

The MAPK pathway is variably active across breast cancer subtypes and increased activity may be associated with hormonal therapy resistance

Background

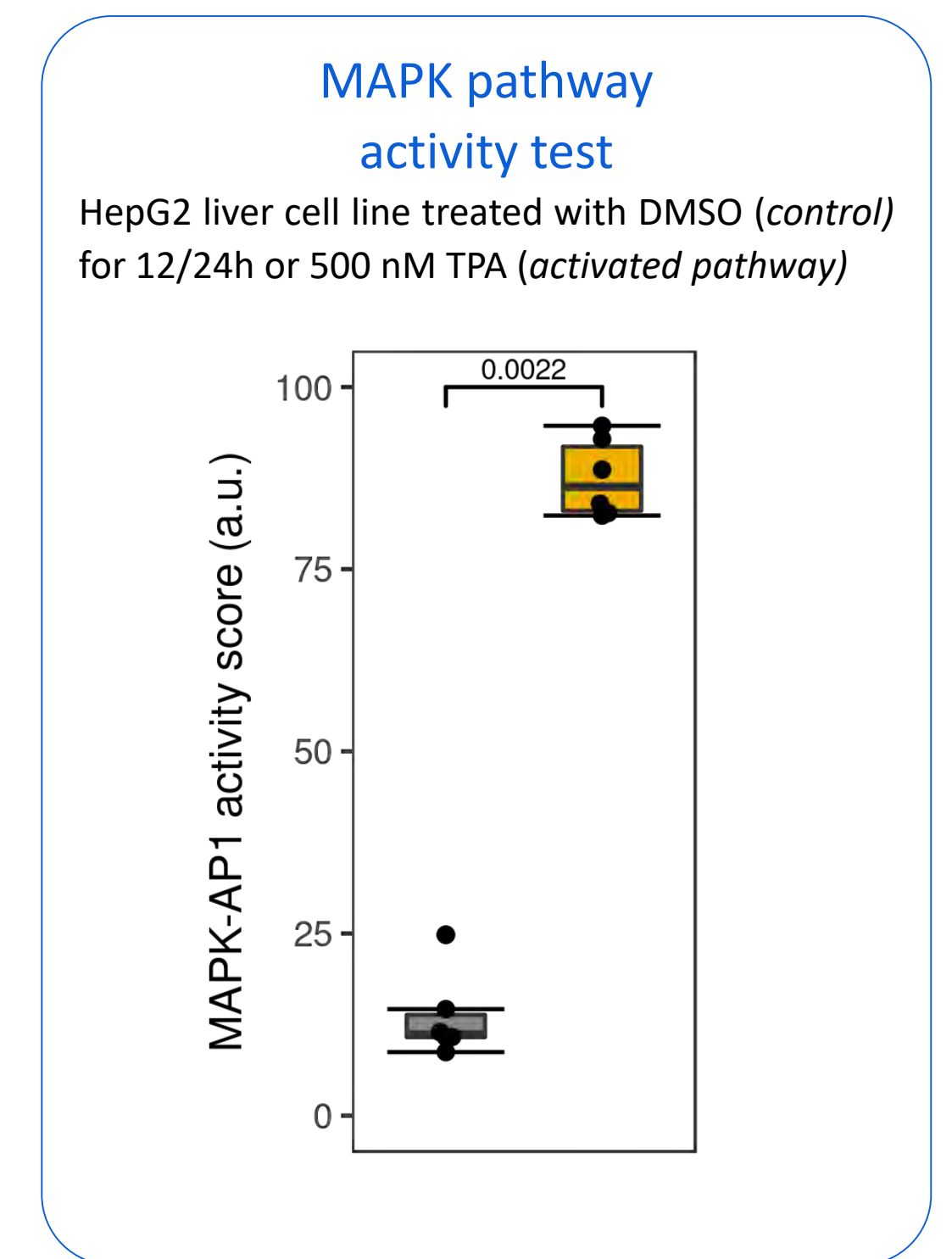
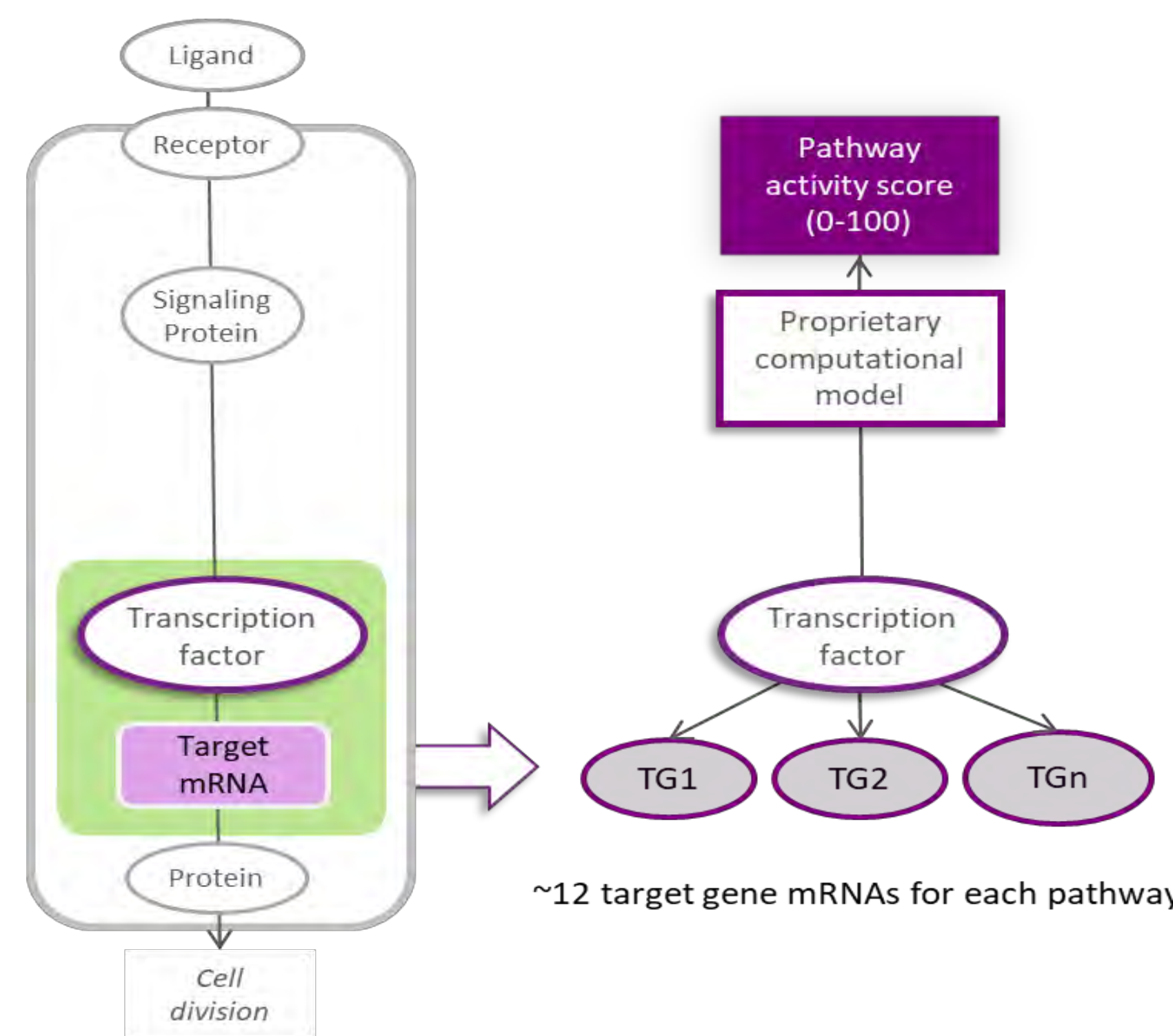
