PHILIPS

Molecular Pathway Dx

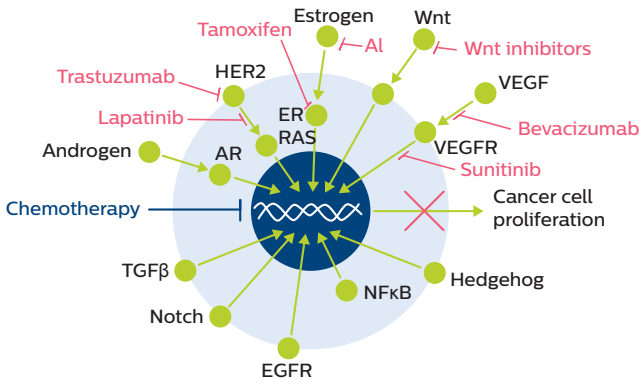
OncoSignal

OncoSignal: Determining the functional activity of tumor-driving signal transduction pathways

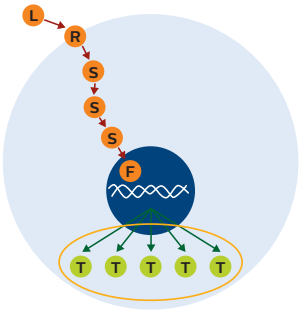
Building on decades of cell biology research, unravelling the mechanisms driving tumor growth.

Essential knowledge has been acquired on the role of signal transduction pathways in cancer growth, providing input for development of drugs targeting signaling pathways. Identification of the tumor-driving pathway and its causative defect is crucial for selecting the most effective therapy.

Philips OncoSignal Molecular Pathway Diagnostics determines the activity of tumor-driving signal transduction pathways by measuring mRNA transcribed from target genes of the pathway transcription factors, and data interpretation with computational pathway models.
(W Verhaegh et al, Cancer Research 2014 74(11): 2936-45).



10-15 Signal transduction pathways are known to drive cancer growth; Targeted drugs target the following pathways: Estrogen receptor (ER) and androgen receptor (AR), Wnt, Notch, Hedgehog, TGF-ß, NF-κB, and the growth factor stimulated signaling pathways: phosphoinositide 3-kinase/AKT /FOXO, RAS/ MAPK/ERK, and JAK/STAT.



Testing "down-stream" for mRNA transciption of the target genes of pathways

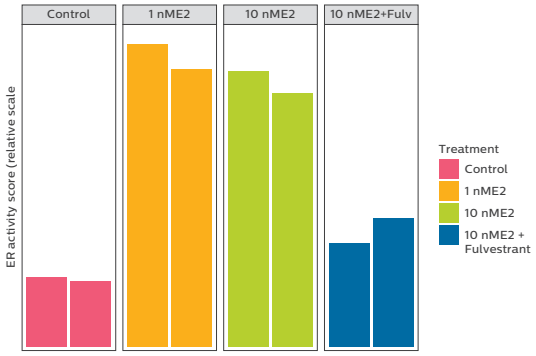
OncoSignal enables functional assessment of pathway activity in tumor samples. The expression levels of selected target genes of these pathways are measured using our qPCR test kit; our sophisticated computational models interpret the data and indicate the activity scores of the different pathways. OncoSignal Molecular Pathway Dx is applicable across a broad range of cancer types.

OncoSignal qPCR kits are in development, not available for sale. OncoSignal pathway analysis is already available through our dedicated service lab for Research Purposes Only. Not for use in diagnostic procedures.

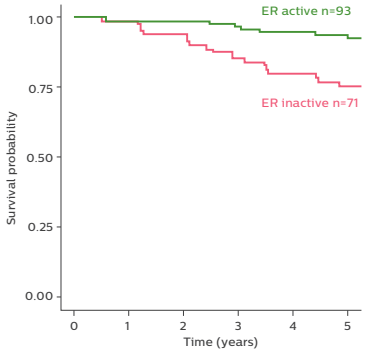
Breast Cancer: OncoSignal pathway activity & response

ER pathway

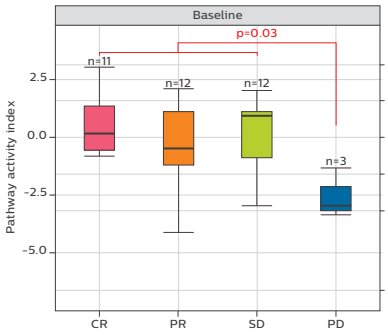
ER pathway activity in MCF7 breast cancer cell lines, ER activity stimulated by estrogen. ER pathway activity inhibited by fulvestrant.
Ref: EJ Blok et al, SABCS 2015

