Selection of Personalized Patient Therapy through the Use of Knowledge-Based Computational Models That identify Tumor-Driving Signal Transduction Pathways

Paul van de Wiel, PhD
CEO and Co-Founder InnoSIGN

Dutch Life Sciences Conference
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www.innosignbio.com/www.oncosignal.com

Cancer Research, 2014

InnoSIGN, a precision medicine company, is a spin-off of Philips founded in March 2022

- Technology developed during 10 years by Philips
- InnoSIGN founded in March 2022 as an independent company
- Key shareholders: Casdin, LSA (US); Thuja, BOM, Philips (NL)
- Legal entities in NL and US
  - InnoSIGN BV: R&D, labs (ISO13485)
  - InnoSIGN Inc: Commercial, CLIA lab (future)
- R&D facilities at the High Tech Campus in Brainport Eindhoven

The mission of InnoSIGN is to make the promise of oncology precision medicine come true

Few patients benefit from genome-targeted therapy

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07 July 2021

The percentage cancer patients eligible for genome-targeted therapy increased from 5.13% in 2006 to 13.6% in 2020. Response rates increased from 2.73% in 2006 to 7.04% in 2020.

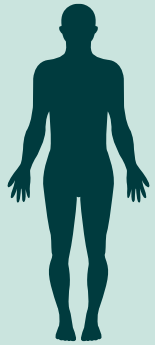
Selection of patients that benefit from targeted therapy is difficult

frontiers in Oncology

11 March 2021

The response rate to immunotherapy is still far from satisfactory and most patients are refractory to such treatment. In addition, escalating costs of cancer care and unnecessary immune-related adverse events also are pertinent considerations.

Current big data approaches link genomic data to patient information



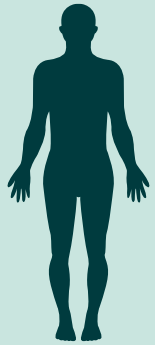
Patient

disease symptoms

Genome

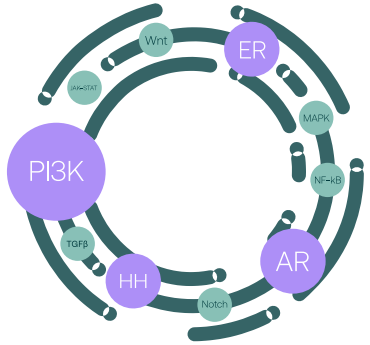
cell blueprint

Signaling pathways bridge the gap



Patient

disease symptoms



Signaling pathways

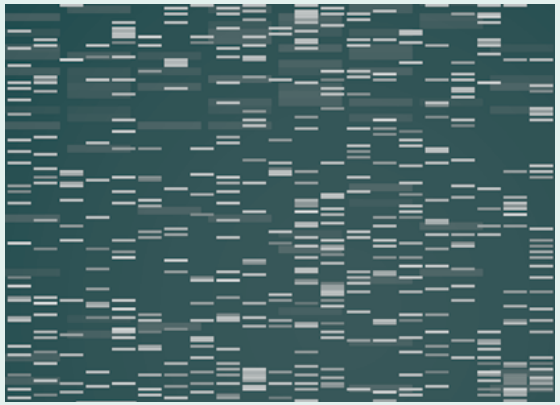
cell behavior

Genome

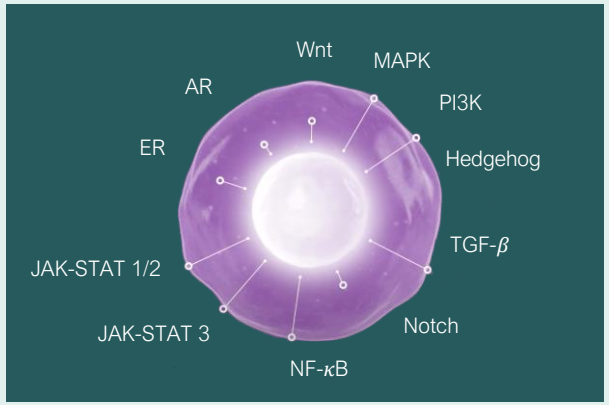
cell blueprint

Simplify complexity of genomics by focusing on the mechanism determining cell behavior

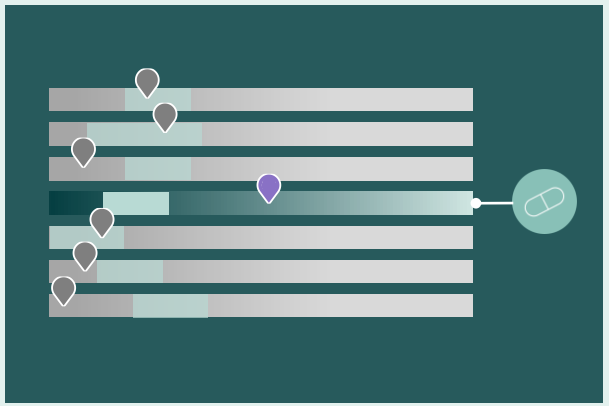
30,000+ genes



12 signaling pathways*



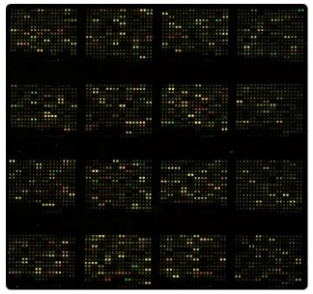
1 clear answer



* Vogelstein et al., Science 2013: “Driver genes can be classified into 12 signaling pathways that regulate three core cellular processes: cell fate, cell survival, and genome maintenance.”

