

# The importance of preclinical models and value of trial-clinical samples in translational research

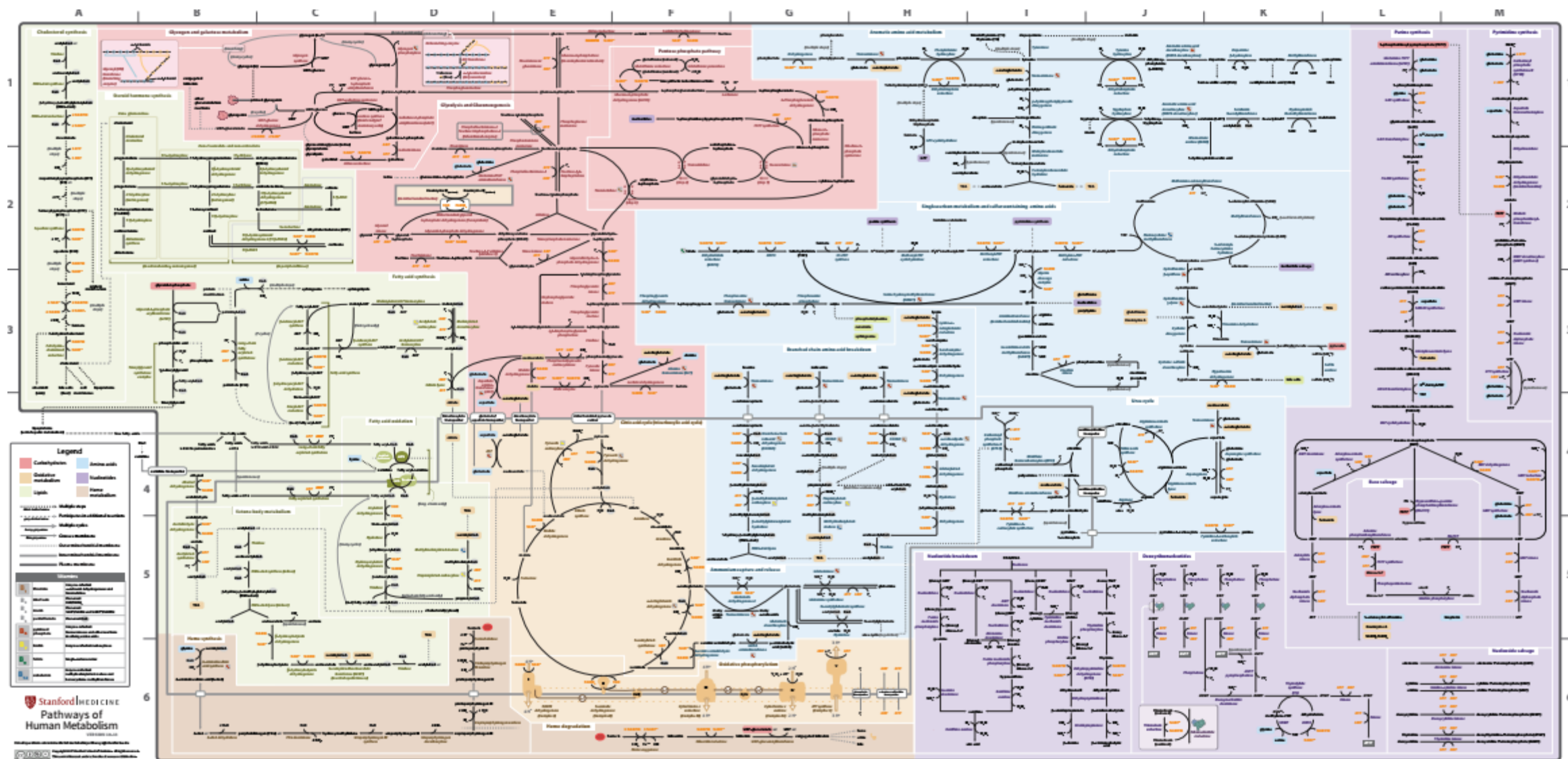
Frédéric Amant MD PhD

NSGO-CTU investigator meeting  
November 24<sup>th</sup> 2022

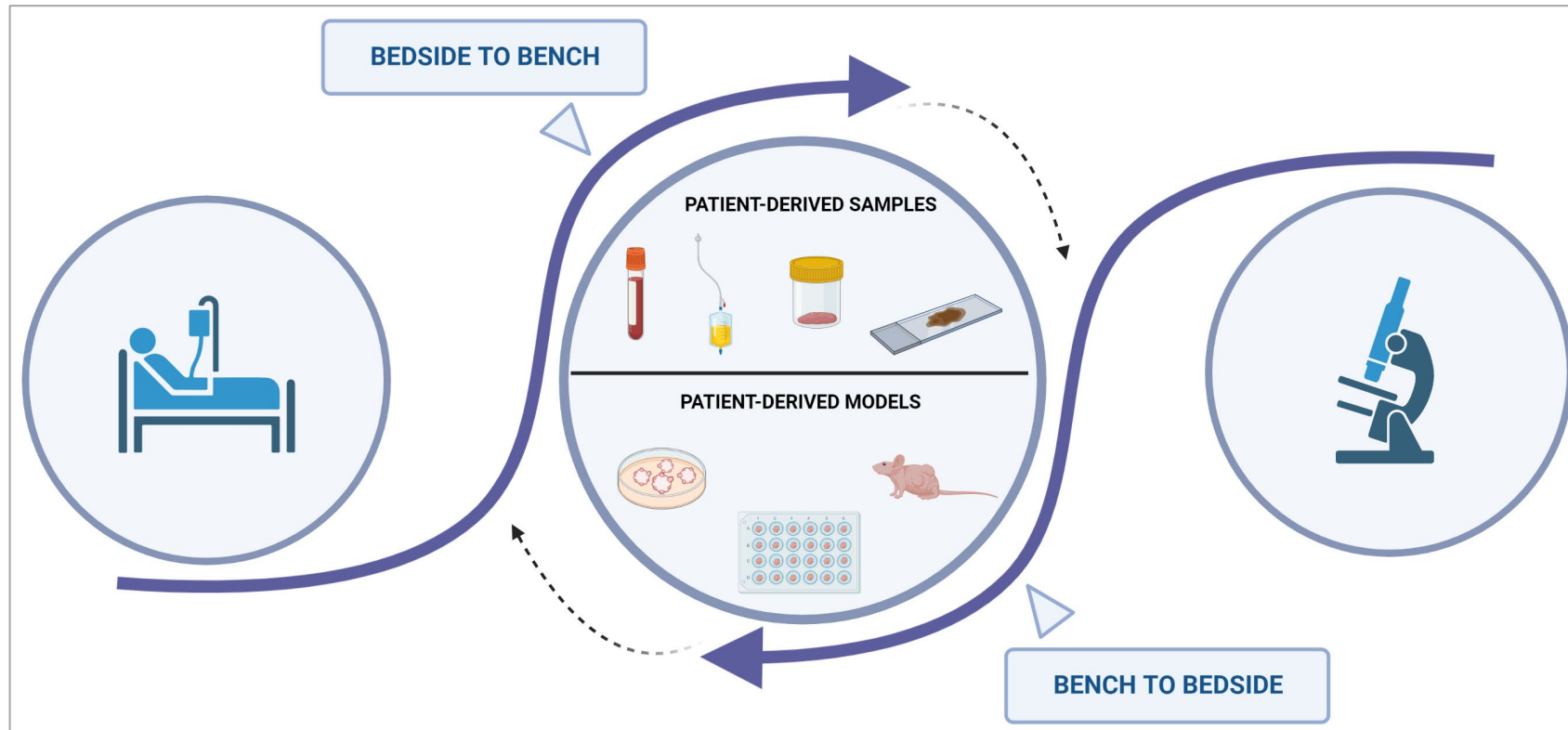




Take home message  
the map of TR resembles the map of the human central metabolic pathways



# Translational research is a broad concept



Basic biomedical science  
aims to understand the processes  
underlying  
physiological functions and dysfunctions

