Next Generation Cancer Diagnostics

For First Time Right Therapy Choice

Anja van de Stolpe

innovation + you

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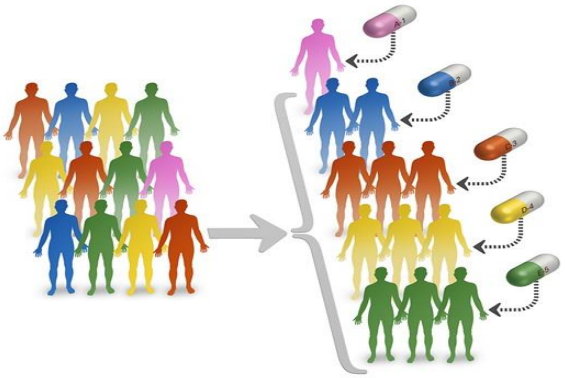
Paradigm shift in cancer treatment

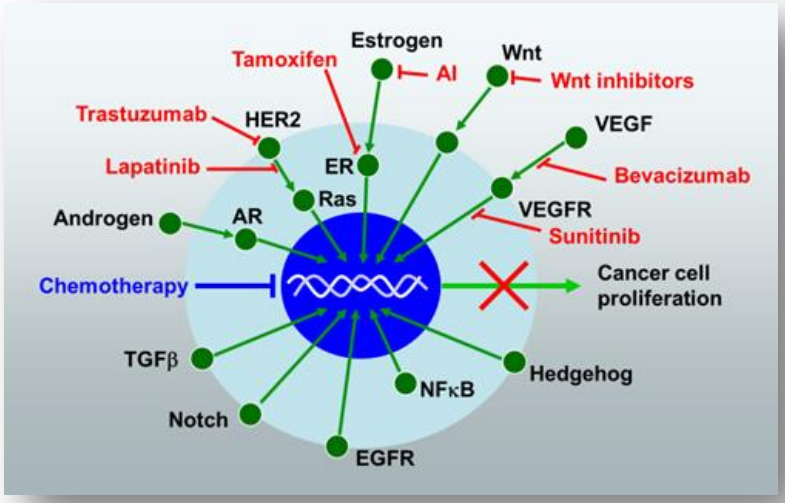
towards personalized treatment

Chemotherapy for all

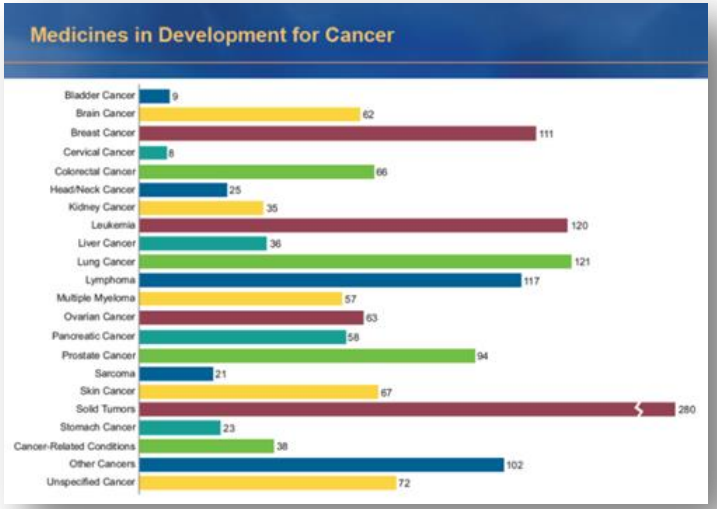


therapy targeting **cancer pathophysiology** of individual patient

Cancer pathophysiology: 12 signal transduction pathways **drive cancer**

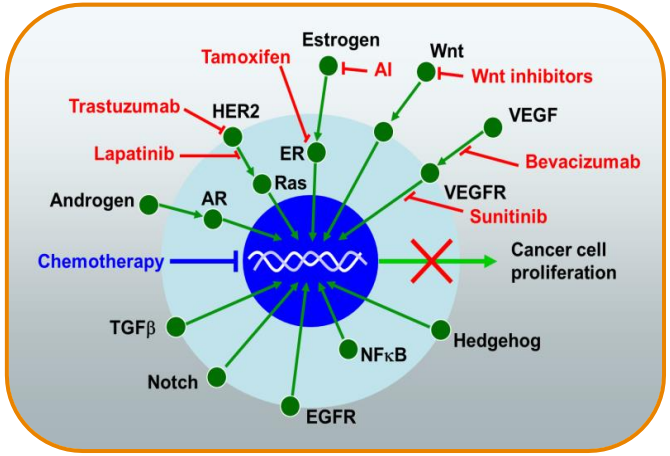


New "targeted" drugs **target signal transduction pathways**



Need for diagnostic tests

to identify activity of each of these 12 signal transduction pathways in a cancer tissue sample



If we know which pathway is active in the tumor
we know which therapy will be effective for the patient

Our solution

Pathway analysis for identification of active pathways in any cancer tissue sample

based on cell biology knowledge, not data-mining

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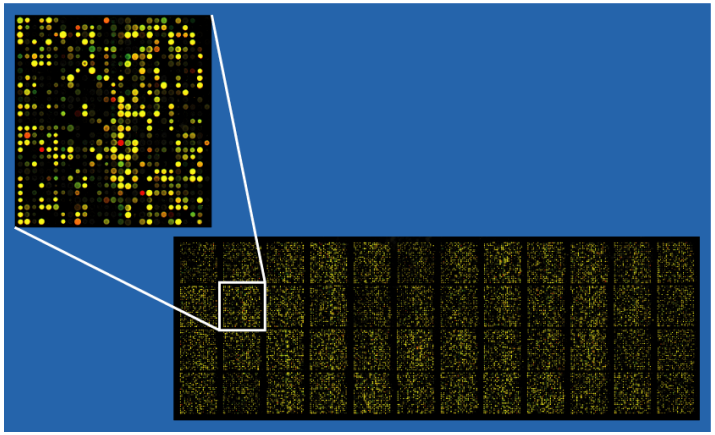
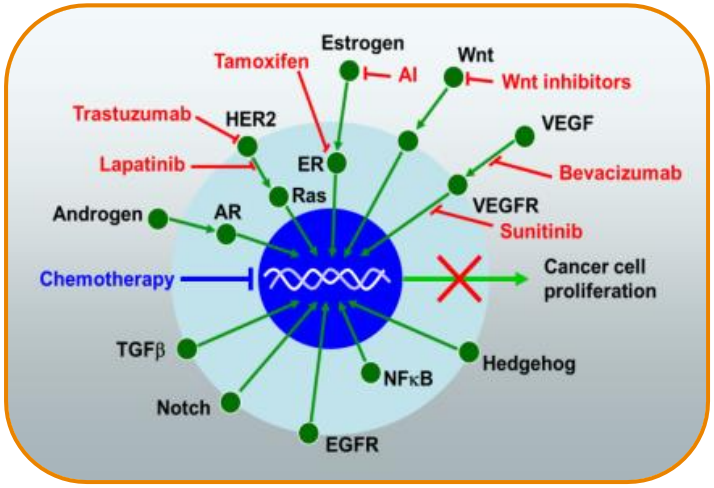
Pathway analysis for identification of active pathways in any cancer tissue