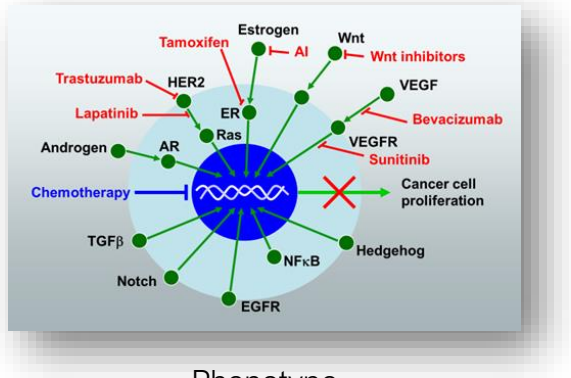
Aberrant activity of signaling pathways can be caused by mutations in the DNA or by changes in the microenvironment of the cell

Genotype + *Microenvironment* = *Phenotype*



Genotype
1000's of mutations

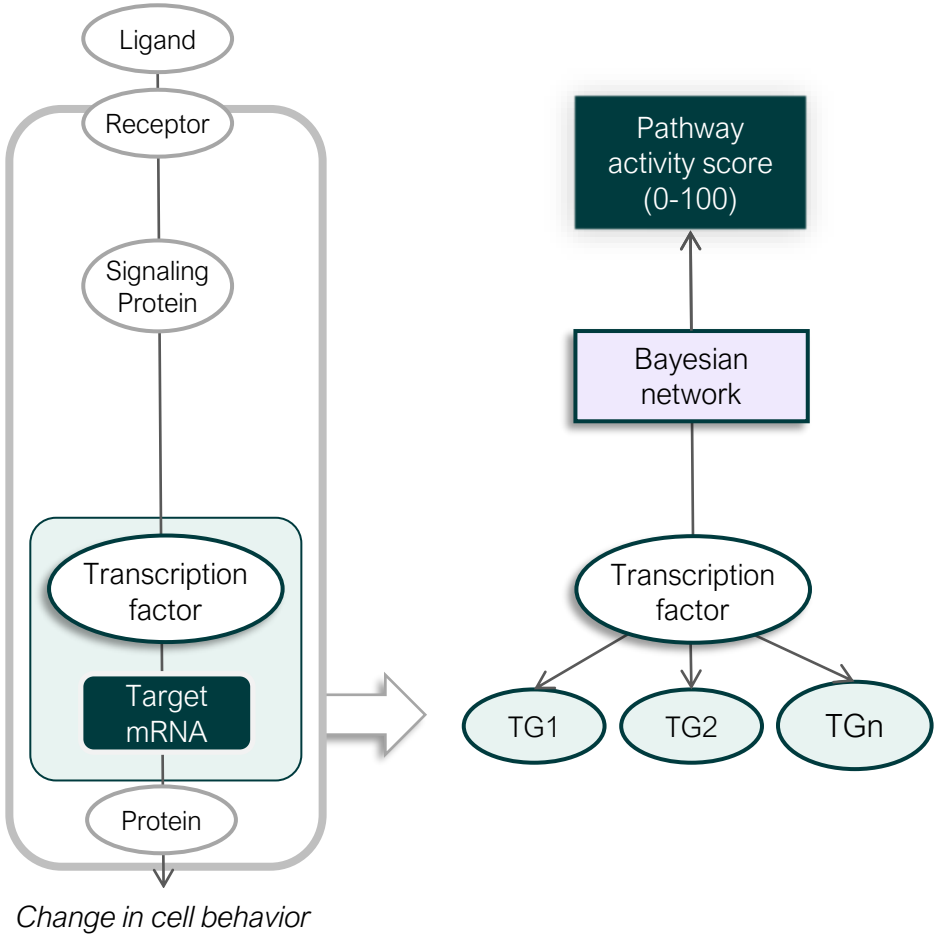
Microenvironment of the cancer cell



Phenotype
10-15 signal transduction pathways

- Coordinated activity of 10-12 cellular signal transduction pathways enables cells to communicate and adapt function to control physiological processes.
- Abnormal activity of (multiple) signaling pathways represents a clinically actionable mechanism of disease *(cancer, sepsis, auto-immune diseases, inflammatory diseases, and inherited diseases)*

OncoSIGNal measures functional activity of signaling pathways based on the mRNA expression of the pathway transcription factor