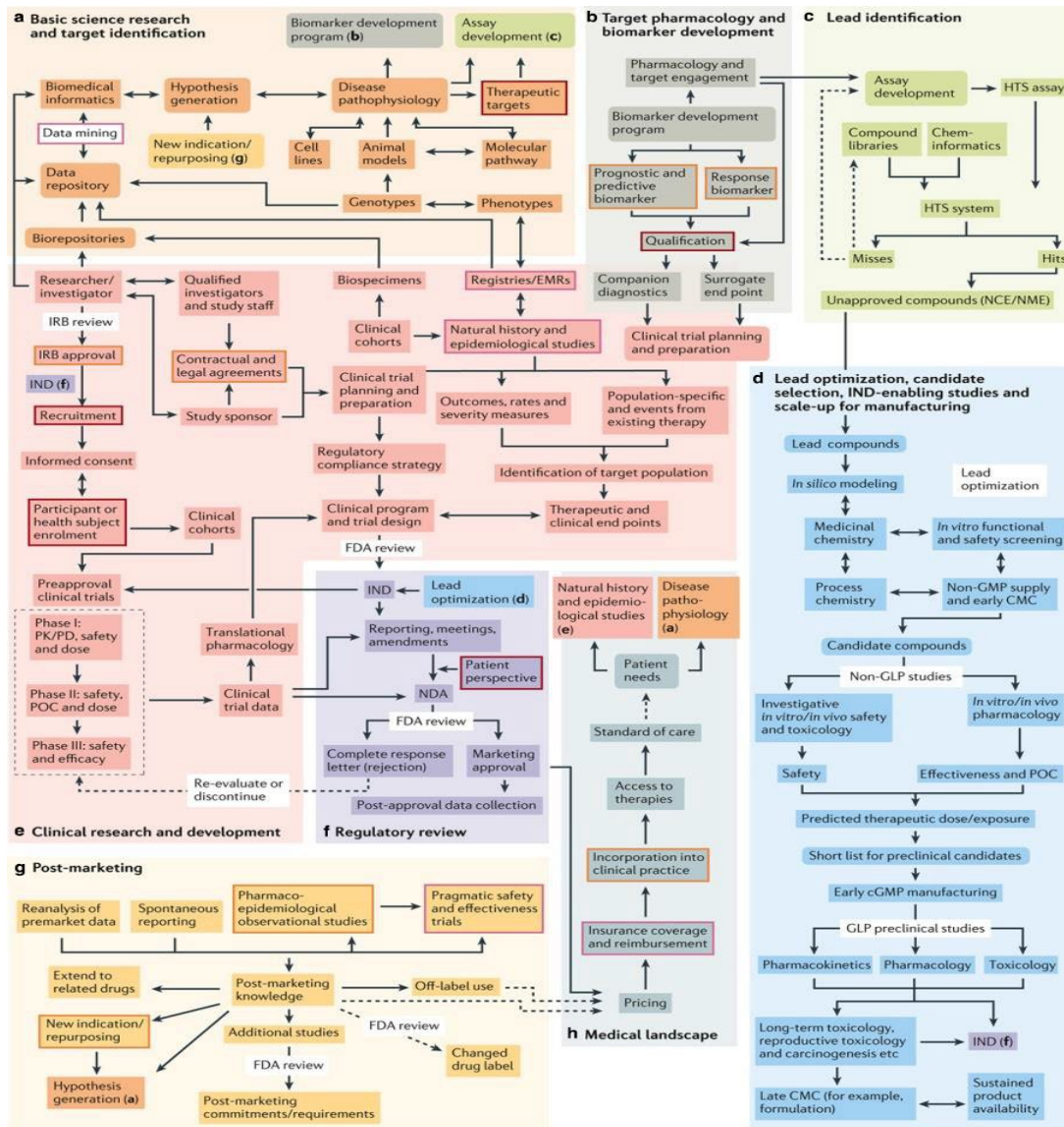
Translational science  
has its historical roots  
in medical practice and is driven  
by clinical observations and needs

*Created with BioRender.com*

# The map of the translational processes for drug development

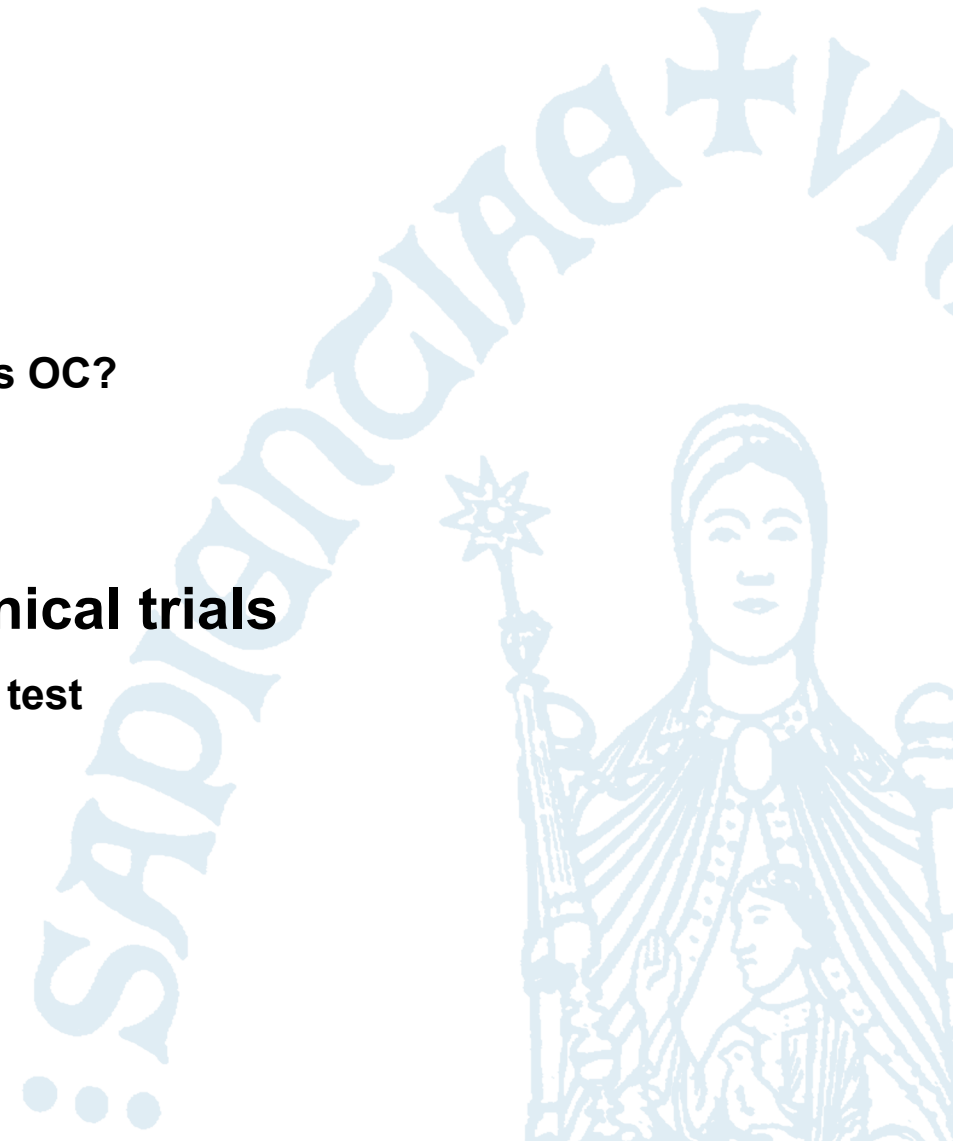
Common misconceptions:

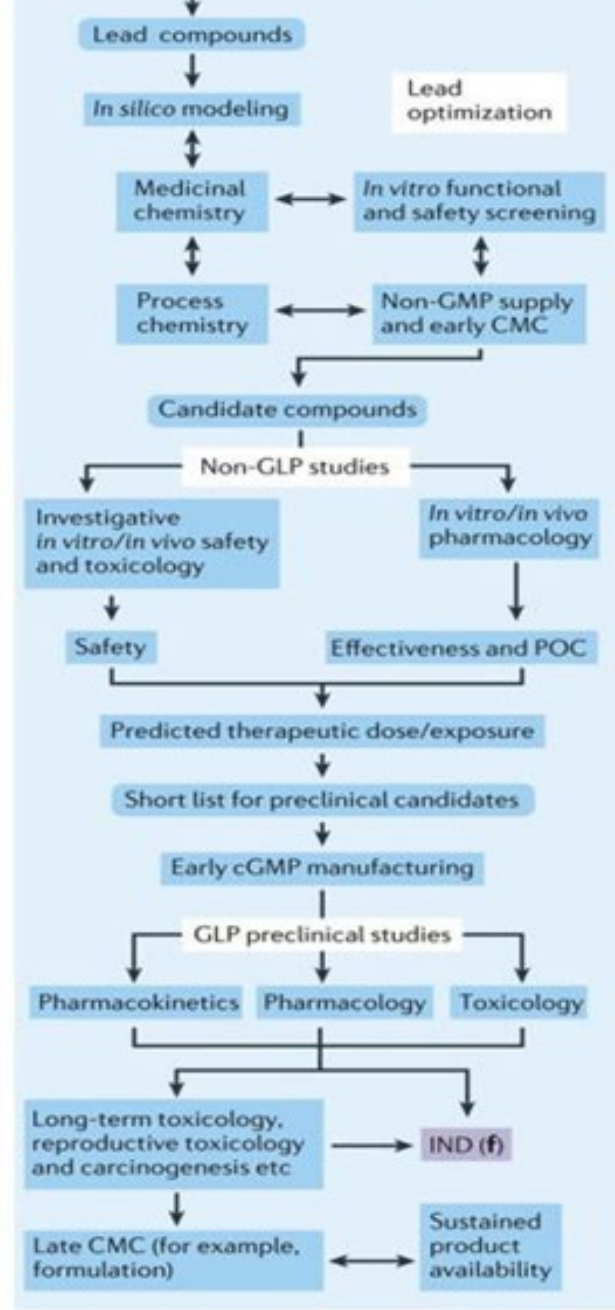
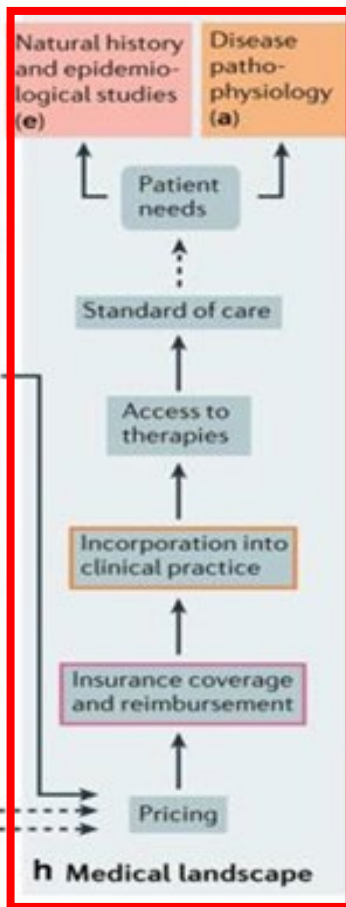
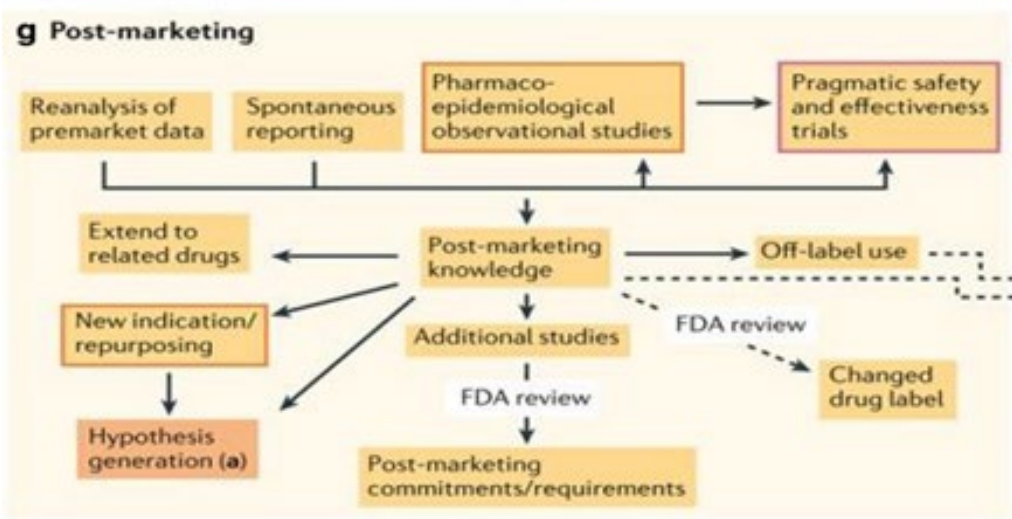
- Translation of basic findings is straightforward
- Translation is an unidirectional process
- Once an investigational medicine gets into humans for the first time, then approval is almost sure
- Regulatory approval is the end of the translation process



