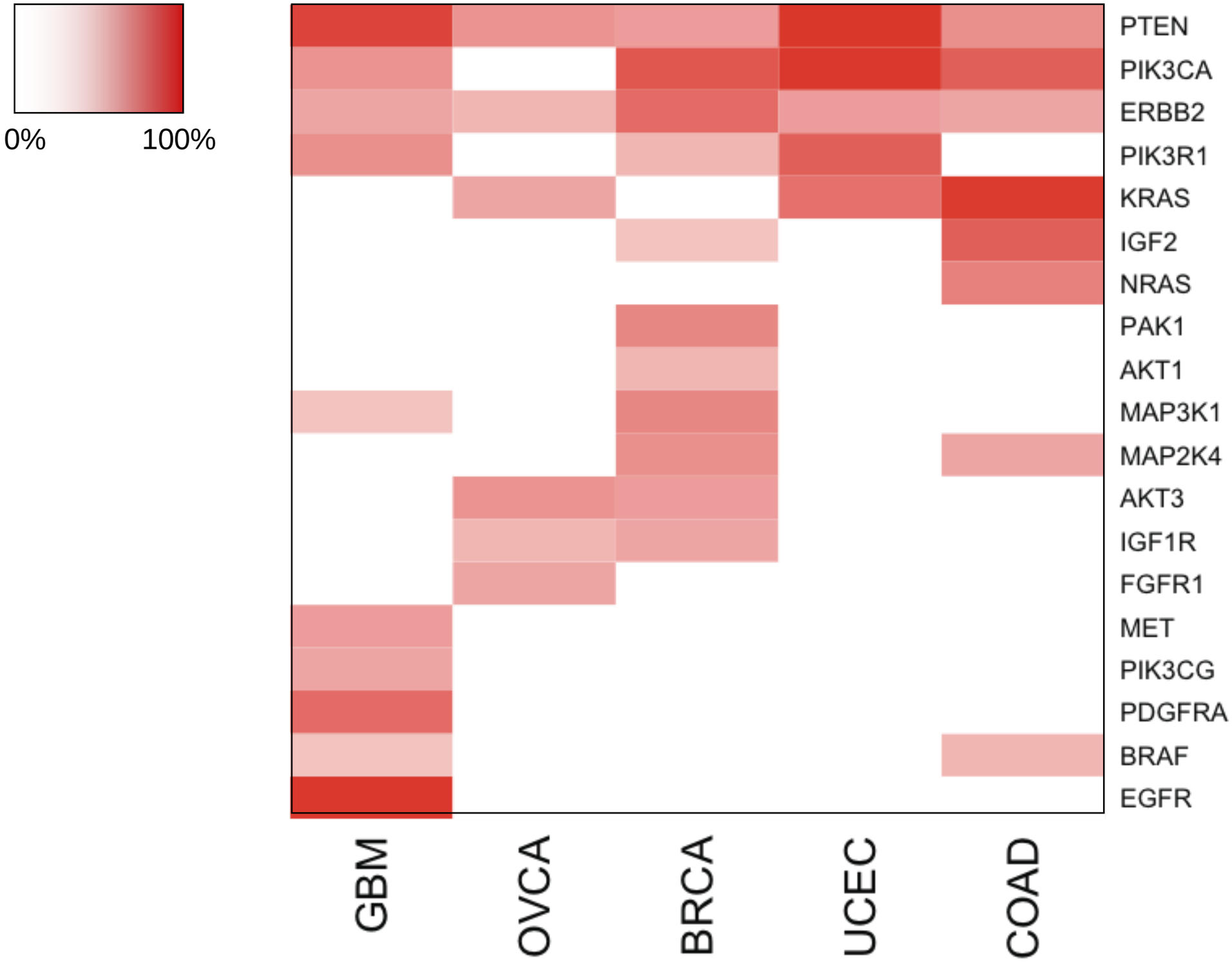



# AKT3 is over-expressed in Basal Breast Cancer



# Overall Extent of Alteration



# Conclusions

- **MEMo** systematically identifies **mutually exclusive** alterations targeting oncogenic pathways across multiple cancer types

- **PI(3)K /Akt** signaling is consistently altered in cancers, with different **extents of alteration**, and by **different mechanisms**

- Mutual exclusivity analysis **across multiple cancers** unveils the underlying heterogeneity of the disease,
thus suggesting candidate **therapeutic targets in different subtypes**

# Thanks!

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Nils Weinhold
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... and everyone at cBio!