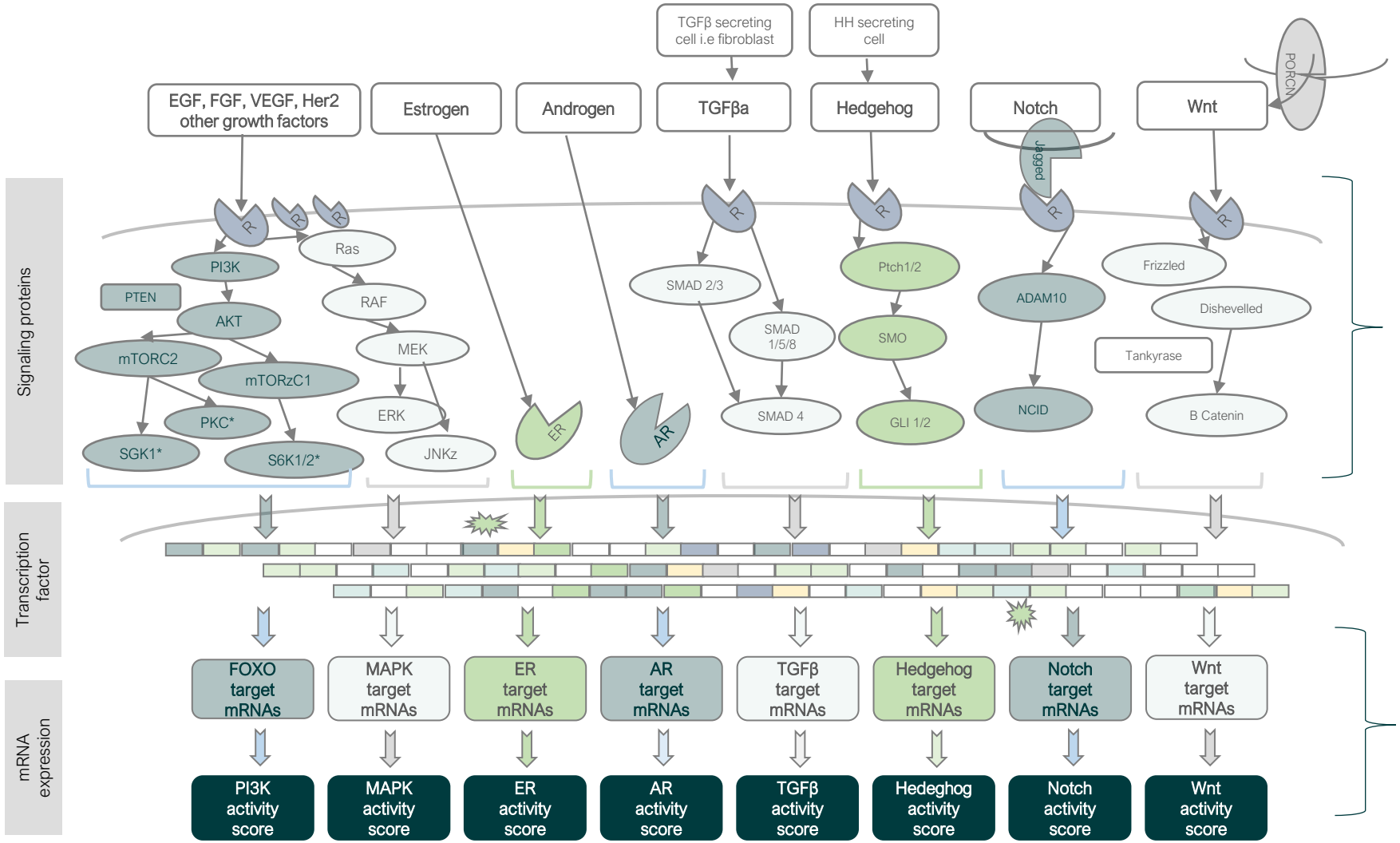
OncoSIGNal

Measuring mRNA levels transcribed from direct target genes of the pathway transcription factors and translation by a Bayesian (probabilistic) model into quantitative pathway activity scores.

OncoSIGNal tests are available for the following pathways:

- ✓ Nuclear receptor pathways: Estrogen (ER), Androgen (AR)
- ✓ Growth factor pathways: PI3K, MAPK
- ✓ Developmental pathways: TGFβ, Notch, Hedgehog (HH), Wnt
- ✓ Immune pathways: JAK-STAT1/2, NFkB

Measuring downstream signaling pathway activity to assess the effect of upstream mutations in DNA



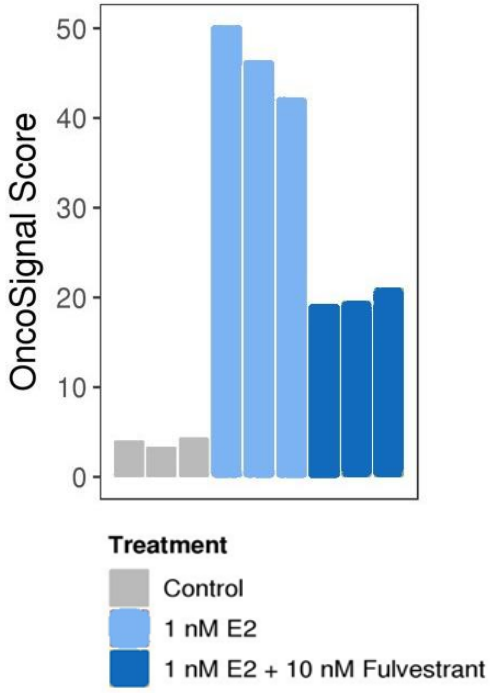
Mutations in driver genes coding for signaling proteins.
Biological effect of mutations often unclear.

OncoSIGNal measures mRNA expression of downstream signaling pathway target genes to assess the transcription factor complex activity.