We simplify cancer characterization for therapy selection



37,500 probe spotted oligo microarray



Genotype

1000's of mutations

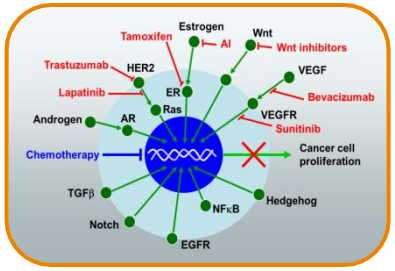
→

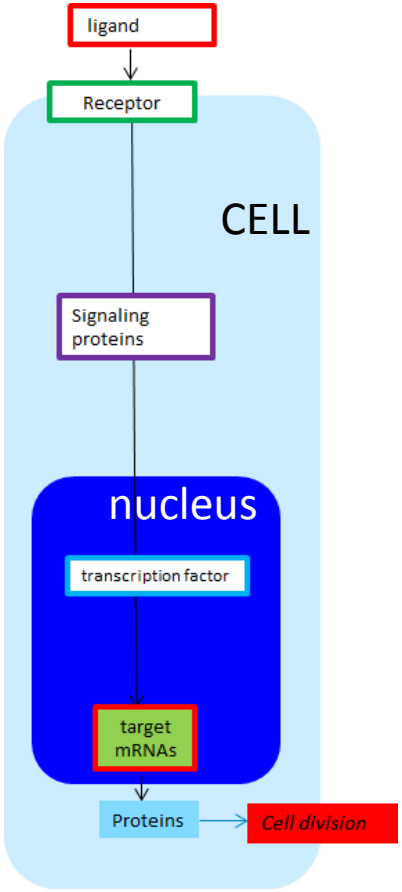
Phenotype

12 pathways

Because you do not want to treat genotype, but phenotype!

Pathway analysis for identification of active pathways in any cancer tissue





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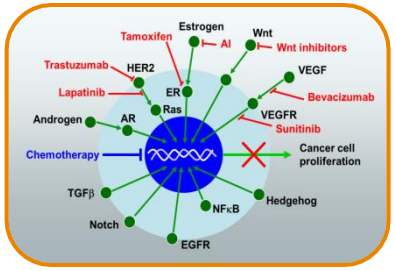
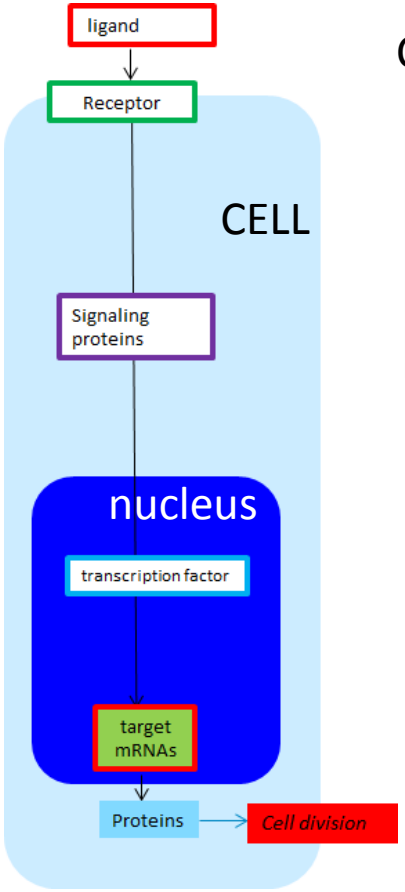
Pathway analysis for identification of active pathways in any cancer tissue





Cancer tissue

RNA

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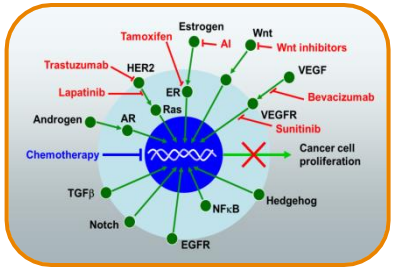
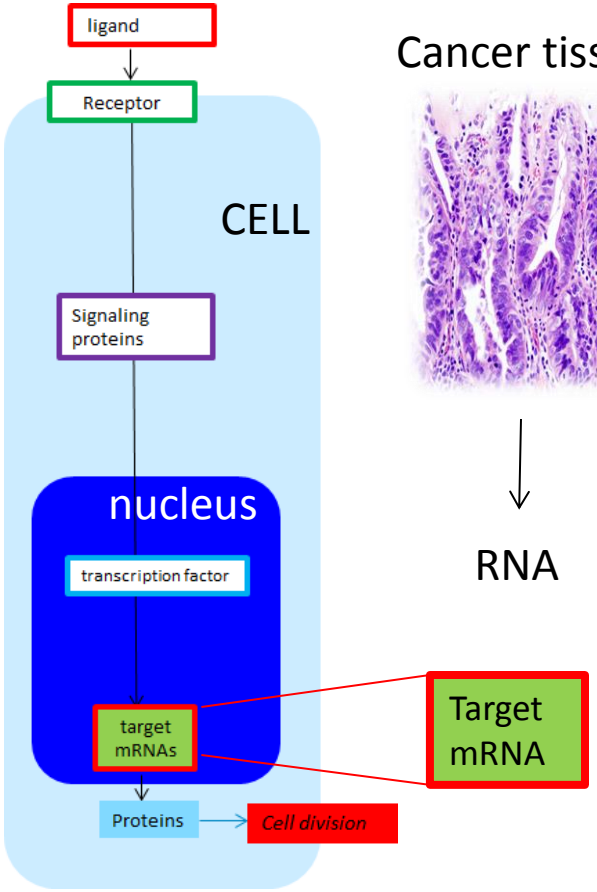
Pathway analysis for identification of active pathways in any cancer tissue