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- 1. Inspiration and plan of action**
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  - PI3K/mTOR pathway inhibition in uLMS
- 4. Value of clinical samples originating from clinical trials**
  - PAOLA-1 trial: academically laboratory-developed HRD test

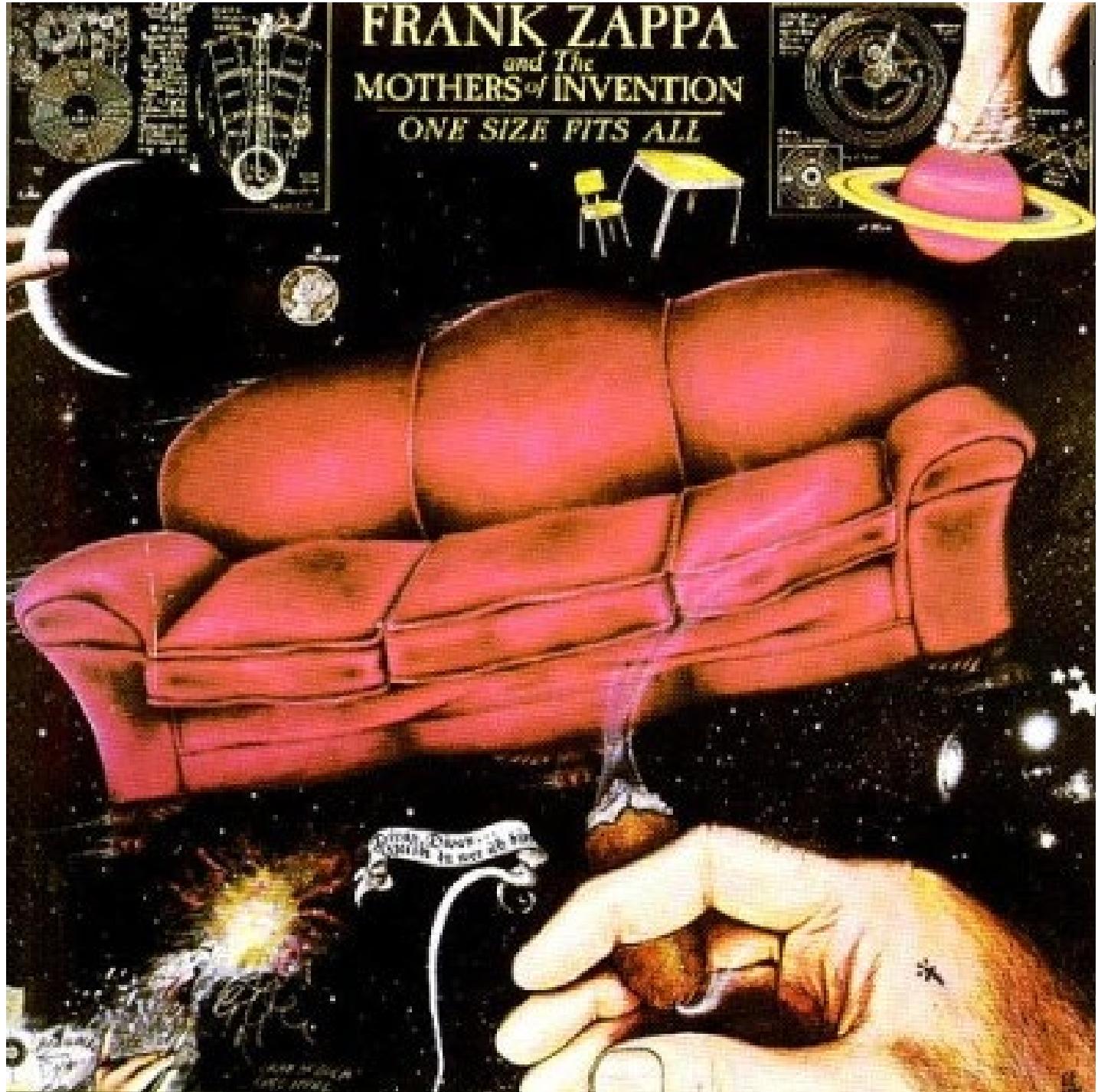




# My inspiration and some general thoughts

- **Clinical need**
  - Cancer in pregnancy
  - Lack of treatment options
- **Focus, and keep the focus since a long term project only will deliver solid data**
  - Rare cancers
  - Resistance
  - Uterine sarcomas
  - Cancer and pregnancy
  - Vulvar cancer
- **Competitors?**
  - Including internally
  - Search for alternative and complementary research area's

**FRANK ZAPPA**  
*and The*  
**MOTHERS of INVENTION**  
*ONE SIZE FITS ALL*



# The KUL PDX Platform (TRACE)

Develop PDX models of different tumor types

Accelerate drug discovery in oncology by:

- Preclinical drug screening and biomarker analysis
- Co-clinical trial approach
- Personalized medicine strategy



## Trace

Patient Derived Tumor Xenograft  
Platform



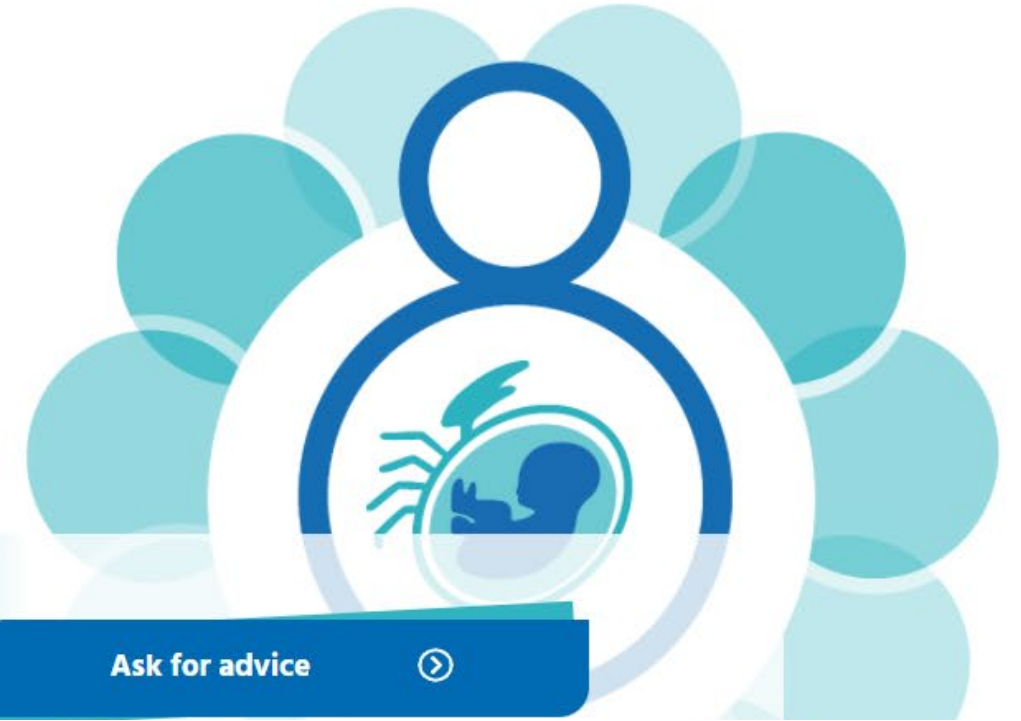
Els Hermans  
Coördinator PDX Platform





# ABCIP

## Advisory Board on Cancer, Infertility and Pregnancy



The ABCIP provides a platform where physicians from all over the world can request recommendations regarding the medical care of pregnant women diagnosed with cancer or regarding fertility preservation. Your requests will be sent to the national advisory board of your country or to the overarching international board.