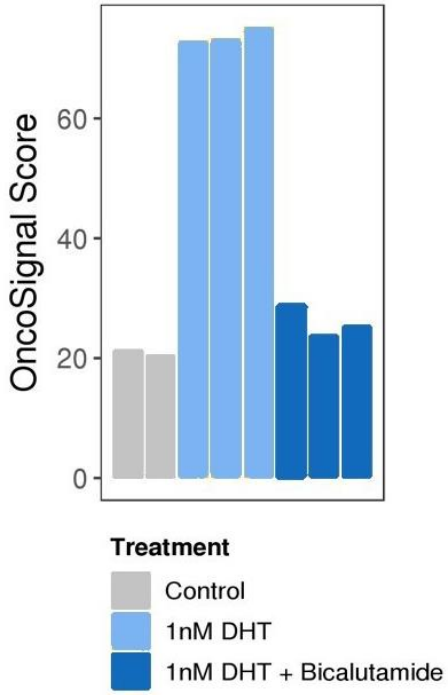
Calibration of OncoSIGNal tests using ground truth cell line models

Quantifying dose-dependent drug inhibitory effects on pathway activity and cell growth in cancer cell lines

ER pathway in MCF7

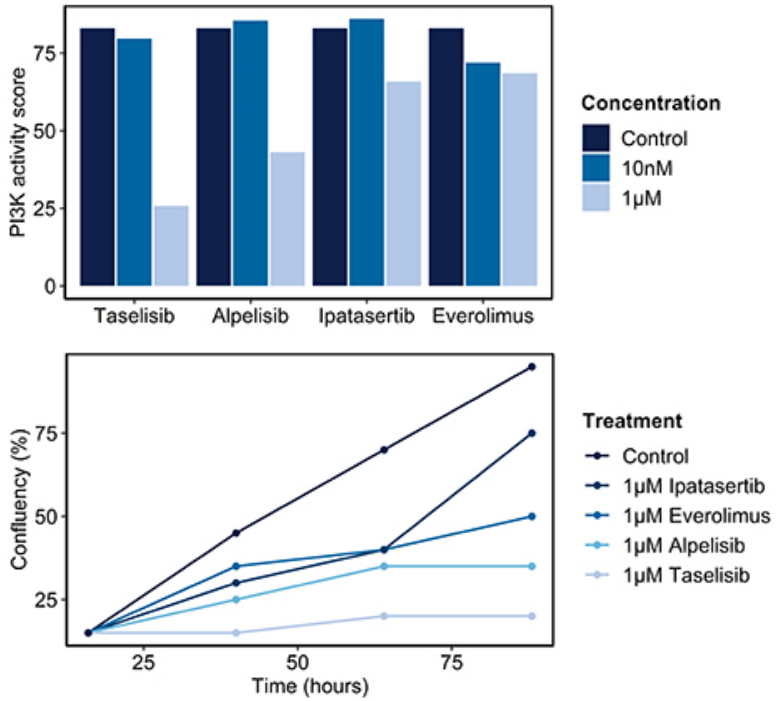


AR pathway in LNCaP



Hormone receptor pathway activity levels monitored in hormone sensitive cell lines under hormone stimulated and drug inhibited conditions