Cancer tissue

RNA

Target mRNA

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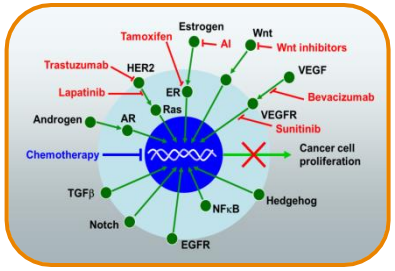
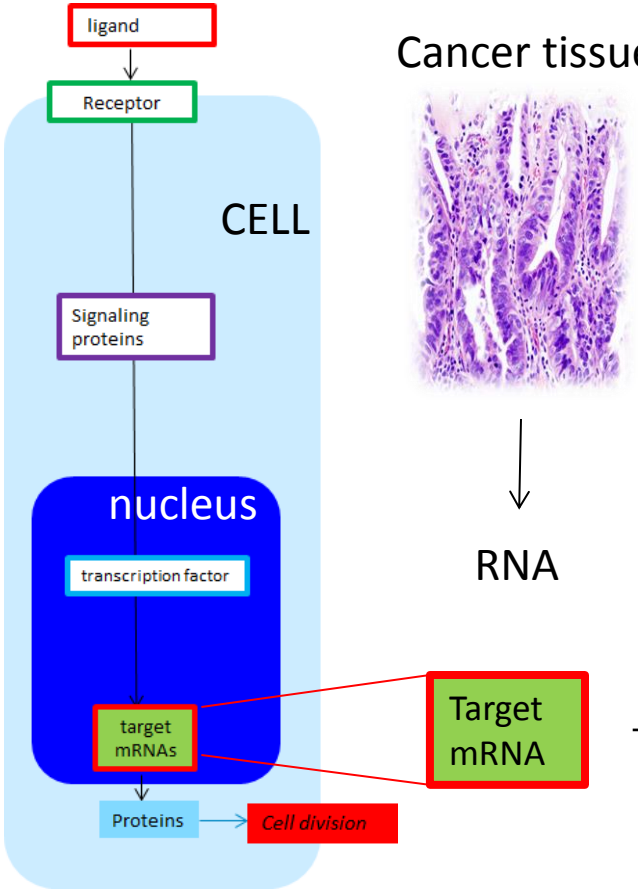
Pathway analysis for identification of active pathways in any cancer tissue





Cancer tissue

RNA

Target mRNA → *Microarray / qPCR/Sequencing*

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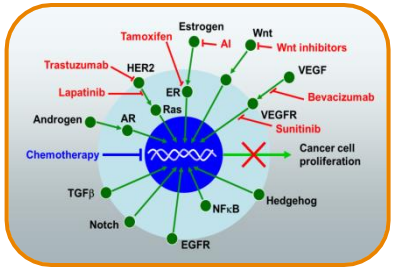
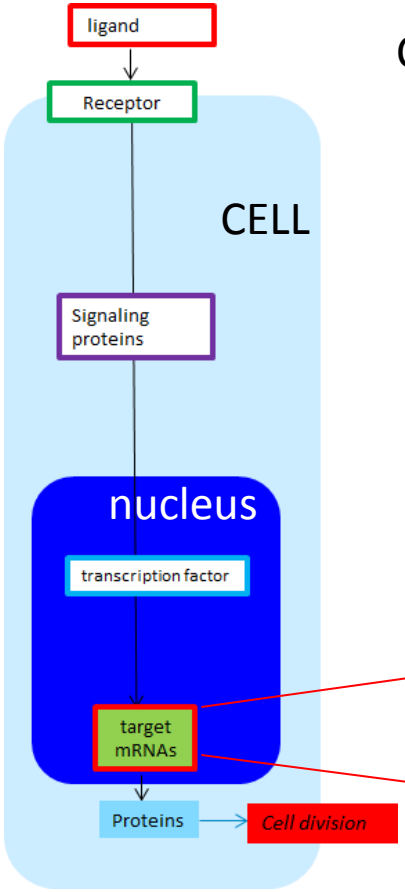
Pathway analysis for identification of active pathways in any cancer tissue





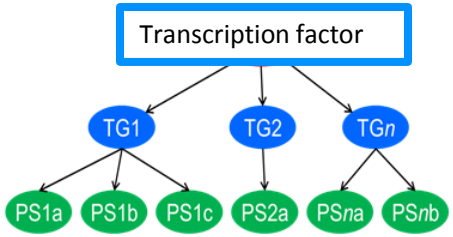
Cancer tissue

RNA

Target mRNA

Microarray / qPCR/Sequencing

Computational model



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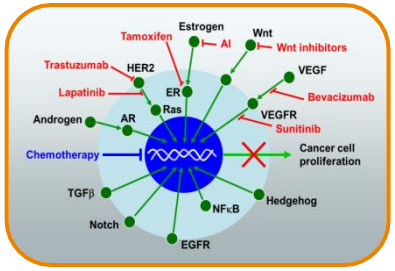
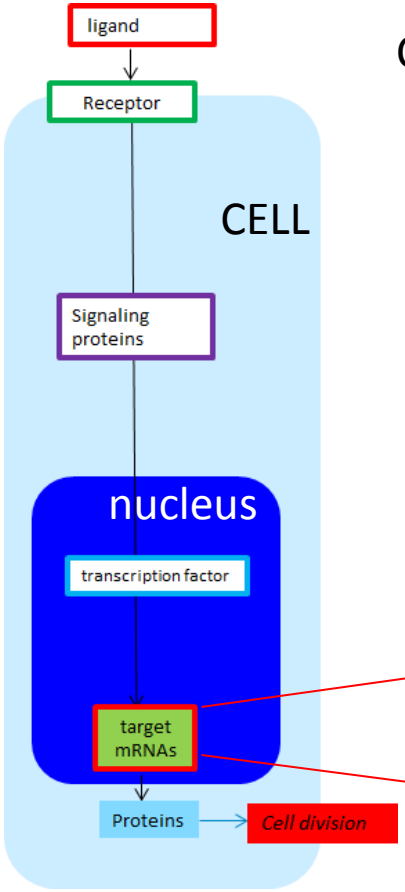
Pathway analysis for identification of active pathways in any cancer tissue





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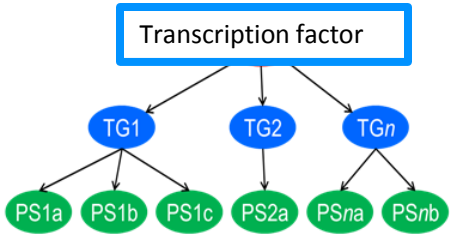

cell biology knowledge

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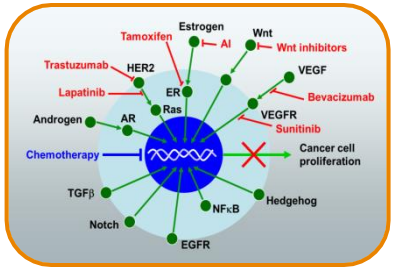
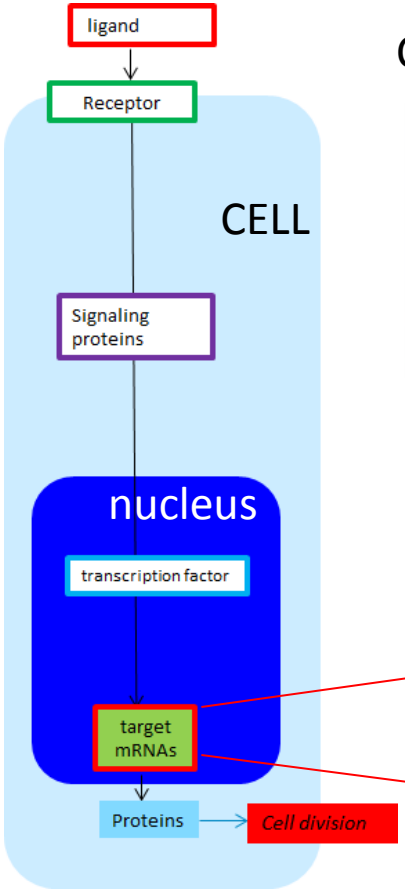
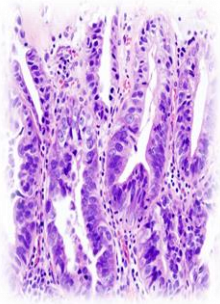
Pathway analysis for identification of active pathways in any cancer tissue