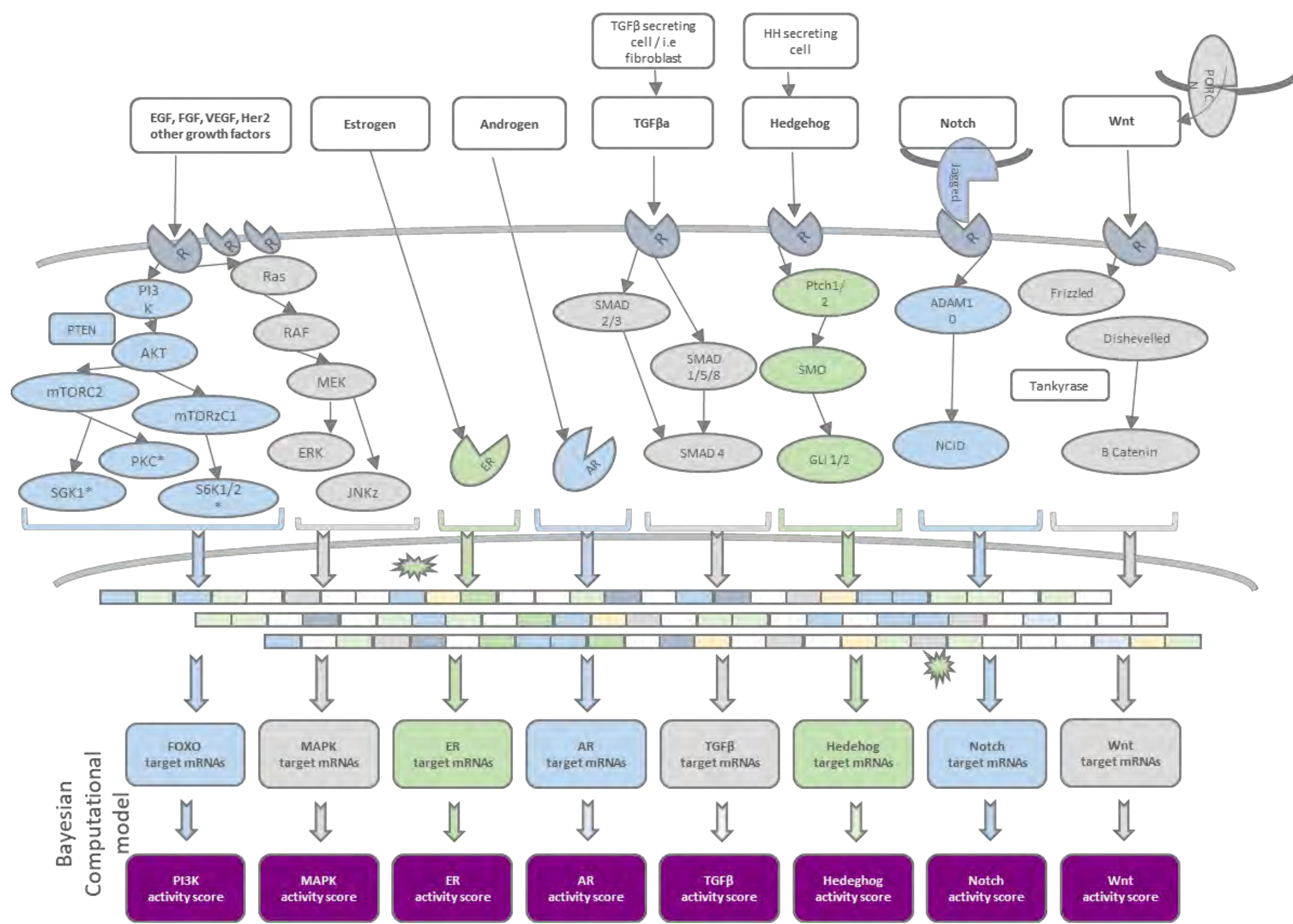
Based on preclinical research, the MAPK growth factor pathway is thought to be a driving oncogenic pathway in breast cancer, potentially in association with the ER pathway. In patients it is unclear how functional MAPK pathway activity relates to the activity of the ER pathway to drive cancer growth. Based on previous experience with development of the ER pathway¹, we developed a MAPK pathway test. We now present:

- (1) MAPK pathway activity and its relation to ER pathway activity in breast cancer
- (2) Emergence of MAPK pathway activity associated with hormonal therapy resistance

Test for quantitative measurement of signal transduction pathway activity

Specific signal transduction pathway activity can be determined by measuring mRNA levels of the specific transcriptional target genes belonging to that pathway, using a Bayesian computational model¹. These mRNA based tests* have been developed for androgen and estrogen receptor (ER), Hedgehog, TGFβ, Notch, NFκB, PI3K, and Wnt. The MAPK pathway model* was developed on Affymetrix mRNA data from samples with non-activated and with induced MAPK pathway activities.

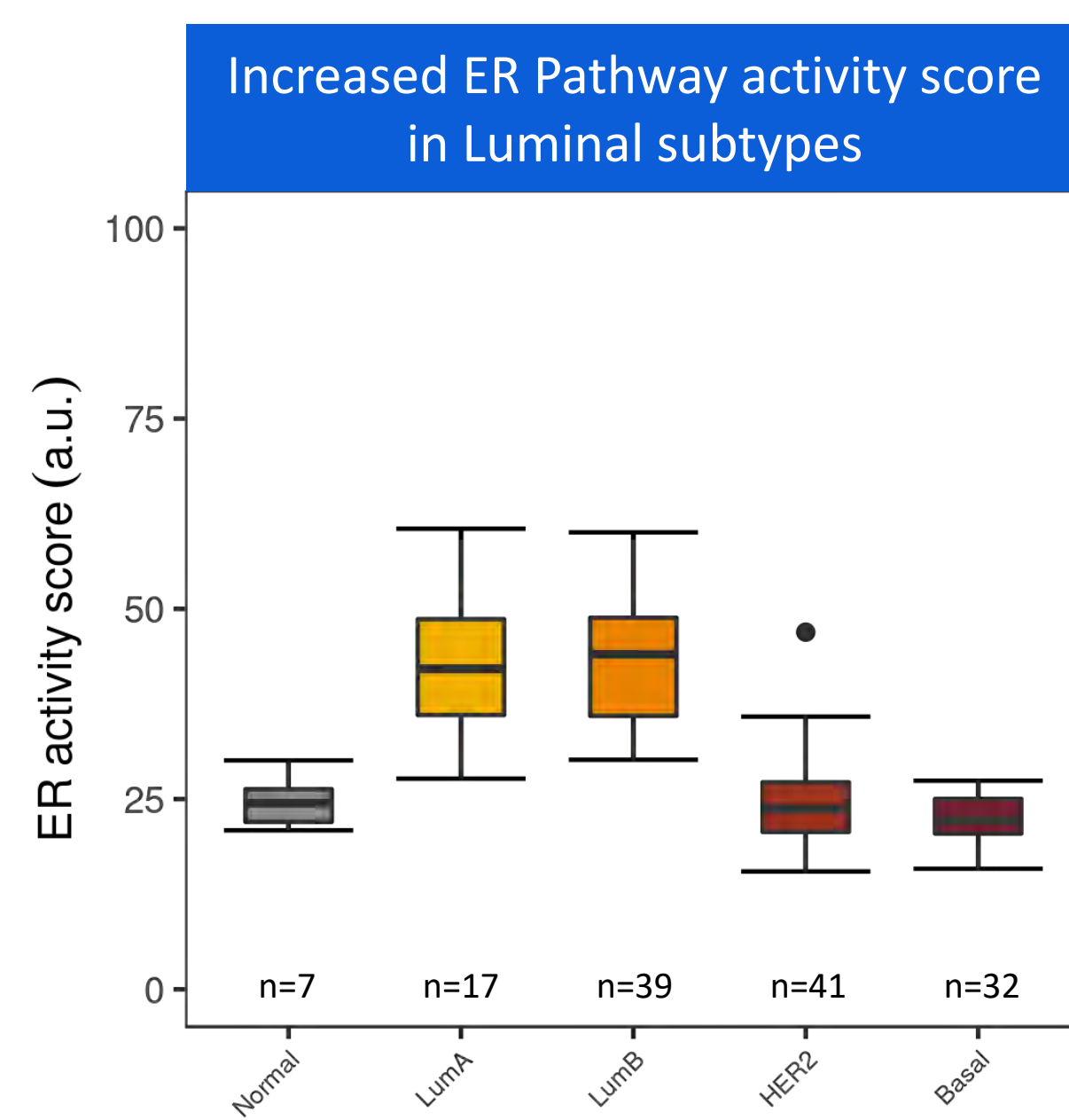
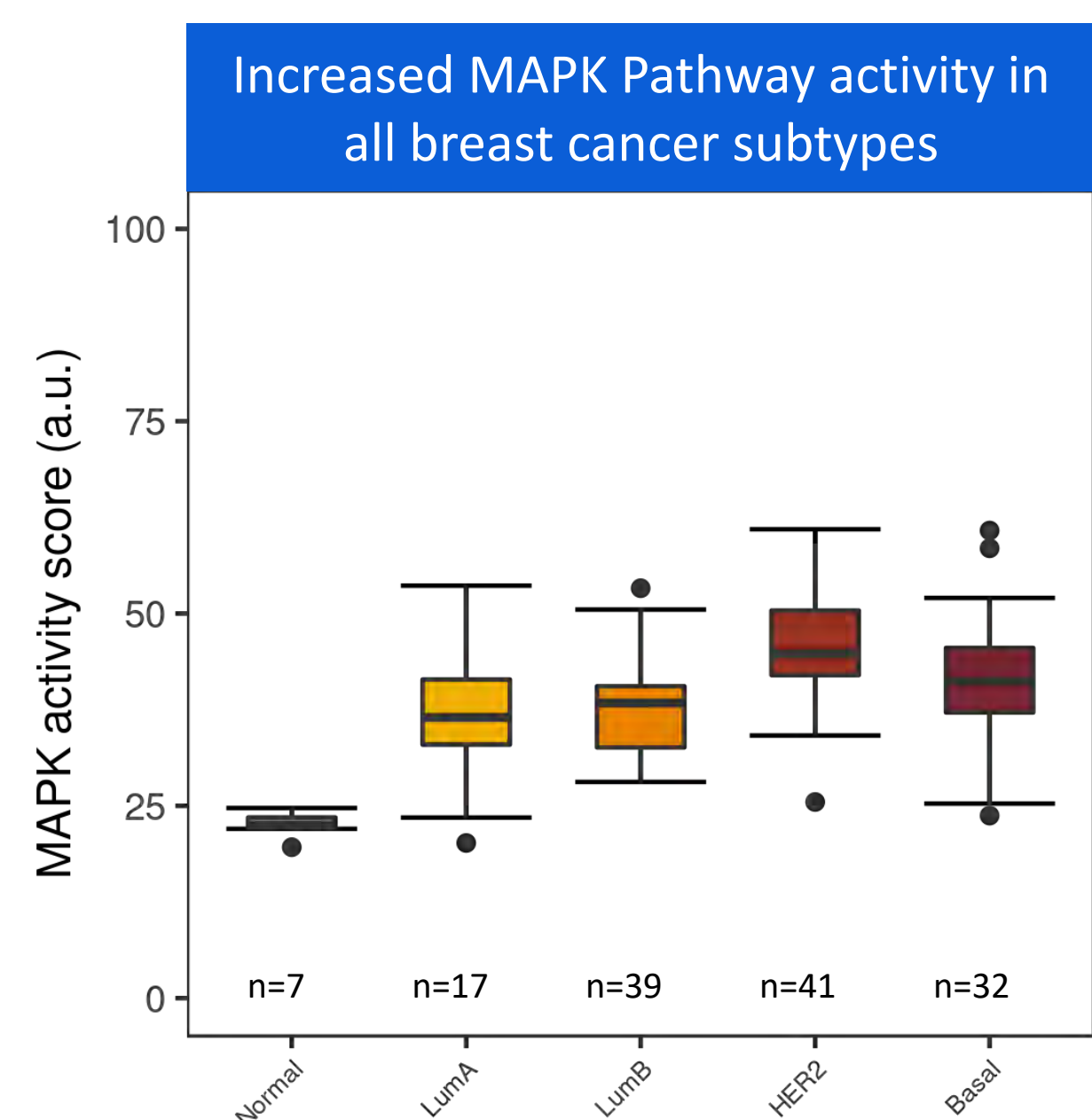
On single tissue or cell culture sample, Affymetrix HG-U133 Plus 2.0 microarray, qPCR or RNA-sequencing can be used to measure several pathways from the same sample and provide quantitative and repeatable *pathway activity scores* (PAS) expressed on a 0-100 scale.¹