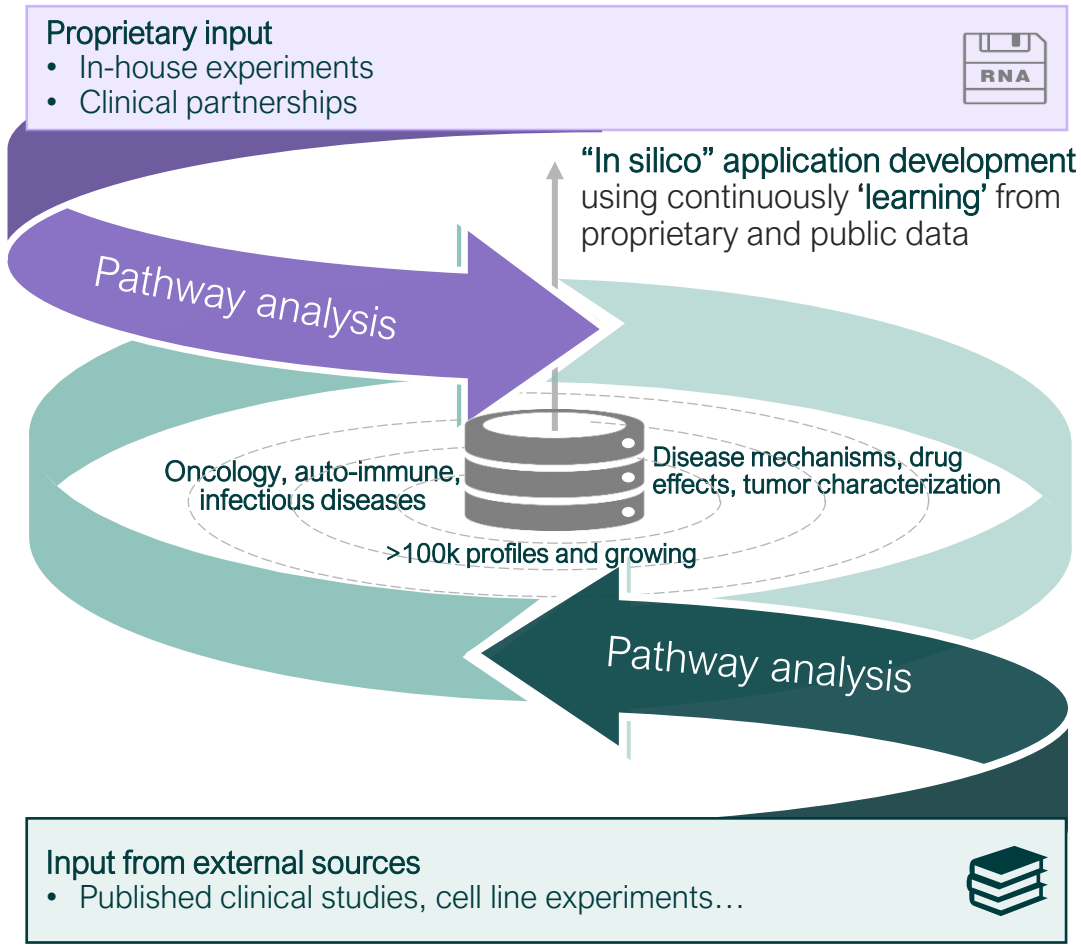
PI3K pathway in MCF7



Capacity of different drugs to inhibit pathway activity is related to inhibition of cell growth
Most efficient drug compound can be selected in vitro

Verhaegh et al. Cancer Res (2014), vd Stolpe et al. Nature Scientific Reports (2019)

Proprietary database with pathway activity profiles of >100k samples to support diagnostics and drug development



Diagnostics development and validation

Enabling activities

- In-silico proof of concept analysis
- Test development
- Clinical validation
- LDT/IVD

Drug development in oncology, autoimmune and infectious diseases

Enabling activities

- Aberrant pathways in diseases
- Representative disease models
- Drug mode of action
- Drug repurposing

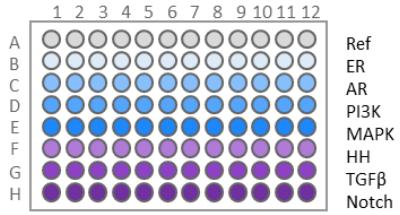
Feasibility demonstrated for a broad range of applications

Domain	Applications	Test	Benefits
 Oncology	Breast and prostate cancer	• Cancer tissue	• Better treatment of hormone sensitive cancer patients
	Metastatic cancers	• Cancer tissue	• Identify effective targeted treatment options for metastatic cancer patients
	Immuno-oncology	• Immune	• Selection of patients that benefit from novel immunotherapies
 Infectious diseases	COVID-19	• Immune	• Prediction of disease progression of patients infected with COVID-19 • Assessment of cell-mediated immunity induced by vaccine candidates
	Sepsis	• Immune	• Early diagnosis and prediction of clinical outcome of sepsis patients • Identify new or better treatment options
 Auto-immune	Autoimmune disease (IBD, RA)	• Immune	• Identification of patients benefitting from immuno-modulatory drugs (anti-TNF / JAK inhibitors)
 Drug development	Companion diagnostics	• Cancer tissue • Immune	• Prediction of response to targeted drugs (blocking signaling pathways) • Prediction of response to immunotherapy drugs or therapies
	Preclinical research	• Cancer tissue • Immune	• Development of in-vitro disease models representing human physiology • Identify mode of action of compounds in disease models

qPCR or RNA-seq gene expression data are translated by cloud-based software into pathway activity scores

Available as qPCR test and RNA sequencing data analysis service

OncoSIGNal RT-qPCR tests



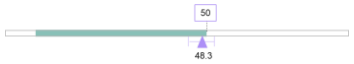
Easy, fast and suitable for current clinical workflow.
Developed under ISO13485

OncoSIGNal Data Service (RNA-seq data)

Analysis of whole transcriptome RNA sequencing data

OncoSIGNal cloud-based pathway activity analysis

OncoSIGNal pathway activity scores

Pathway	Pathway activity score [95% CI]	Normal range	Perc.	Interpretation	Results
ER	73.4 [70.5 – 75.8]	22 – 40	70 %	HIGH aberrant activity	
AR	30.2 [28.6 – 31.1]	25 - 34	40 %	No aberrant activity	
PI3K	14.1 [12.8 – 15.5]	15 – 21	3%	No aberrant activity	
MAPK	14.7 [13.1 – 16.4]	3 - 15	25 %	No aberrant activity	
HH	48.3 [47.2 – 51.3]	20 - 50	70 %	No aberrant activity	
Notch	68.1 [65 – 70]	35 – 43	83 %	HIGH aberrant activity	
TGFβ	5.3 [2.0 – 6.9]	20 – 30	10 %	LOW aberrant activity	

Regulatory pathways: RUO, IVD or LDT?