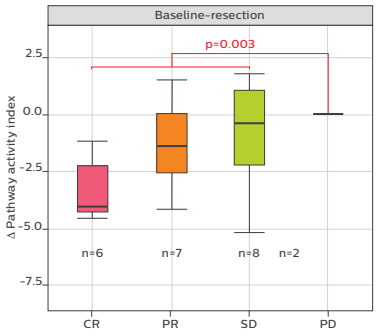


ER stain positive breast cancer patients with active ER pathway show better response to adjuvant hormonal therapy.
Ref: W Verhaegh et al, Cancer Research 2014 74(11): 2936-45



TEAM IIa study: ER receptor positive patients, neo-adjuvant hormonal treatment, treatment response assessment by palpation. (CR complete response, PR partial response, SD stable disease, PD progressive disease).
Ref: EJ Blok et al, SABCS 2015



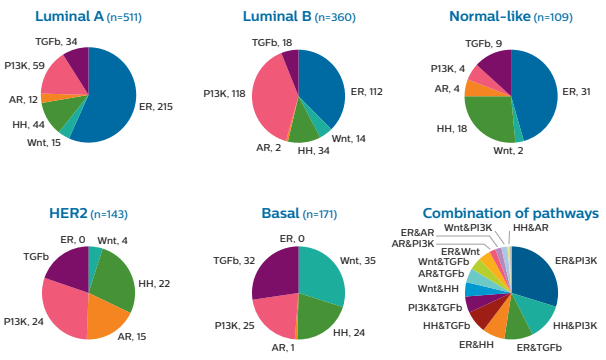


Progressive disease (PD) is associated with low baseline ER pathway activity.

Response to hormonal therapy is correlated to decrease in pathway activity.

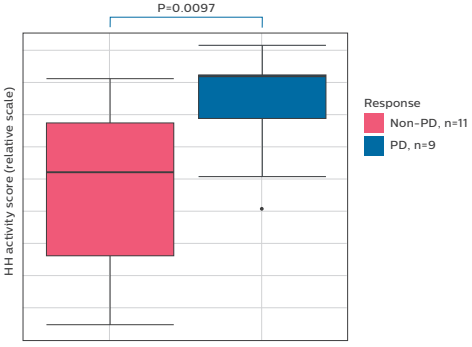
Multiple pathways

Dominant pathway activity varies across breast cancer subtypes. Pathway analysis in individual patients may guide therapy choice. In 13% of patients combinations of active pathways were observed.
Ref: H van Ooijen, AARC 2015



HH pathway

20 M1 ER positive patients with 1st line tamoxifen. High Hedgehog pathway activity in metastasized breast cancer patients is indicative of more aggressive tumor progression.
Ref: AM Sieuwerts et al, AACR 2016



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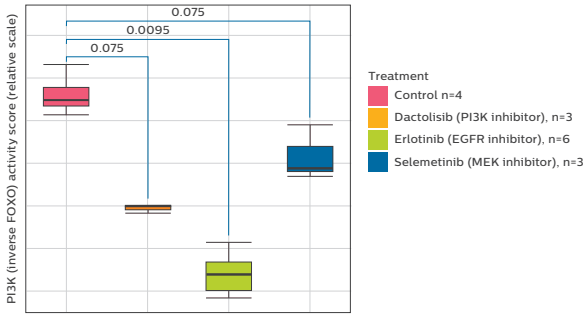
Other Cancers: OncoSignal pathway activity & response

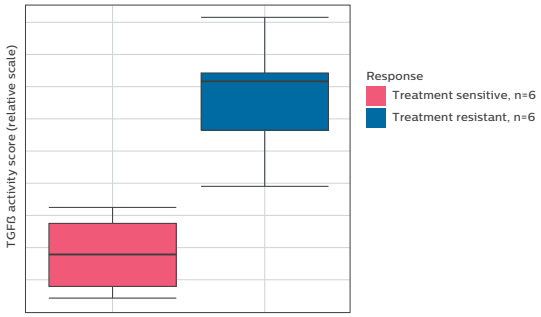
PI3K – lung / cell lines

HCC877 lung cancer cell lines with mutated EGFR. Addition of different PI3K inhibitors causes decrease in PI3K activity (recovery of FOXO activity).



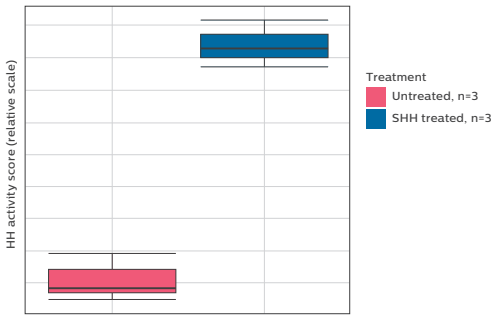
TGF-ß – glioblastoma / cell lines

Glioblastoma stem cells were treated with radiation and with or without temozolomide (GSE46531). TGF-ß pathway activity is higher in treatment resistant cells (p=0.002).



