Support for targeted therapy selection in triple-negative breast cancer (TNBC) patients using aberrant signal transduction pathway activity profiles

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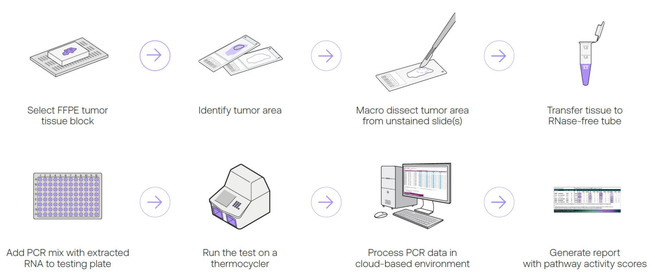
Introduction:

Success of therapeutic interventions largely rely on the pathological and biological characteristics of the tumor and varies due to the heterogeneous nature of breast cancers. Triple negative breast cancers (TNBC) stain IHC negative for both hormone receptors (ER, PR) and HER-2. TNBC is usually treated with chemotherapy because of absence of a molecular target. This study is initiated to characterize TNBC based on a new methodology that measures and quantifies signal transduction pathway (STP) activities to reveal potential tumor-driving STPs in TNBC and create new options for existing targeted therapy.

Method:

- 22 TNBC and 39 healthy breast tissue FFPE samples
- Normal tissue samples were mostly obtained from breast reduction surgery
- Total RNA isolated from areas where tumor/epithelial cell percentage is at least 50% (RNeasy FFPE kit Qiagen, including DNase step)
- RT-qPCR performed (Bio-Rad CFX96)
- OncoSIGNal pathway activity profiling test performed. Quantification of 7 signaling pathways and presented on a scale ranging from 0 to 100.

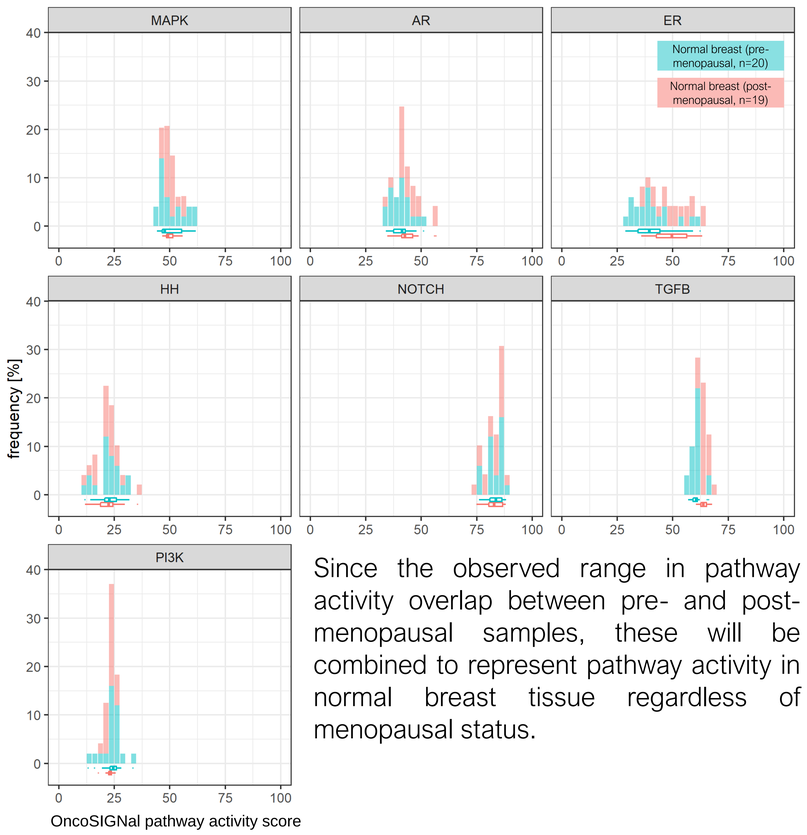


The STP activity of normal breast tissue is representing the normal physiological activity and is used as reference value to assess aberrant STP activity in breast tumor samples:
Aberrant high pathway activity in a patient tumor sample was concluded when this score was above twice or triple the standard deviation of the mean of normal breast tissue STP activity.