RESEARCH MARKET

Research-use-only (RUO)

- Product can be used for research, drug development and (retrospective) clinical studies.
- Product cannot be used for clinical decisions.
- Not regulated

CLINICAL MARKET

In-vitro diagnostic (IVD)

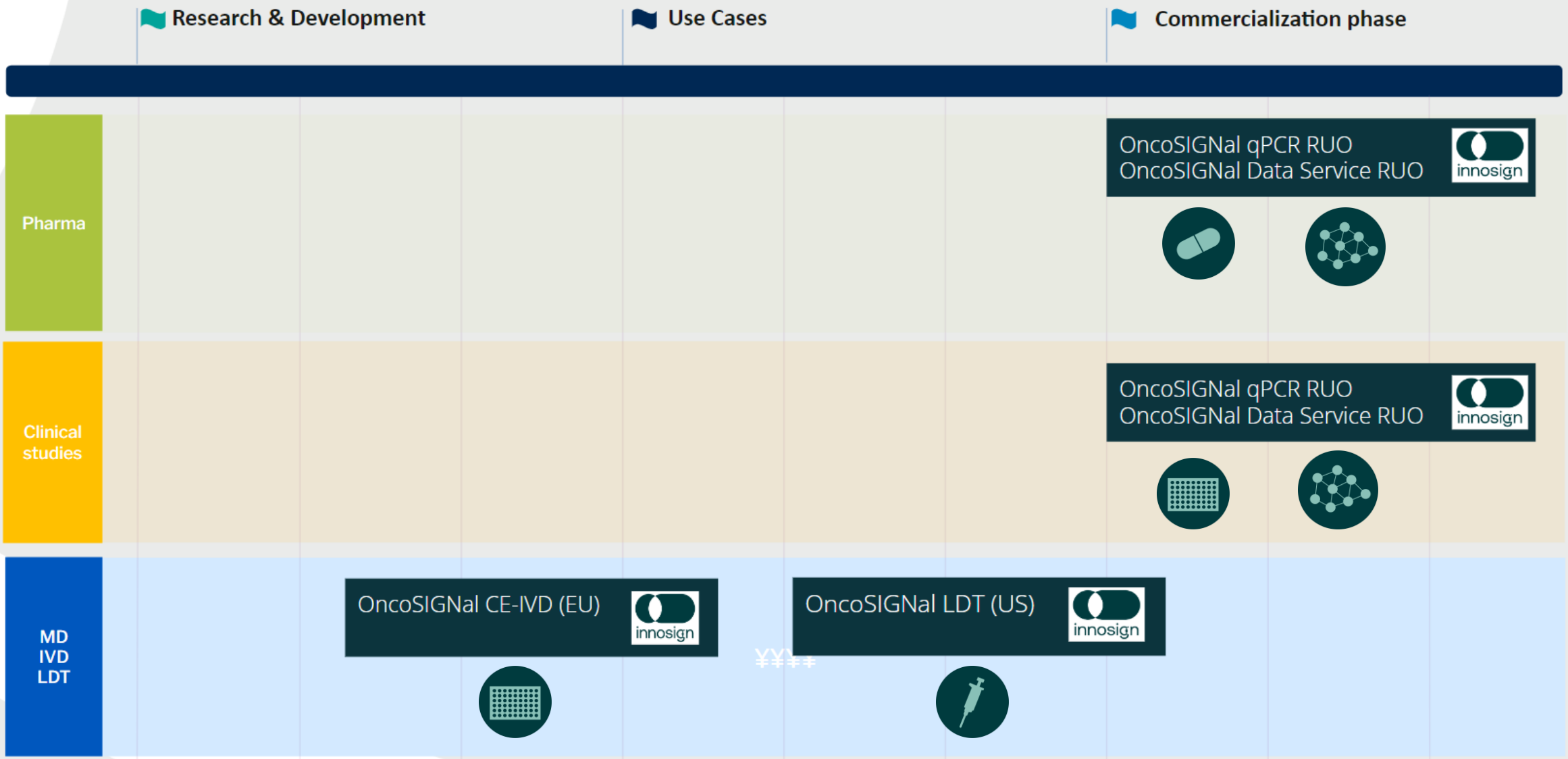
- Results can be used for clinical decisions
- Decentralized model: product can be executed by customers (e.g. hospitals, labs or patients)
- Well defined intended use and (validated) clinical utility
- Europe: CE-IVD (approval by notified bodies), US: IVD (PMA/510(k), approval by FDA)

Laboratory-developed test (LDT)

- US-specific regulation, results can be used for clinical decisions
- Centralized model: test is executed in CLIA-certified lab responsible for the design, validation and manufacturing
- Regulated by CLIA (not FDA), focus on procedures
- Common business model in US for high complexity tests