Cancer tissue

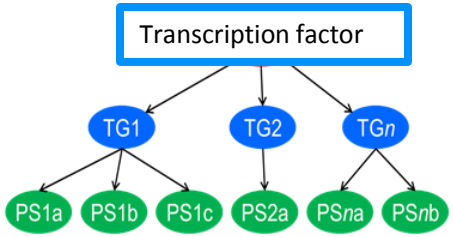


RNA

Target mRNA

Microarray / qPCR/Sequencing

Computational model



Pathway active

Pathway inactive

cell biology knowledge

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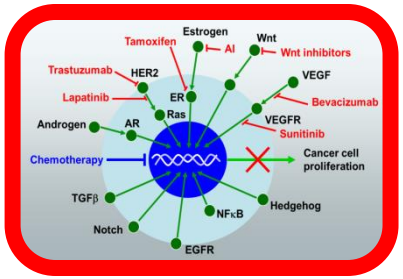
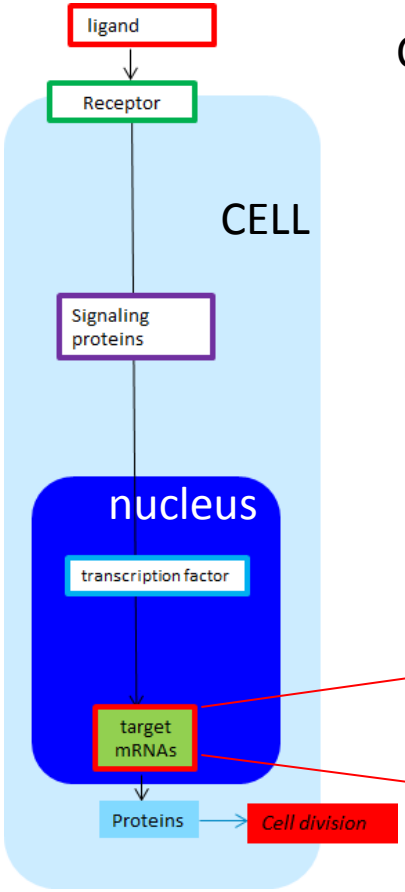
Pathway analysis for identification of active pathways in any cancer tissue





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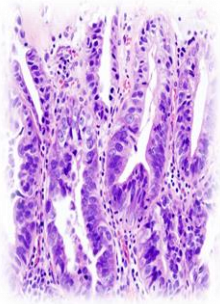

RNA

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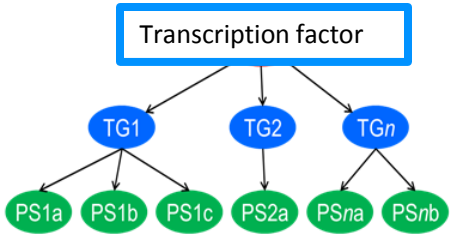

Pathway active

Pathway inactive

cell biology knowledge

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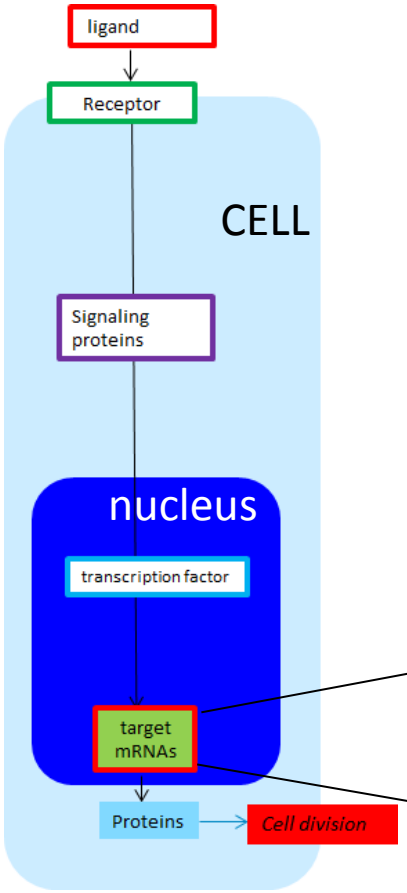
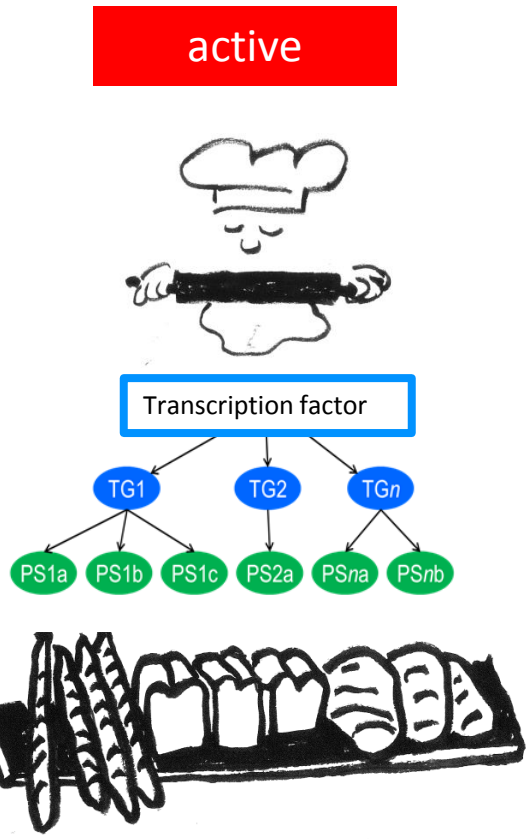
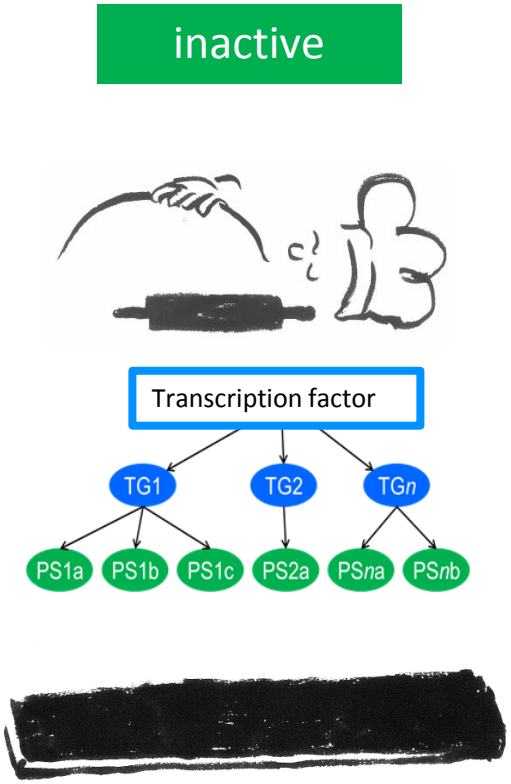
Pathway analysis for identification of active pathways in any cancer tissue