Your request can only consist of **anonymous** patient information. We try to send the recommendations back to you within **4-7 days**.

[Ask for advice](#)



### The Advisory Board on Cancer, Infertility and Pregnancy: a virtual on-demand multidisciplinary tumour board



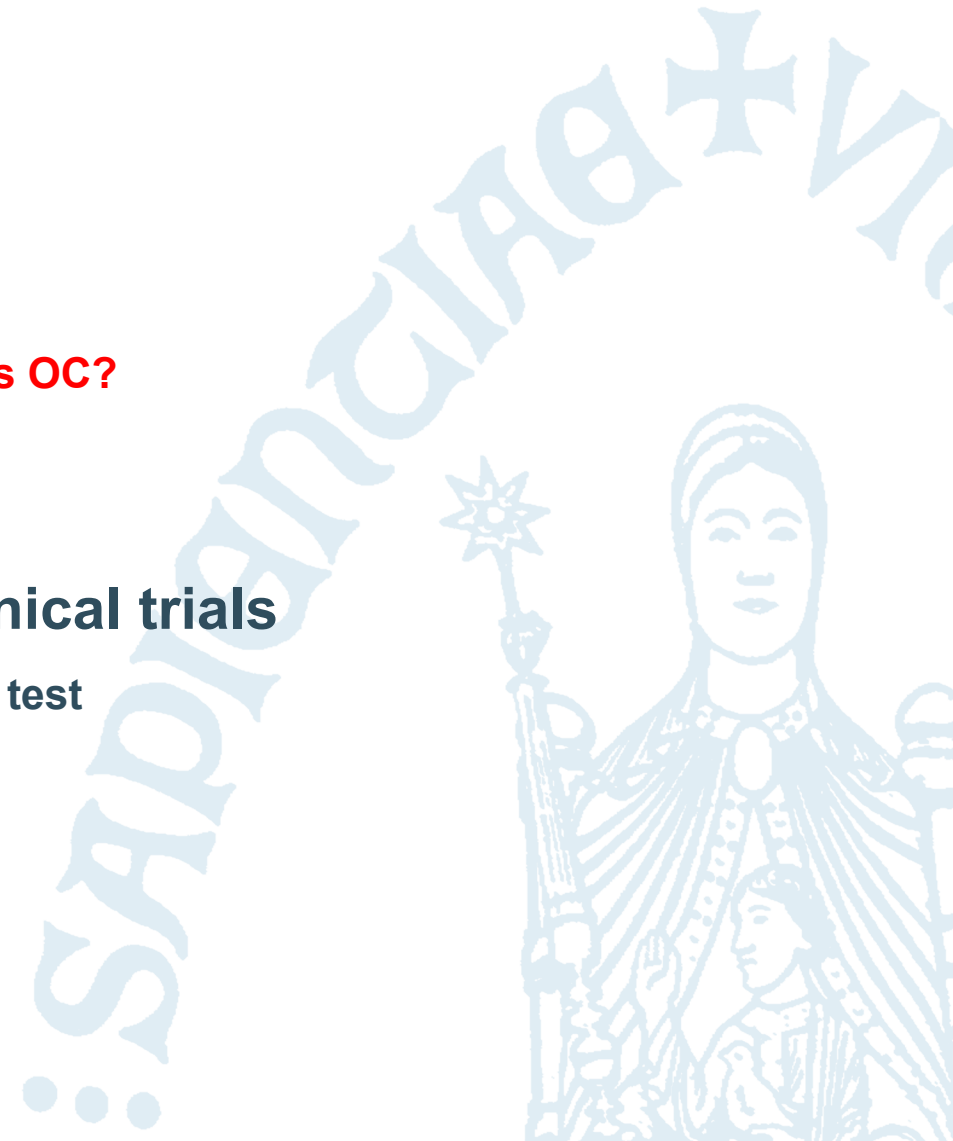
Multidisciplinary consultations are part of standard oncological care. These consultations ensure that patients' cases are discussed by all involved specialists and that a consensus is reached on the most appropriate treatment course.<sup>1</sup> The multidisciplinary consultation model is adequate for most patients with cancer, but teams might have insufficient expertise for people with rare cancers or conditions. Cancer during pregnancy is an example of such a rare condition, for which the traditional

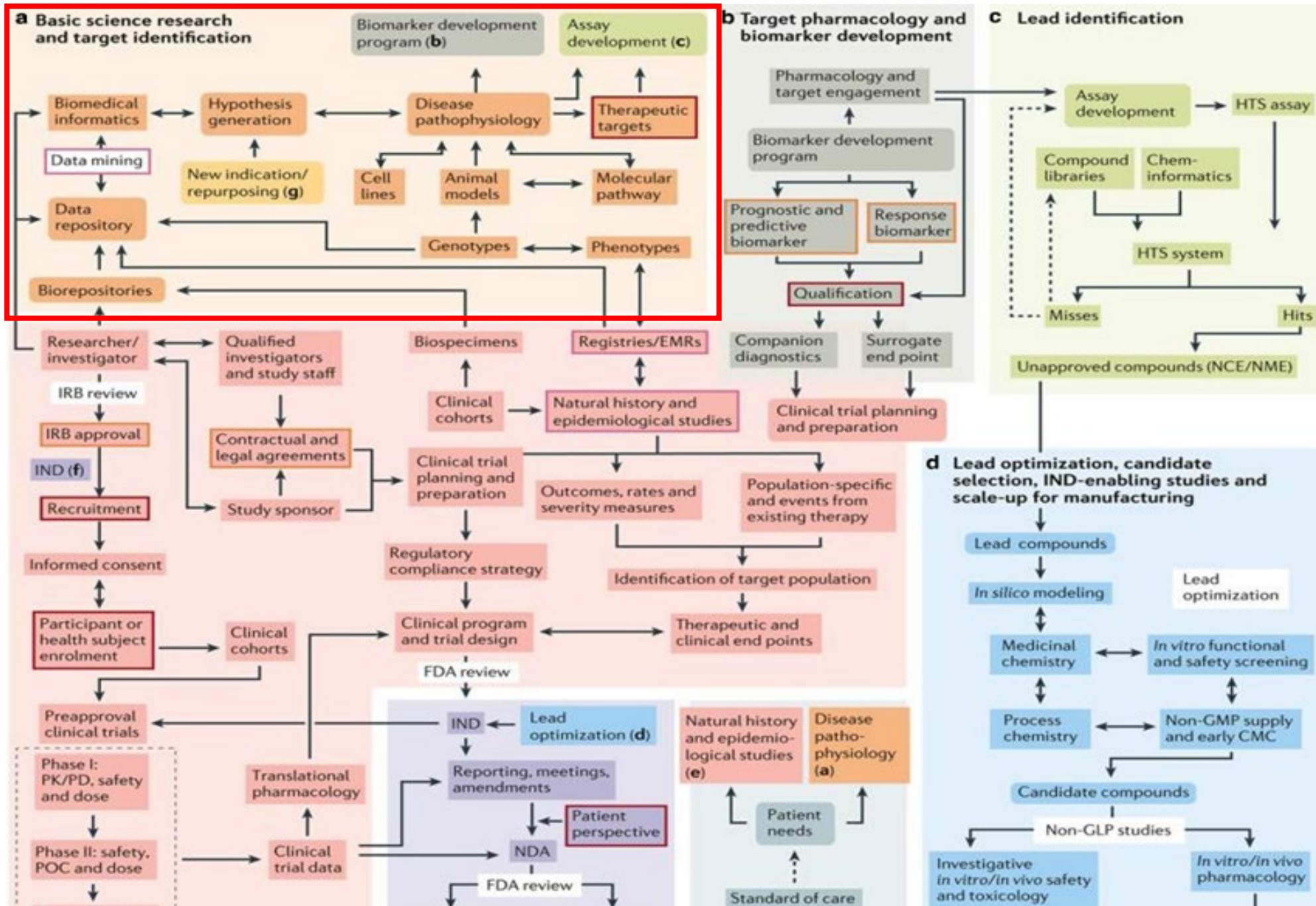
pregnant and have cancer. However, a multidisciplinary team for patients who are pregnant and have cancer in every hospital providing oncological care might still need to deal with the challenges of low incidence and insufficient expertise. Furthermore, geographical and logistical barriers can hinder referral of patients to hospitals with these dedicated multidisciplinary teams. Alternative ways to provide the most optimal multidisciplinary care to patients who are pregnant and