A What B Where

C Landscape

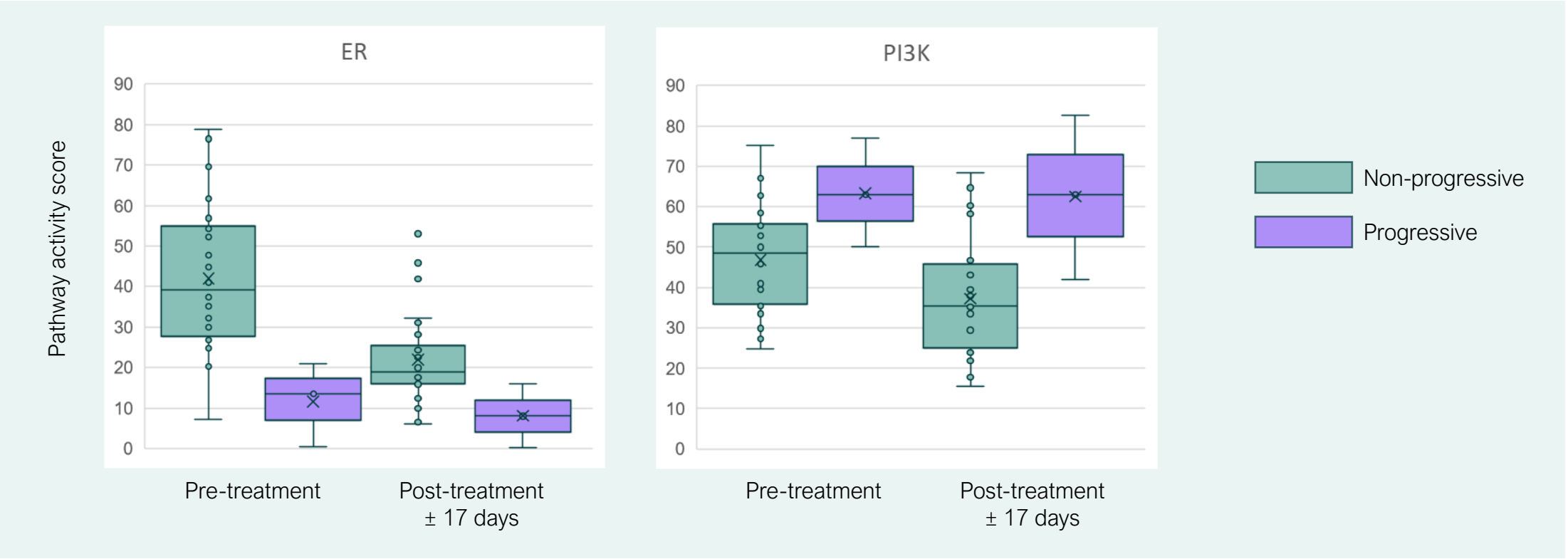


Blockchain ML / AI Cybersecurity Digitalisation

OncoSIGNal pathway profiling identifies the tumor-driving signaling pathways, targetable with drugs

Inda et al. Mol Cancer Ther (2020)

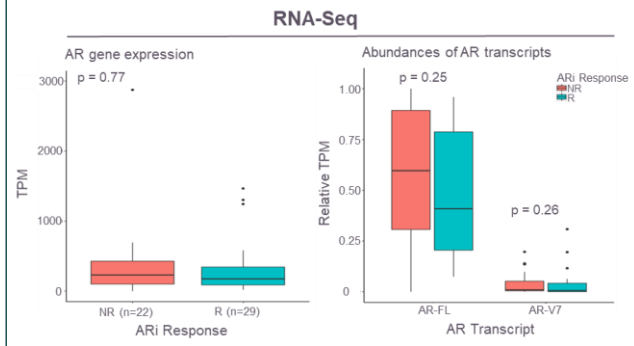
Pathway profiling is predictive for response of ER+ breast cancer patients to neo-adjuvant hormonal therapy



Turnbull et al., ESMO (2019)

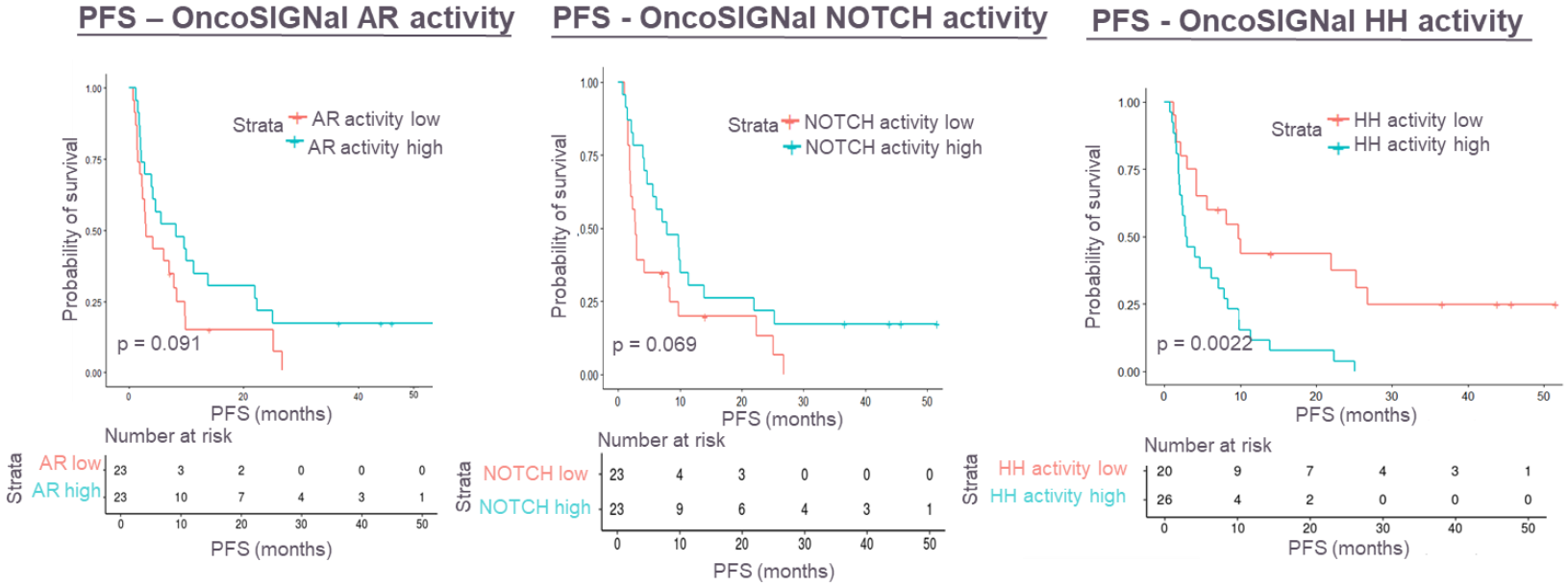
Low AR/Notch and high HH pathway activity predict poor PFS to AR-directed therapies in metastatic castrate-resistant prostate cancer (MATCH-R trial)