For dummies…..compare a cell with a bakery







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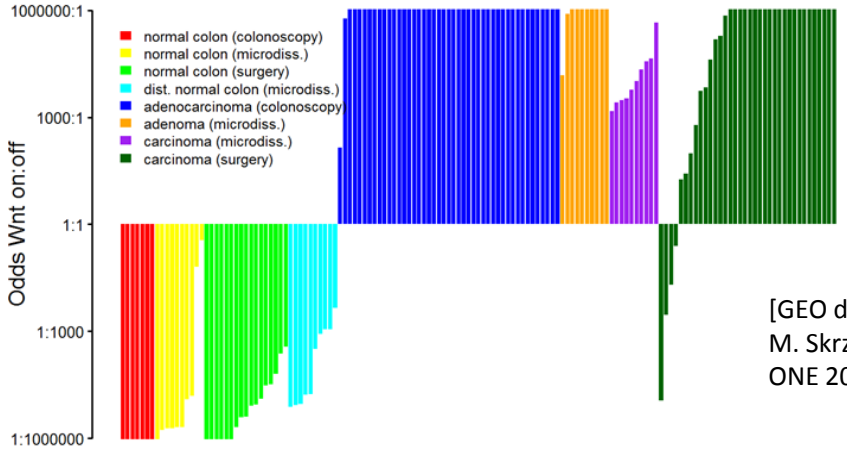
Pathway model development and validation using “ground truth” samples

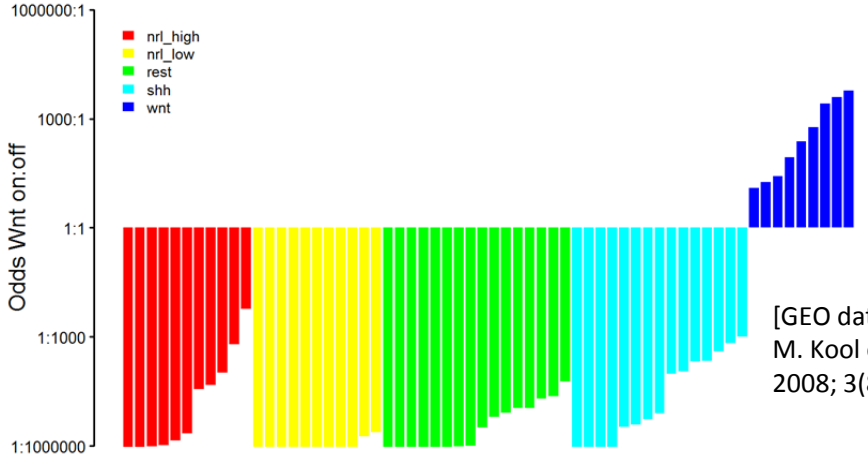
Example: Wnt pathway model



[GEO data set GSE20916]
M. Skrzypczak et al., PLoS ONE 2010; 5(10):e13091

Colon adenoma and carcinoma

- *Wnt is active*



[GEO data set GSE10327]
M. Kool et al., PLoS ONE 2008; 3(8):e3088

Medulloblastoma

- *Subset Wnt is active*

Models can be used across different cancer types

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Wim Verhaegh, et al. Cancer Res 2014 Jun 1;74(11):2936-45.
Wim Verhaegh, Anja van de Stolpe. Editorial, Oncotarget, 2014;5(14):5196-7.

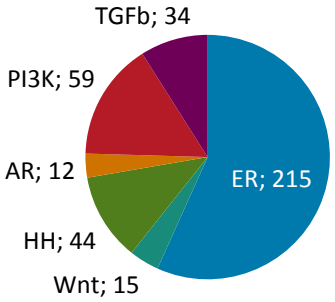
Clinical utility: selection of most effective therapy

Example: Breast cancer patients

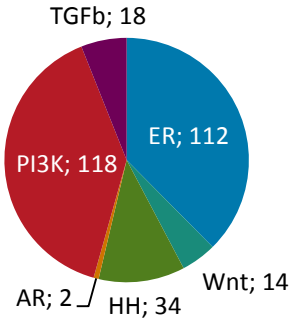
PAM50 subtyping

Pathway subtyping

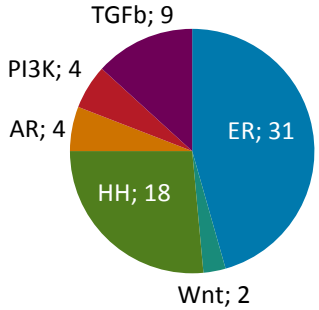
Luminal A (n=511)



Luminal B (n=360)



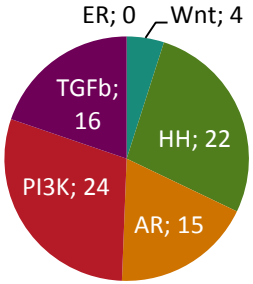
Normal-like (n=109)



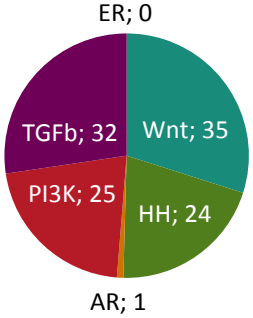
PAM50 subtyping

Pathway subtyping

HER2 (n=143)



Basal (n=171)