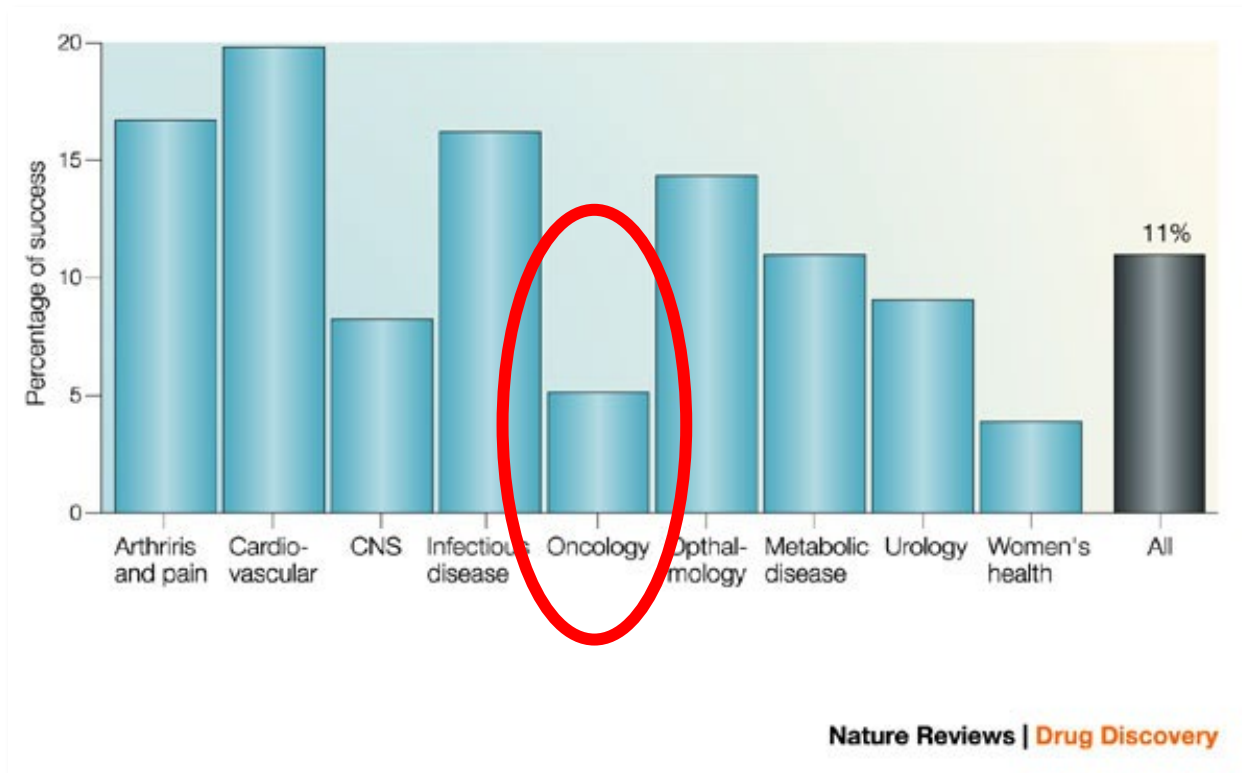
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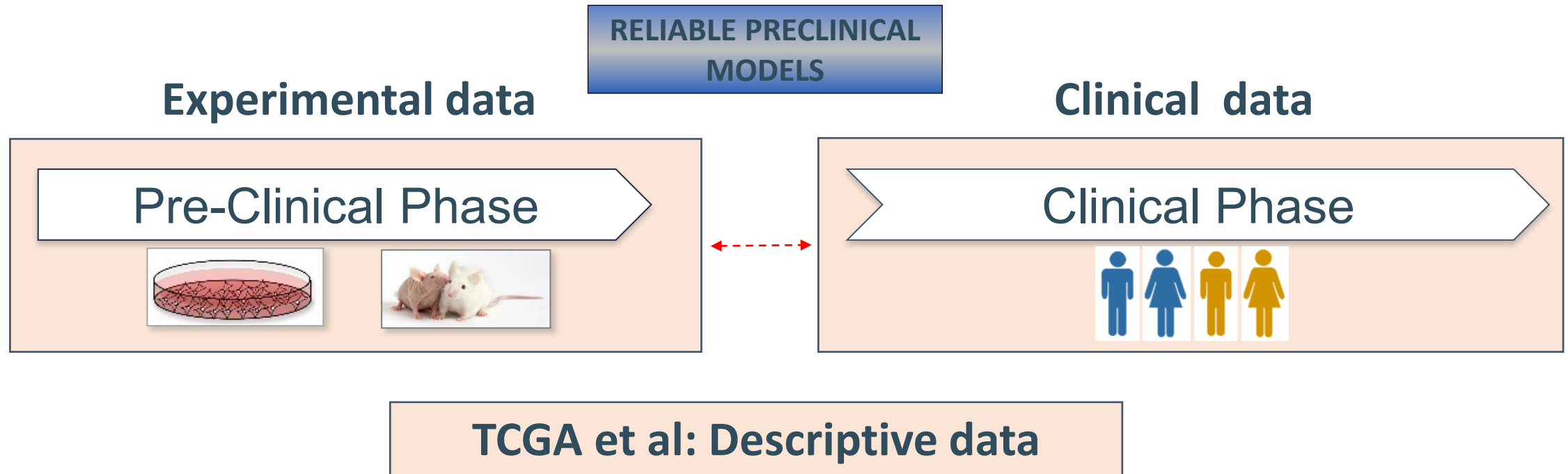


# The high attrition rate in oncology



# Mind the gap!

The need of reliable patient-derived models

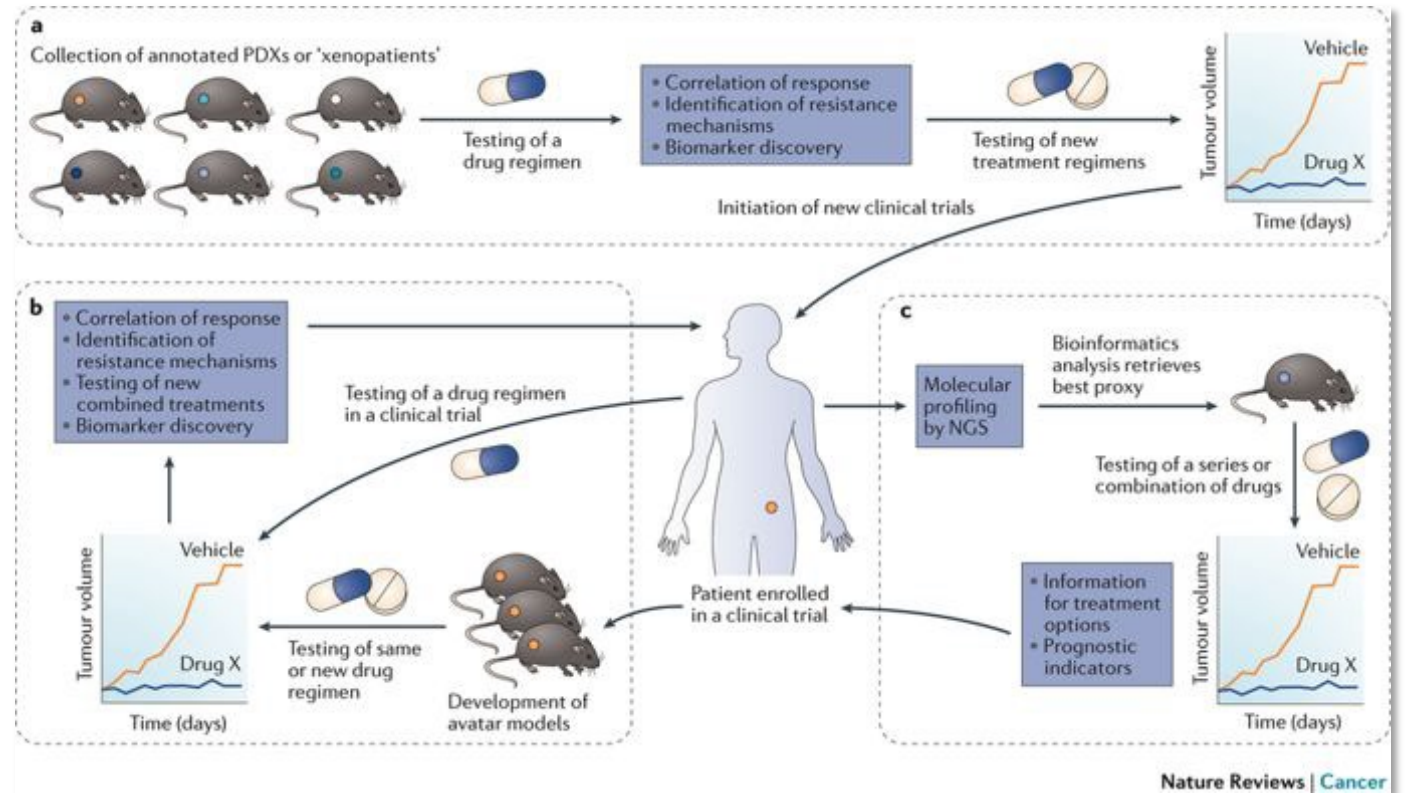


# Towards better models: patient-derived xenograft models - PDXs

Established by implanting freshly-isolated tumor fragments into immunocompromised mice