MAPK pathway activity is increased in breast cancer samples and independent of ER pathway activity

GSE45827² Affymetrix microarray data were used, containing:

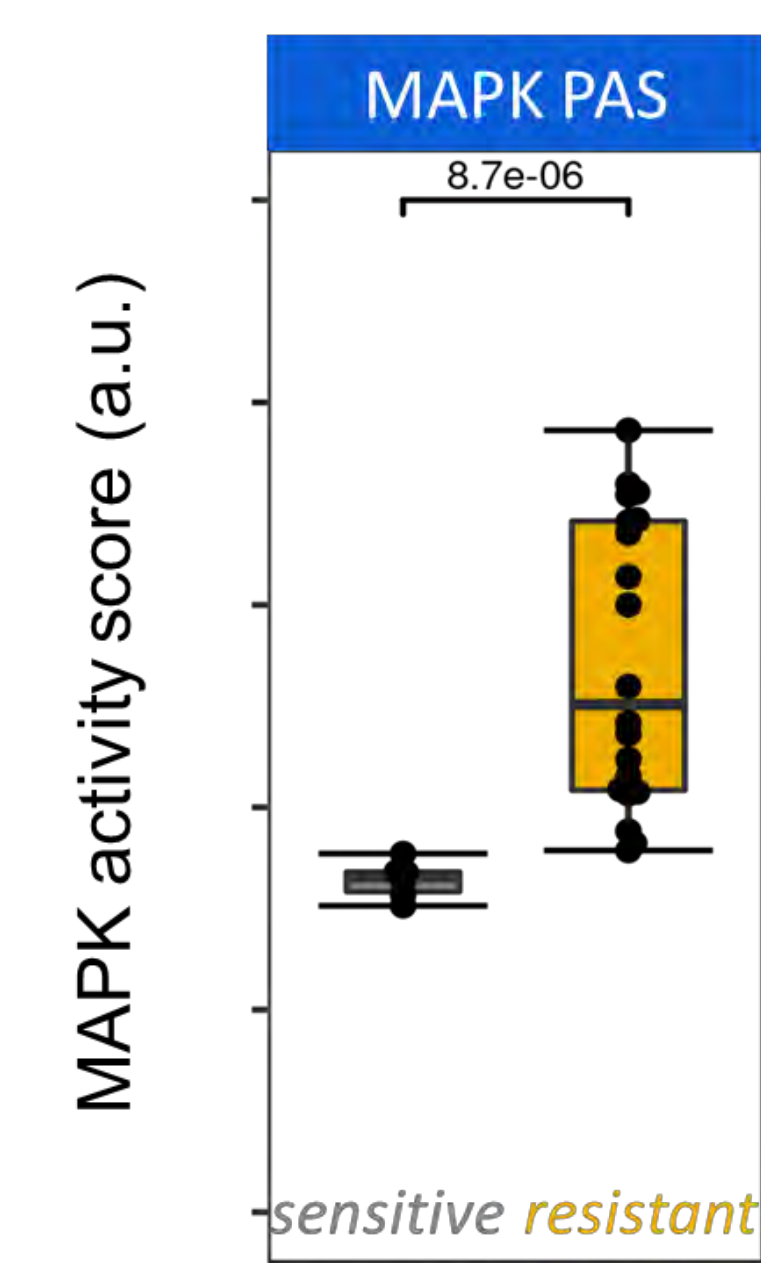