Choose therapy based on pathway analysis, rather than only subtyping

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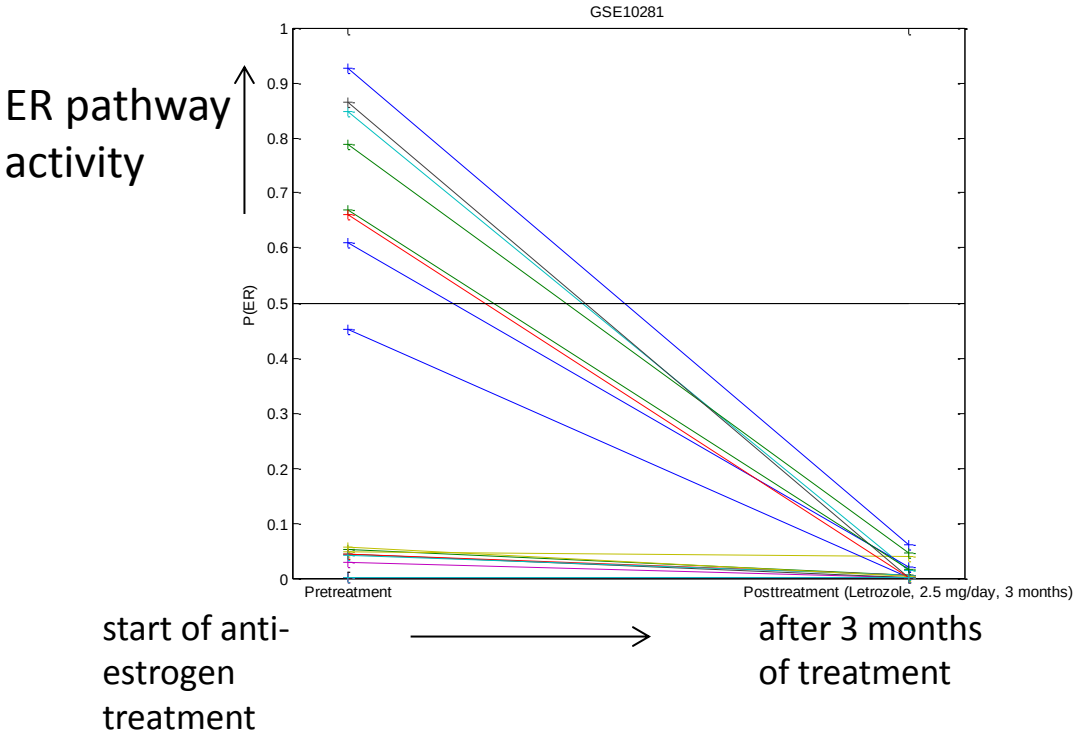
Clinical utility: monitoring therapy response

Example: ER positive breast cancer patients (luminal A)

- *neoadjuvant anti-estrogen therapy prior to surgery*

GEO dataset, GEO reference C.J. Creighton et al., PNAS 2009; 106(33):13820-5 [GSE10281]



Pathway analysis after treatment to measure therapy response

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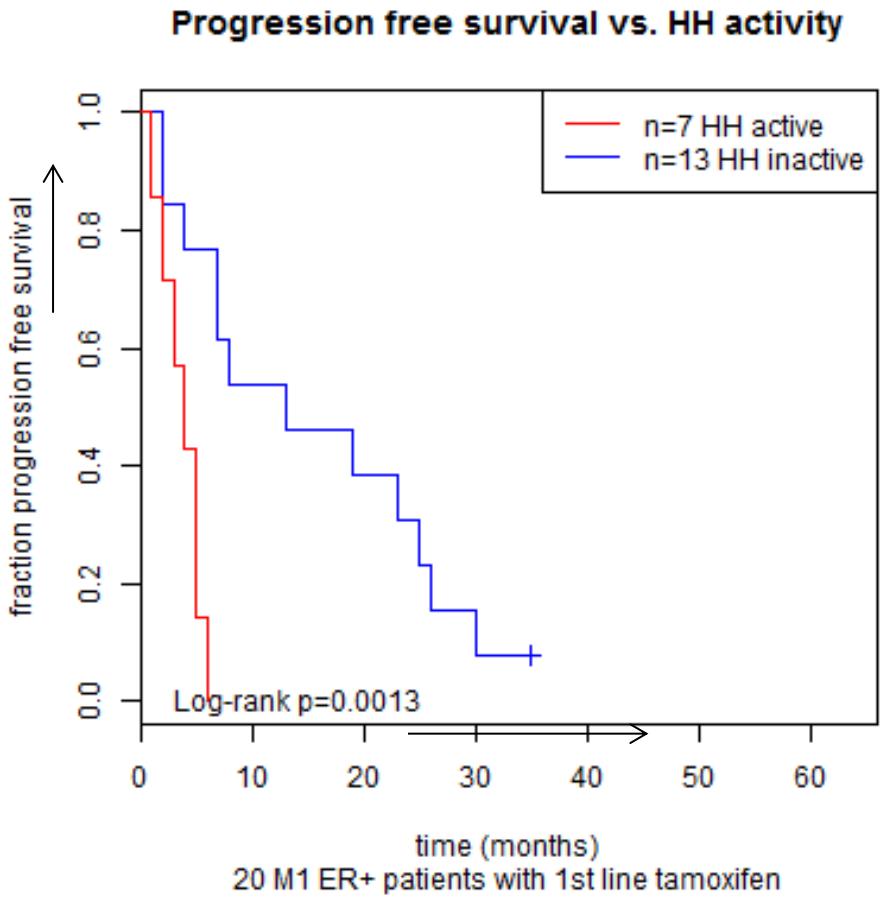
Clinical utility: prognosis

Example: ErasmusMC patients with primary metastasized breast cancer, treatment with tamoxifen

patients without cancer progression



Active Hedgehog Pathway indicates bad prognosis.

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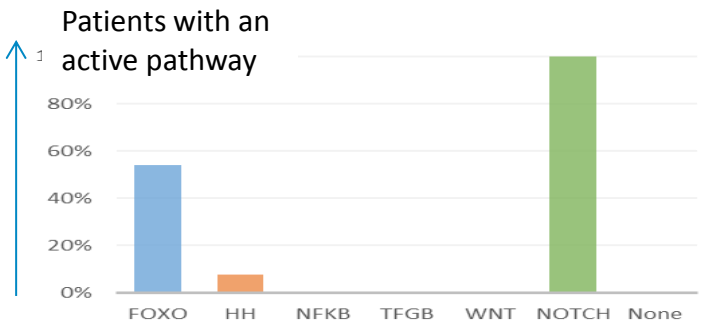
Poster AACR 2016

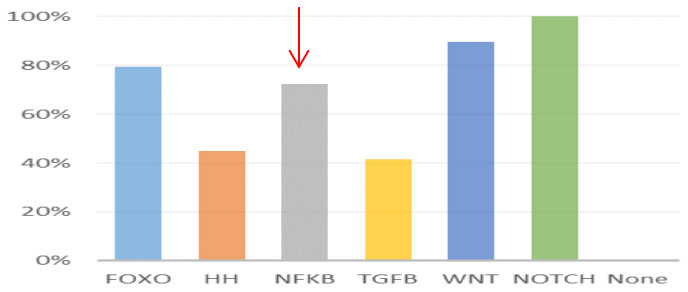
Clinical utility: immune response typing for choice of immunotherapy

Example: Patients with brain tumors
(tumor type in abstract AACR 2017)