Standard genomic analysis
AR gene expression / transcripts



AR alterations in mCRPC. No statistically significant differences in genomic alterations between responders and non-responders to enzalutamide and abiraterone treatment. AR gene expression, and its transcripts AR-V7 (AR splice variant) and AR-FL (Full-Length) are not significantly different between responders and non-responders (Wilcoxon test). Similarly, IHC does not show different expression of AR between the two groups.

OncoSIGNal pathway analysis
Progression free survival in mCRPC upon enzalutamide, abiraterone acetate

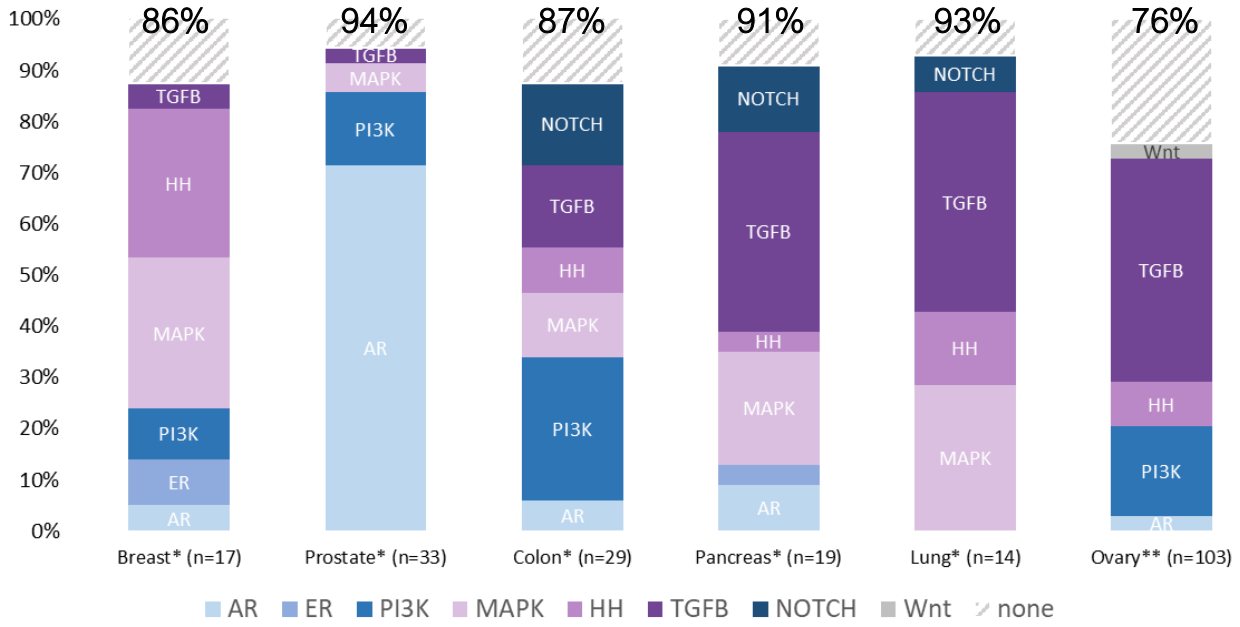


Menssouri et al ESMO 2022

- ✓ Standard genomic and transcriptomic analysis did not show significant differences between responders and non-responders to AR-directed therapy
- ✓ OncoSIGNal pathway analysis revealed that high HH and low AR and Notch pathway activity is related to resistance to AR-directed therapy

More actionable results in hard-to-treat (metastatic) cancers with OncoSIGNal compared to DNA sequencing

Primary aberrant pathway per tissue type



HUS Helsinki University Hospital

OncoSIGNal implemented in **national prospective clinical trial** in Finland (FINPROVE, start Q3 2021)

https://www.hus.fi/en/newsroom/hus-comprehensive-cancer-centre-designated-top-level-european-cancer-hospital-second-time

✓ 50% actionable results with DNA sequencing versus ~90% actionable results with OncoSIGNal

Presentations at AACR 2020, ASCO 2020, ASCO 2021 https://eithealth.eu/project/pacman/

Data-driven versus knowledge-based data interpretation algorithms

Data-driven algorithms	Knowledge-based algorithms
✓ Selection of genes based on differential expression in clinical data sets	✓ Selection of genes based on biology, confirmed in cell line experiments
✓ Trained on (large amount of) clinical data, e.g. responders vs non-responders	✓ Trained on (limited amount of) data from ground truth model systems
✓ Dependent on quality of clinical data	✓ Dependent on quality of own (cell line) experiments
✓ Applicable to specfic use case related to the dataset(s) used for training	✓ Applicable to multiple applications, based on biological relevance
✓ Often no biological reasoning making clinical adoption and regulatory approval more difficult	✓ Biological reasoning making clinical adoption and regulatory approval easier

Thank you

www.innosignbio.com