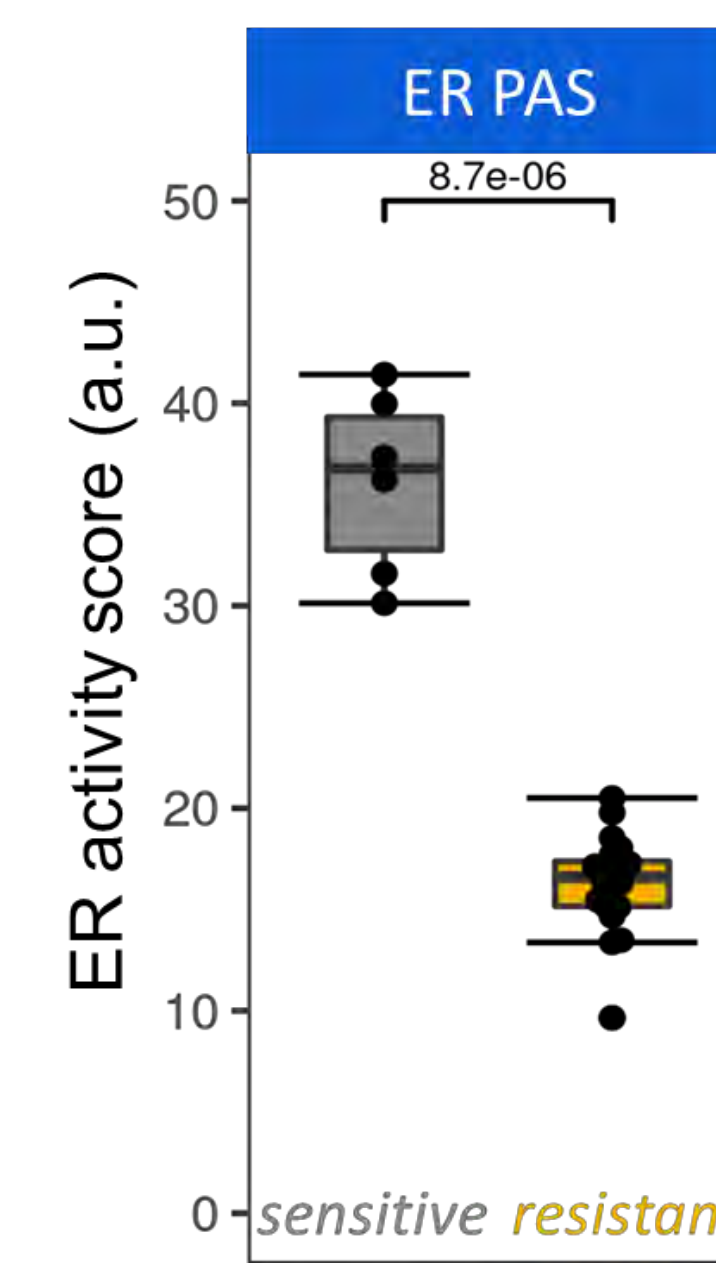
- Primary invasive breast cancer samples obtained at surgery before treatment
- Normal tissue samples
- Intrinsic breast cancer subtypes determined based on Perou's classification³