Results:

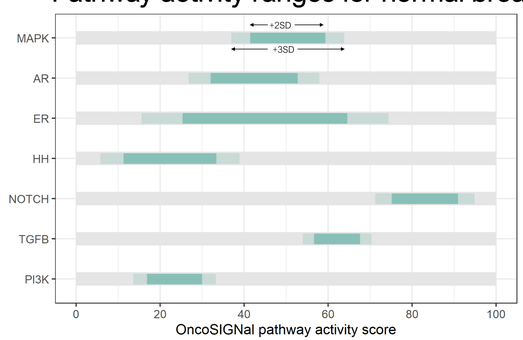
Pathway activity in normal breast tissue

Obtained from pre- (n=20; age 17-20) and post-menopausal (n=19; age 58-70) samples.



Since the observed range in pathway activity overlap between pre- and post-menopausal samples, these will be combined to represent pathway activity in normal breast tissue regardless of menopausal status.

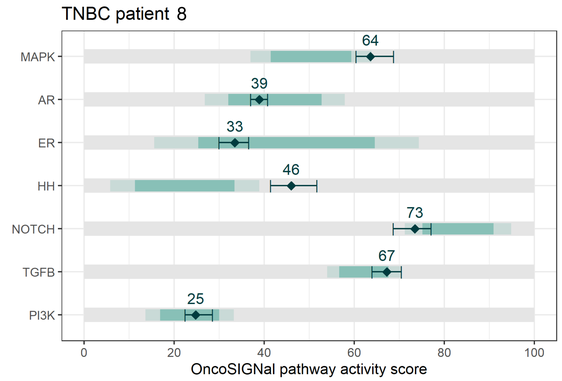
Pathway activity ranges for normal breast tissue



Normal breast pathway activity ranges depicted in the green highlighted area (solid green 2SD, light green 3SD).

MAPK: mitogen activated protein kinase
AR: androgen receptor
ER: estrogen receptor
HH: Hedgehog
TGFβ: transforming growth factor β
PI3K: phosphoinositide 3-kinase

Example report: TNBC patient sample as compared with normal range

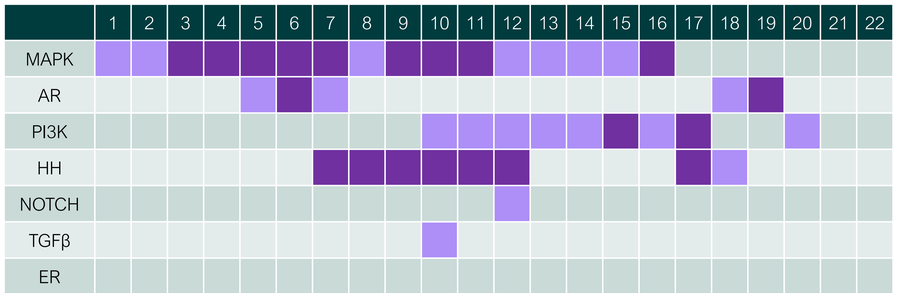


TNBC sample with 95% confidence interval (black) as compared to normal activity range

Interpretation of this example:
Aberrant HH (>3SD) and MAPK (>2SD) pathway activity

Aberrant pathway activity profiles observed in 91% of TNBC samples

- Aberrant activity observed in MAPK (73%), AR (23%), PI3K (41%) and HH (36%) pathways
- As expected, no aberrant activity of ER pathway observed in TNBC
- High heterogeneity in TNBC pathway activities
- Each individual patient has its specific pathway profile



aberrant pathway activity profiles per patient; light purple >2SD, dark purple >3SD from the normal range

Conclusion and next steps:

- OncoSIGNal pathway profiling can be used as new biomarker to identify aberrant signal transduction pathway activities
- Specific and personalized aberrant STP activities can be determined in individual TNBC samples
- Aberrant signaling pathways may create new options for personalized treatment of TNBC patient
- Expansion of the patient cohort and relation of pathway profiling to clinical response parameters is ongoing

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