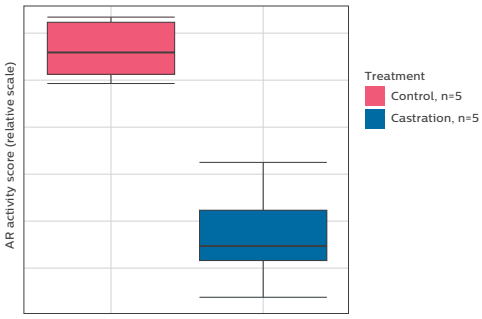
HH - colon / cell lines

Co-culture of colon fibroblasts with HUVEC cells (GSE29316). HH activity strongly increased in cells stimulated with Sonic hedgehog homolog (SHH).



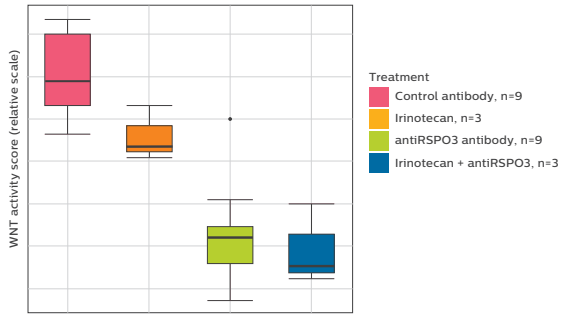
AR – prostate / PDX

LuCaP35 prostate tumor implanted in mice. Androgen deprivation induced by castration (GSE33316). Lower AR activity in castrated mice compared to control mice (p=0.008).



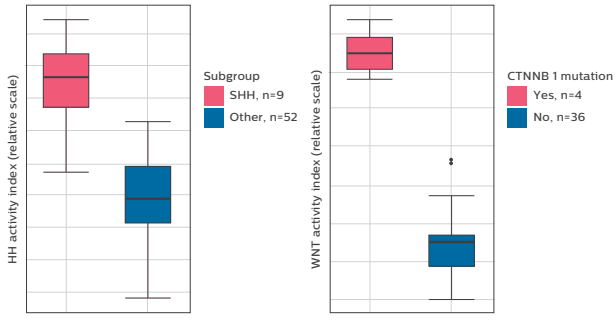
Wnt – colon / PDX

PDX mice containing colon cancer were treated with antiRSPO3 (Wnt inhibitor) and/or chemotherapy (GSE73906). Decrease in Wnt pathway activity after antiRSPO3 treatment. p (control vs irinotecan)= 0.036; p (control vs antiRSPO3)= 1.6·10-4; p (control vs irinotecan+antiRSPO3)= 0.009.



HH & Wnt – medulloblastoma

Medulloblastoma patients: High HH activity in the Sonic Hedgehog (SHH) subgroup compared to the other subgroups (p=9.7·10-6). High Wnt activity in group with Wnt activating mutation in the CTNNB1 gene (p=0.0013).



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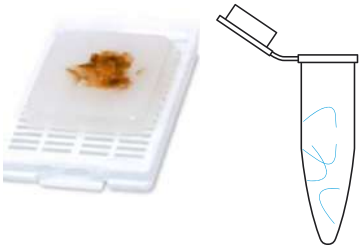
OncoSignal: Test procedure

OncoSignal qPCR tests and services to determine the tumor-driving pathway activity can be carried out using standard lab equipment in combination with cloud-based OncoSignal computational models for data interpretation. The test procedure should be performed in a laboratory suited for molecular diagnostics.

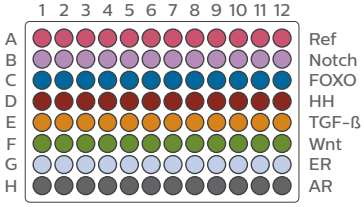
Studies to evaluate prediction of targeted therapy response in different cancer types are ongoing. Not yet available for sale.

RNA extraction



Tumor tissue (FFPE) Purified RNA

OncoSignal qPCR kit



PCR kit runs on standard Lab Equipment

OncoSignal data analysis software

Features

- RNA extracted from FFPE or FF tissue sample or cells can be used as test input.
- Standard procedures and equipment for RNA extraction & qPCR (96-well plate).
- Currently available pathways: ER, AR, FOXO/PI3K, HH, Wnt, TGF-ß, Notch.
- Pathways in development: AP1, PR, JAK/STAT, NF-κB.
- Short turnaround time of qPCR procedure and data analysis (within 1 day)
- Data analytics through stand alone web-based software or as module in Philips IntelliSpace Genomics.

Please contact

jos.rijntjes@philips.com; paul.van.de.wiel@philips.com; sieglinde.neerken@philips.com.