Allow for progressive growth and amplification of cancer tissue for in vivo testing

Retain histological, genetic and biological features of the original tumor in the patient

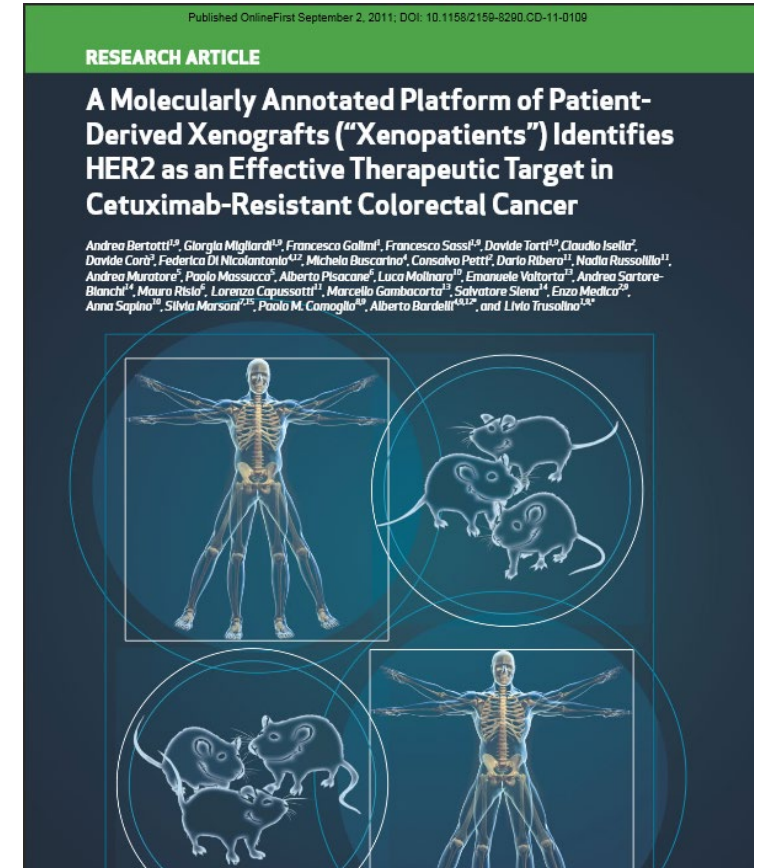
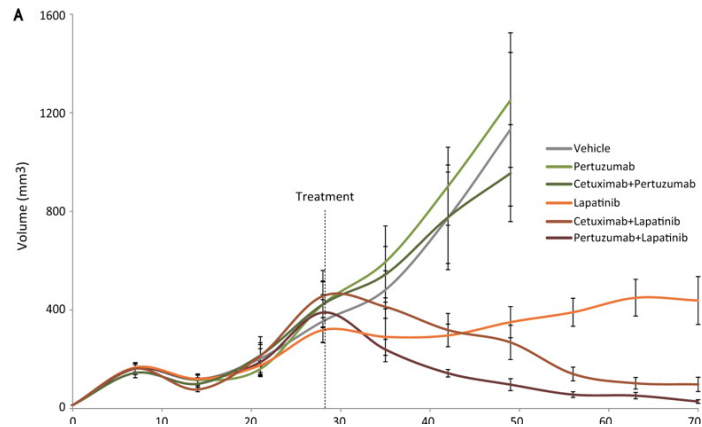
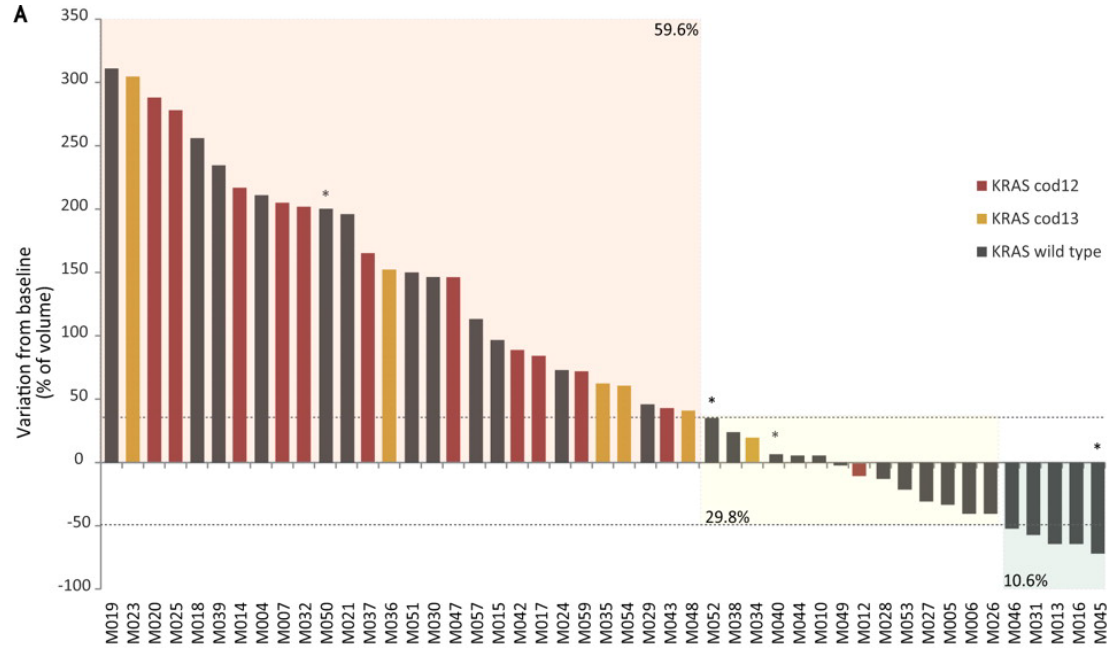


## Towards precision medicine in oncology?

- Robust and reliable preclinical models
- Rationally designed clinical trials

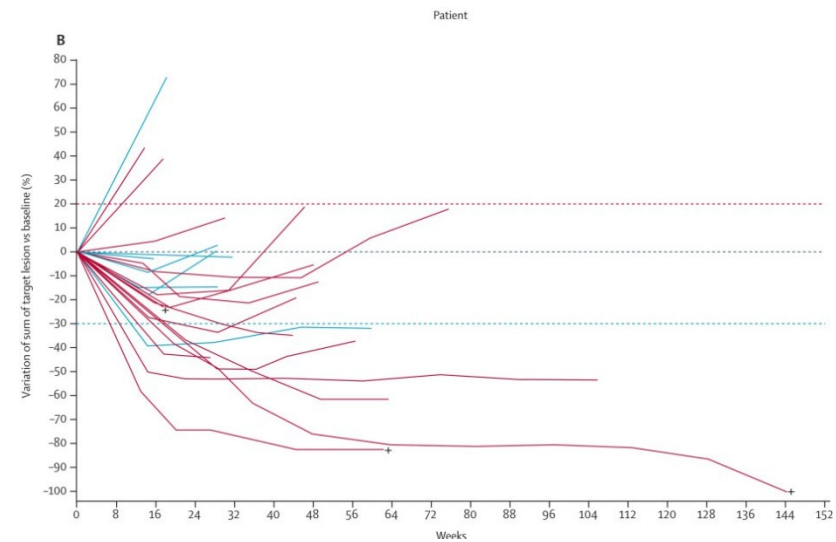
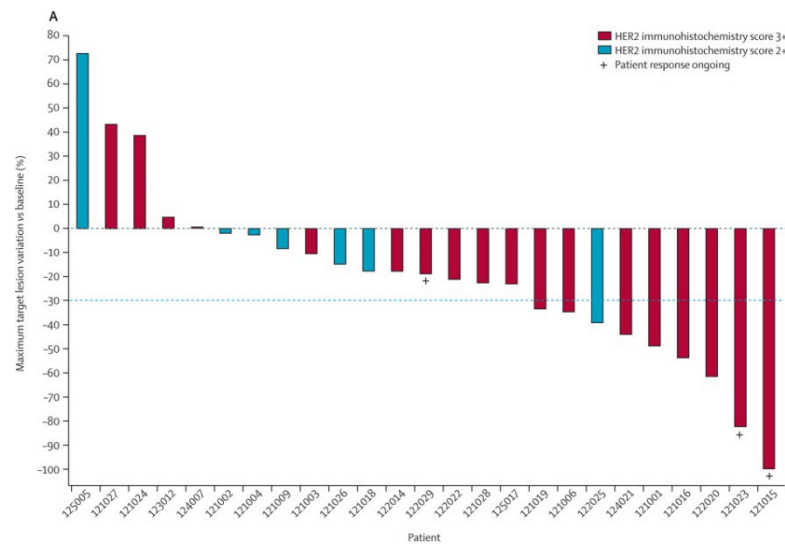


# A molecularly annotated platform of patient-derived xenografts (“xenopatients”) identifies HER2 as an effective therapeutic target in cetuximab-resistant colorectal cancer



# Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial

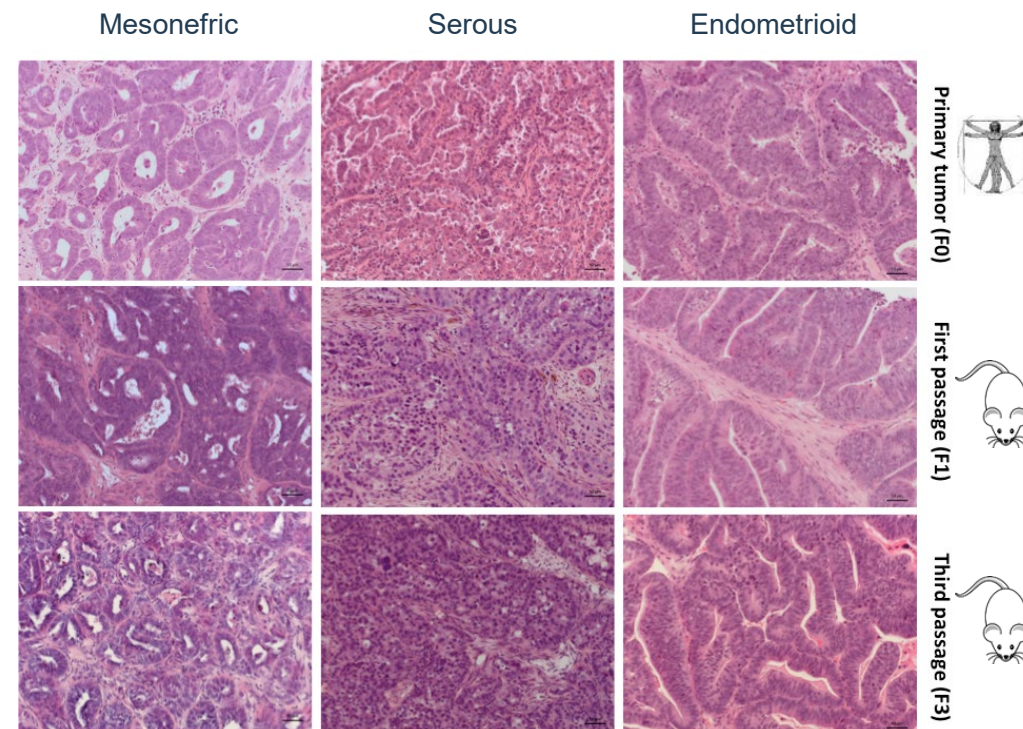
Sartore-Bianchi et al., Lancet Oncol 2016



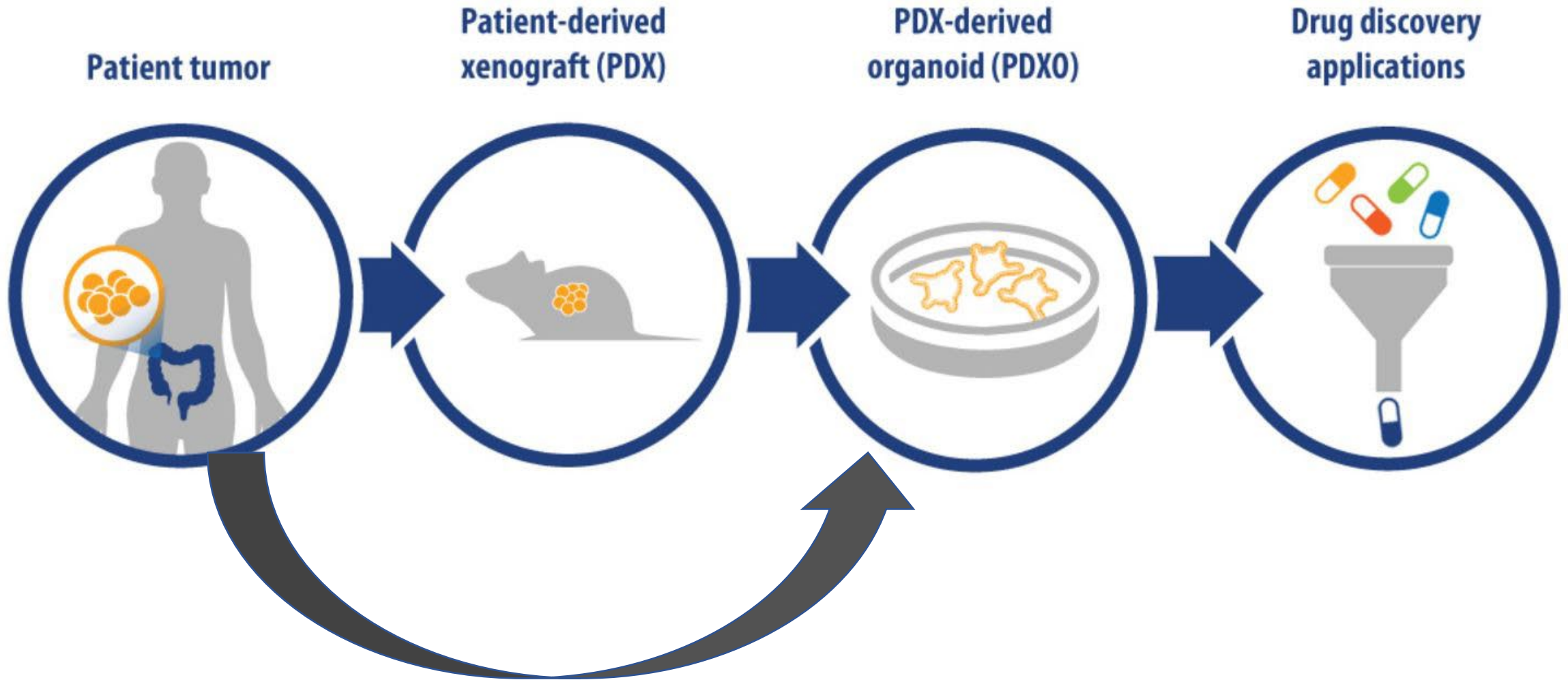
The combination of trastuzumab and lapatinib is active and well tolerated in treatment-refractory patients with HER2-positive metastatic colorectal cancer.

# Endometrial cancer PDXs @ TRACE

Model ID	Histology	Classification			
			FIGO	Grade	TCGA
EMC001	endometrioid	Primary	IV	2	MSI
EMC003	endometrioid	Recurrence (vagina)	n/a	3	MSS
EMC015	endometrioid	Primary	III	1	MSS
EMC016	endometrioid	Primary	I	2	MSI
EMC032	endometrioid	Primary	I	1	POLE
EMC034	endometrioid	Recurrence (vagina)	n/a	2	MSI
EMC046	endometrioid	Primary	III	3	MSI
EMC007	mesonephric	Recurrence (vagina)	n/a	3	n/a
EMC024	mesonephric	Metastasis (pelvis)	n/a	3	n/a
EMC008	serous	Primary	III	3	n/a
EMC053	serous	Primary	III	3	n/a
EMC042	mixed endometrioid/clear cell	Primary	III	3	MSI
EMC047	undifferentiated	Recurrence (abdomen)	III	3	n/a
EMC011	carcinosarcoma	Primary	Ia	3	n/a
EMC054	carcinosarcoma	Primary	Ib	3	n/a

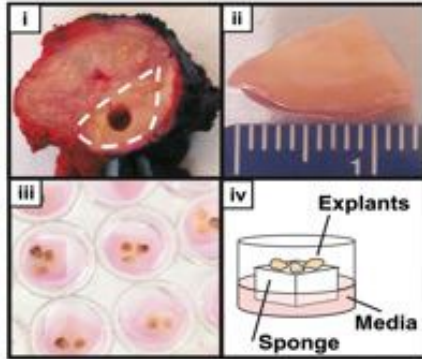


# Patient-derived Organoids - PDOs



# PATIENT-DERIVED TUMOR EXPLANTS (PDEs)

Live fragments/slices of fresh, surgically resected tumors cultured ex-vivo under defined conditions (matrix, serum)