Normal brain



Brain tumor subtype with known strong immune response



Active NFKB pathway indicates active immune response

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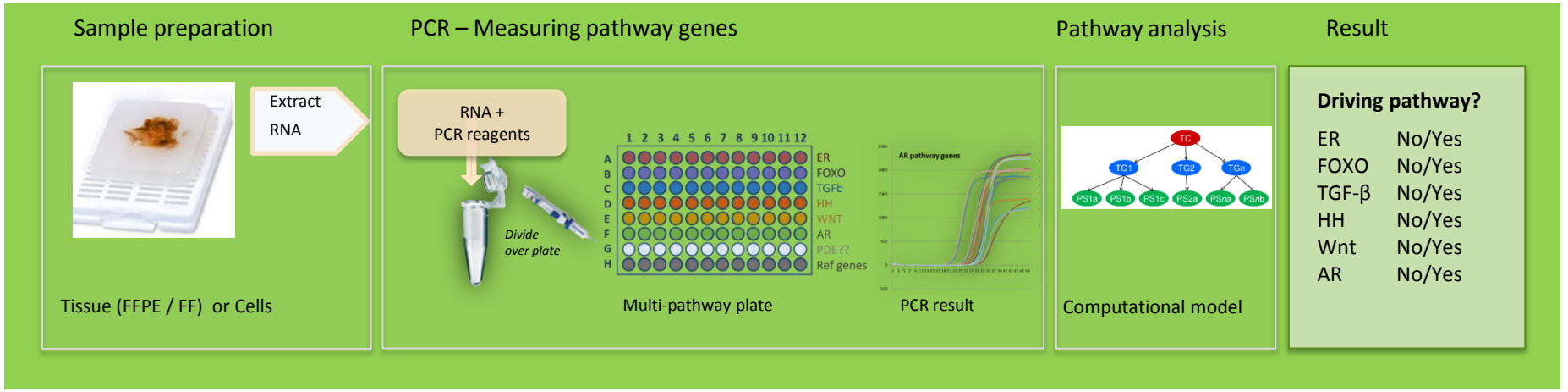
Pathway analysis for identification of active pathways in any cancer tissue

Can be run in hospital diagnostic lab

mRNA measurement	Cancer tissue/cells	
Affymetrix microarray	Fresh Frozen	*Affymetrix service provider*
Multi RT-qPCR plate	Formalin Fixed Paraffin Embedded	*Routine lab equipment*
RNA seq	Formalin Fixed Paraffin Embedded	*Routine lab equipment*



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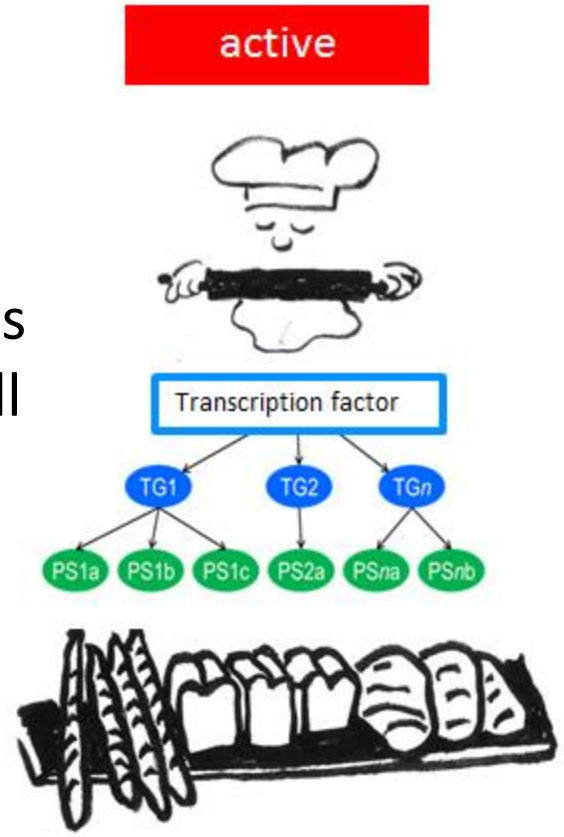
Pathway analysis for identification of active pathways in any cancer tissue

*How to develop for **all cancer types**?*

Available: data of patient samples from thousands of clinical studies, with associated publications, all cancer types

- Exploratory pathway analysis for cancer of choice
- Define potential clinical utility
- Initiate clinical collaboration



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Pathway analysis for identification of active pathways in any cancer tissue

Intellectual property status: 18 patents filed, 2 granted (2016)

Evaluation of applications with clinical partners

- Clinical evaluations: *breast, prostate, ovarian, endometrium, esophageal cancers*
- Exploratory studies: *brain tumors, children's tumors, hematological malignancies, cervical, rectal, bladder cancer*

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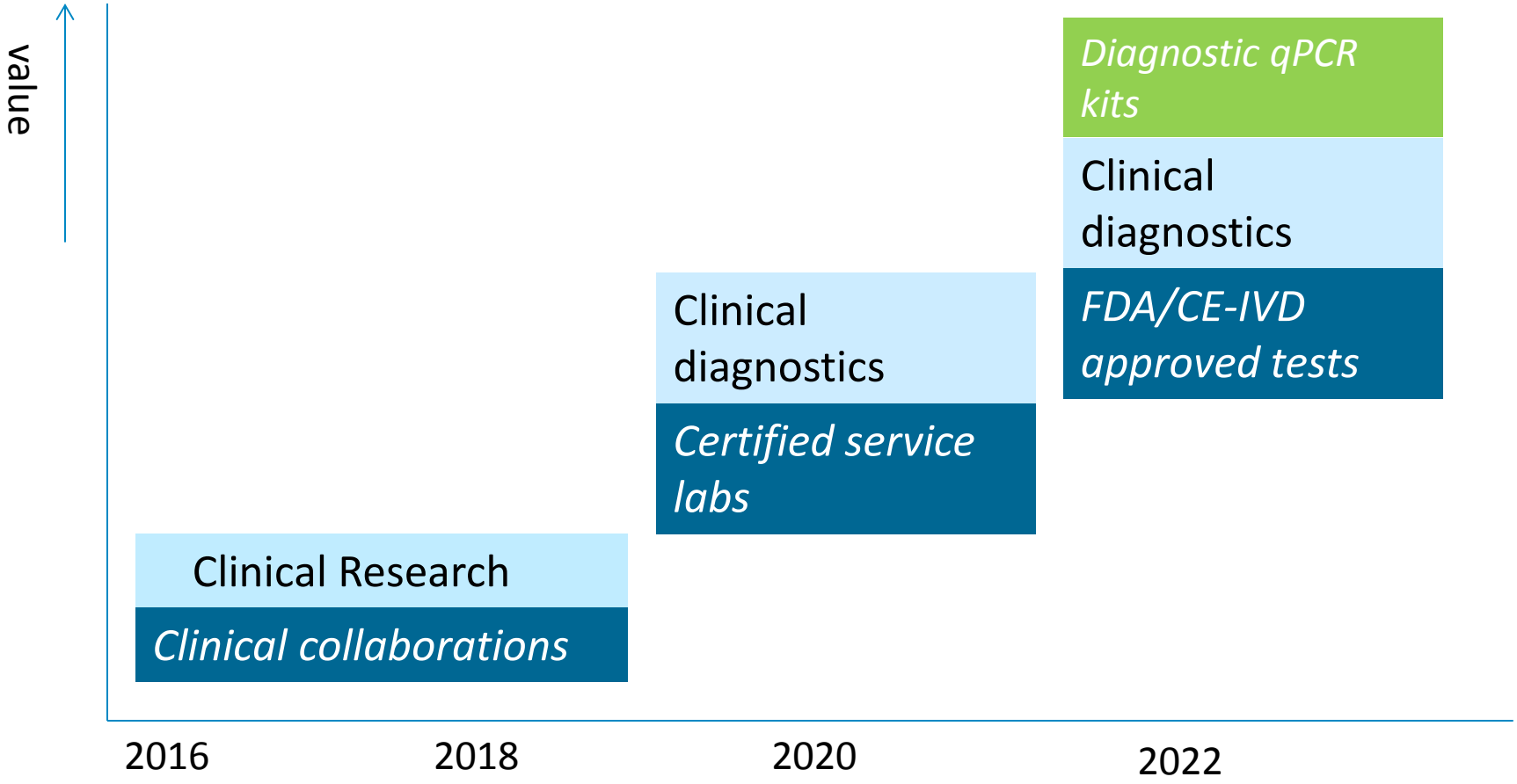
Pathway analysis for identification of active pathways in any cancer tissue