Hormonal therapy resistance is associated with MAPK pathway activity

- GSE74391⁴ Affymetrix microarray data set used (MCF-7/ ER+)
- Fulvestrant resistance induced by long term treatment with 100 nM fulvestrant; still ER+ staining

Fulvestrant resistance shows increased MAPK and decreased ER-PAS



Fulvestrant-sensitive MCF-7 (n=6)

- High ER PAS
- Low MAPK PAS

Fulvestrant-resistance MCF-7 (n=20)

- Low ER PAS
- High MAPK PAS

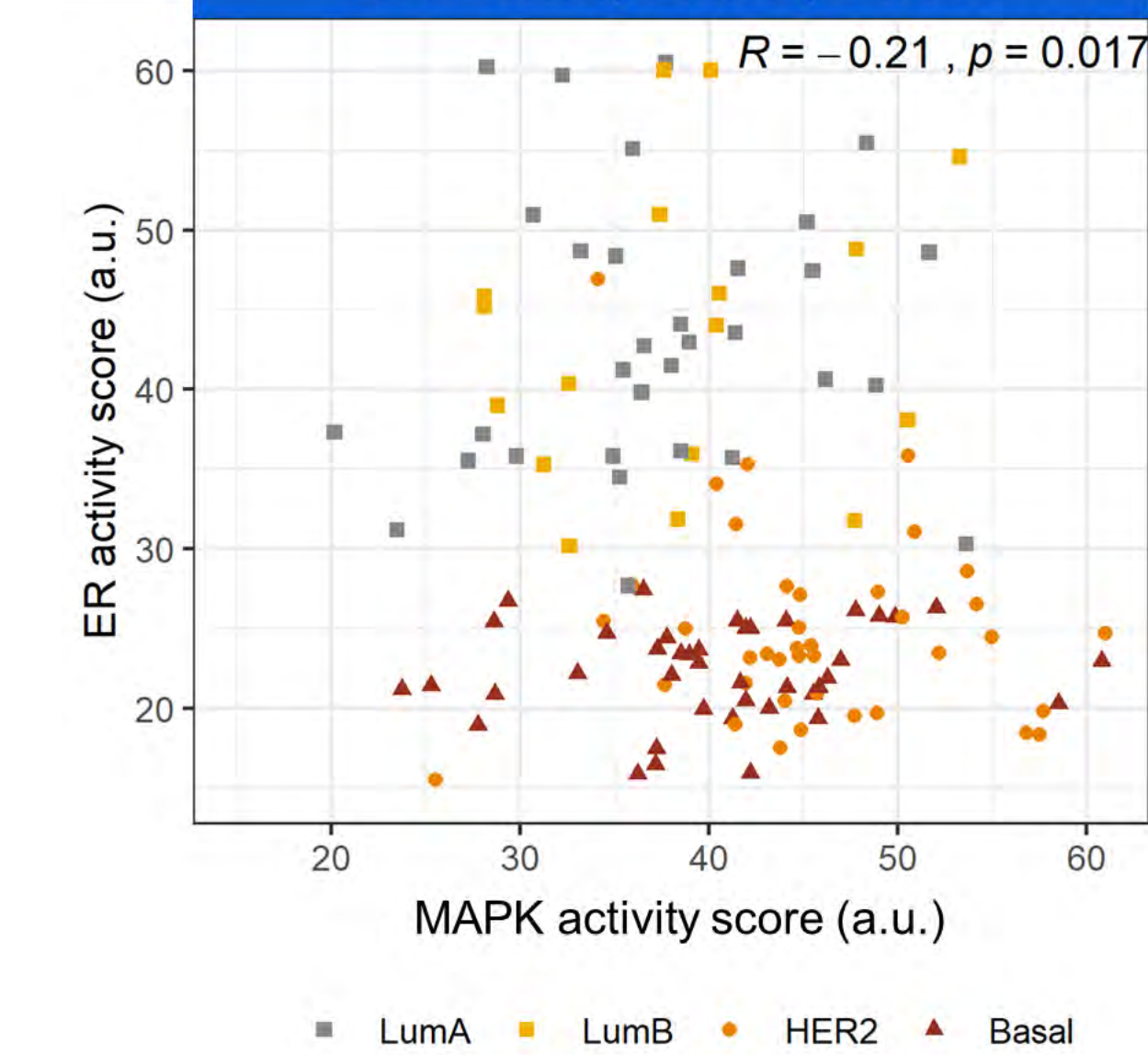
Strongly increased MAPK pathway activity and reduced ER pathway activity may explain therapy resistance to hormonal treatment.

Discussion

- Results support the MAPK pathway as a potential tumor driving pathway in breast cancer
- In hormonal therapy resistant MCF-7 cell lines (ER+), increased MAPK pathway activity is observed, suggesting a possible escape mechanism that could be targeted
- In breast cancer patients the MAPK pathway activity is variably increased
- In a subgroup of luminal patients the MAPK pathway activity may confer resistance to hormonal therapy and may be considered for targeted therapy

Future clinical studies are needed to confirm the role of MAPK signaling pathway in hormonal therapy resistance and treatment.

No correlation between MAPK and ER Pathway activity scores



In clinical breast cancer samples:

- MAPK pathway activity is increased in all BC subtypes (compared to normal)
- Large dynamic range in MAPK and ER pathway activity and BC subtypes, indicating patient specific pathway activities
- No meaningful correlation (R=-0.21) between MAPK and ER pathway activity suggesting different underlying mechanisms of tumor growth in each patient ⇒ important to measure both pathways

References

- ¹ Verhaegh W et al. (2014) *Cancer Res.* 74(11):2936-2945
- ² Gruosso T et al. (2016) *EMBO Mol Med* 9(5):527-549
- ³ Perou CM et al. (2000) *Nature* 406:747-752
- ⁴ Alves CL et al. (2016) *Clin Cancer Res* 22(22):5514-5526