Clinical Adoption and Go to Market

→ ***Partnering opportunities***



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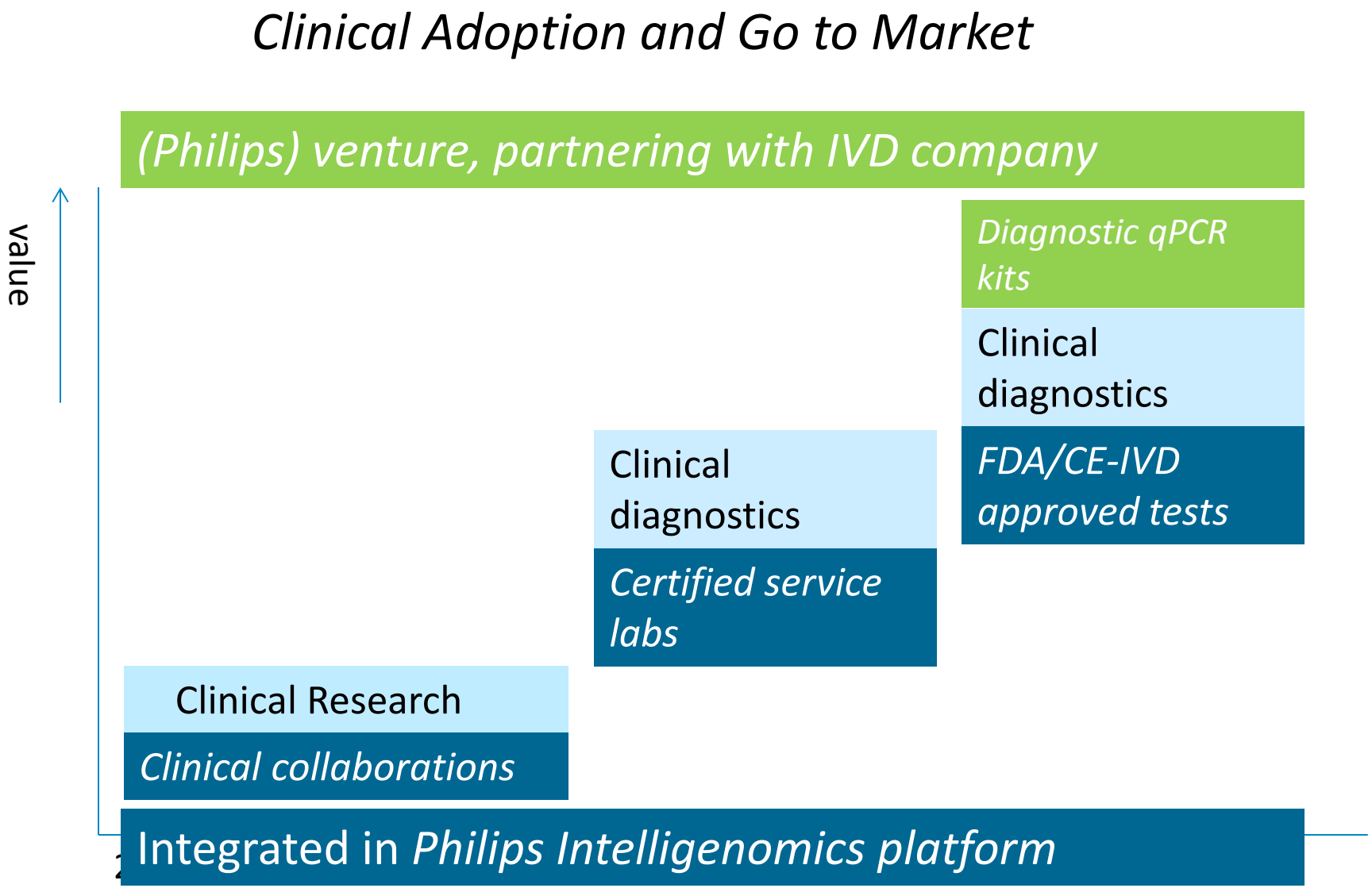

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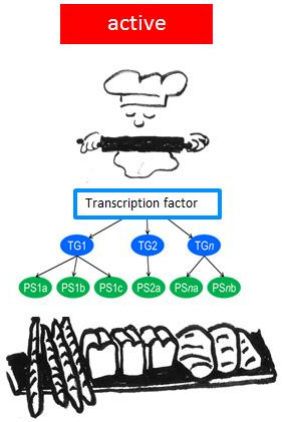
Take away message

Proprietary diagnostic Pathway Analysis:
based on cell biology knowledge
Towards best therapy choice
for each patient with cancer



Applications:

- ***First time right*** **selection of most effective therapy**
- Monitoring of therapy response/resistance
- Prognosis

Clinical applications:

- **All cancer types**
- All sample types
- All measurement modalities (Microarray, RNAseq, qPCR)

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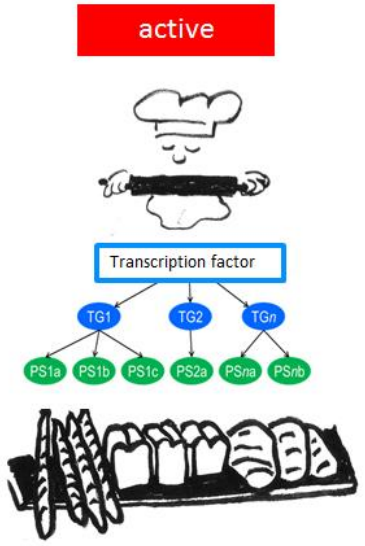
Acknowledgements

Philips Research



Research

- Marcia Alves de Inda
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- Henk van Ooijen
- Monique Stoffels
- Anja van de Stolpe
- Wim Verhaegh

Development

- Eveline den Biezen
- Anne van Brussel
- Janneke Wrobel
- Rick Velter
- Dianne van Strijp

Business Development

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- Sigi Neerken
- Jos Rijntjes

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- John Foekens
- John Martens
- Stefan Sleijfer

LUMC, Leiden

- Peter Kuppen
- Cock van de Velde

Hubrecht Institute, Utrecht

- Hans Clevers

UMCU, Utrecht

- Boudewijn Burgering

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