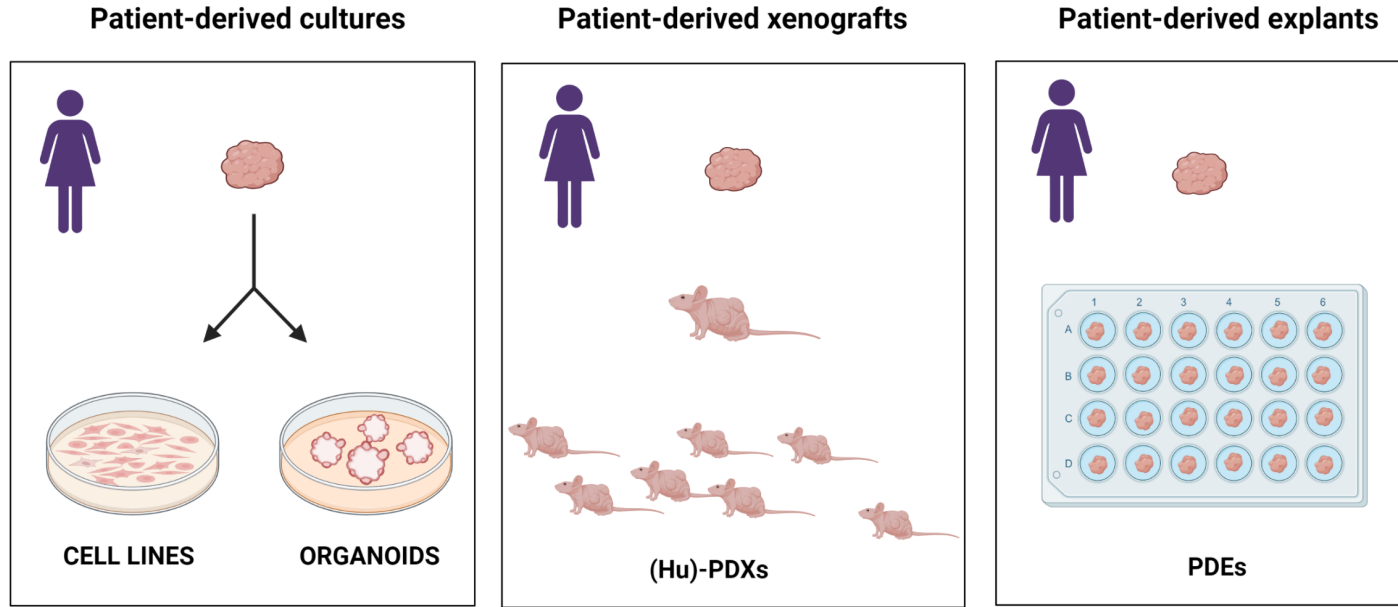
- 1 mm<sup>3</sup> fragments or 150-250µM slices
- FBS or autologous serum
- Defined synthetic extracellular matrix/sponge

Allow for drug testing in mini-tumors that remain intact and maintain tumor-stroma interaction for at least 72h

Predict clinical response in patients (chemo-, targeted- and immuno-therapies)



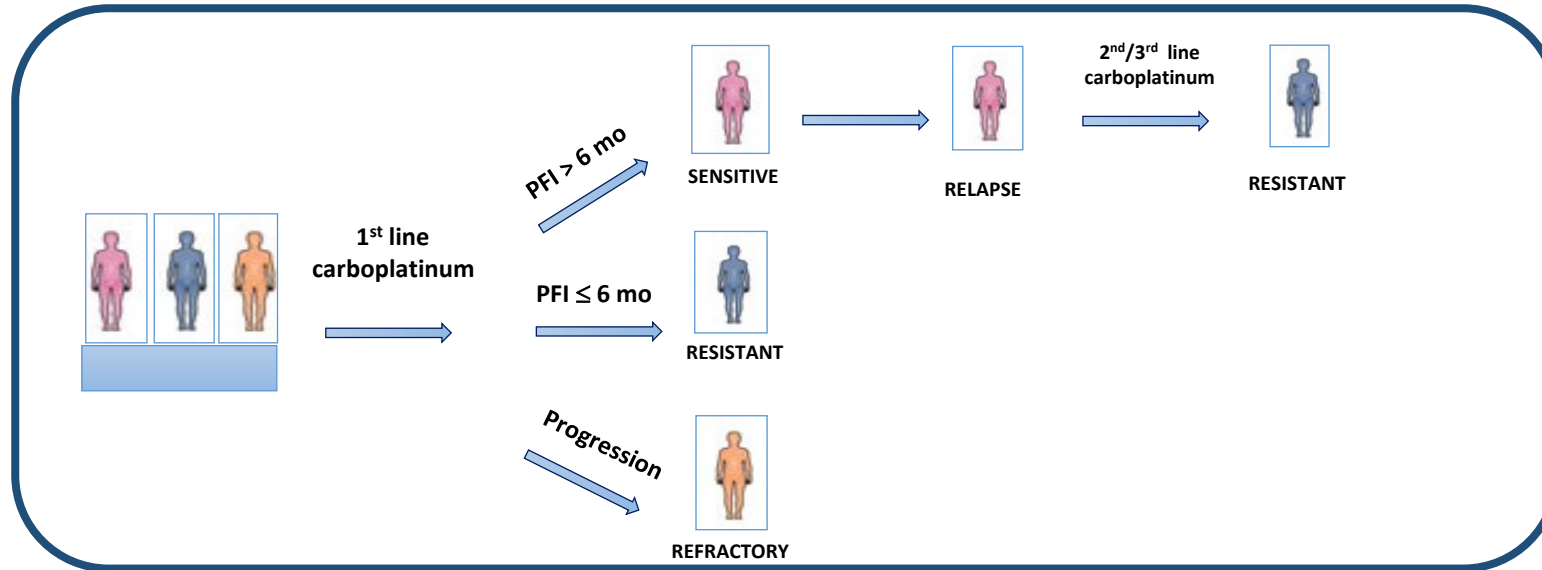
# PATIENT-DERIVED PRECLINICAL MODELS



	CELL LINES	ORGANOIDS	(Hu)-PDXs	PDEs
<b>Time</b>	+++	+++	---	+++
<b>Cost</b>	+++	+	---	+++
<b>Highthroughput</b>	+++	++	---	+++
<b>Genetic manipulation</b>	+++	++	+ / --	---
<b>Tissue architecture</b>	---	+ / --	+++	+++
<b>Heterogeneity</b>	---	--	++	+++



# Epithelial ovarian cancer – patients' journey



## Definitions of Platinum Sensitivity Are Based on Platinum-Free Interval

Time from last platinum exposure to progressive disease:



<1 month

Platinum-refractory

1–6 months

Platinum-resistant

≥6 months

Platinum-sensitive

## Platinum Resistance Is Associated With Poor Prognosis



Platinum-resistant disease  
mOS: 9–12 months<sup>a</sup>



Platinum-refractory disease  
mOS: 3–5 months<sup>a</sup>



ARTICLE

doi:10.1038/nature14410

## Whole-genome characterization of chemoresistant ovarian cancer

ARTICLE

doi:10.1038/nature10166

## Integrated genomic analyses of ovarian carcinoma

The Cancer Genome Atlas Research Network\*

**NO ACTIONABLE RECURRENT POINT MUTATIONS!**

**NO BIOMARKERS!**

### A quantitative proteomics-based signature of platinum sensitivity in ovarian cancer cell lines

Gaofeng Fan<sup>#</sup>, Kazimierz O. Wrzeszczynski<sup>1, #</sup>, Cexiong Fu<sup>2</sup>, Darryl J. Pappin, Robert Lucito<sup>4</sup>, and Nicholas K. Tonks<sup>\*</sup>

Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA

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<sup>3</sup>Molecular Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI, USA

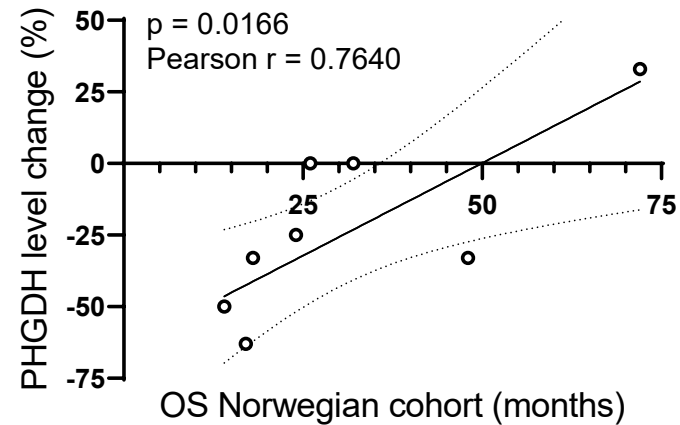
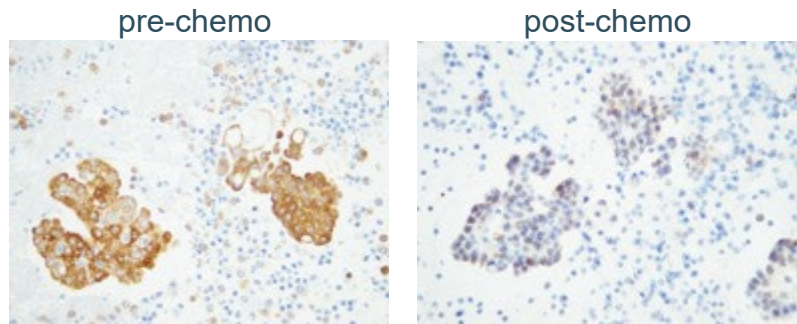
# A subset of relapsed ovarian cancers decrease serine synthesis after platinum exposure: the Oslo cohort



Chemonaive HGSC patient



Cohort	Sample type	NACT	n	PHGDH change at recurrence	n (PHGDH change)
Norwegian	Pleural effusions	No	9	Decrease	6
				Equal	2
				Increase	1



Patients with stronger decrease in PHGDH levels at relapse have worse prognosis

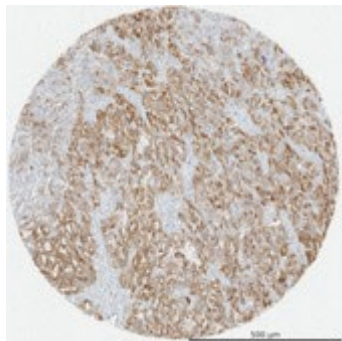
# A subset of relapsed ovarian cancers decrease serine synthesis after platinum exposure: the NKI cohort



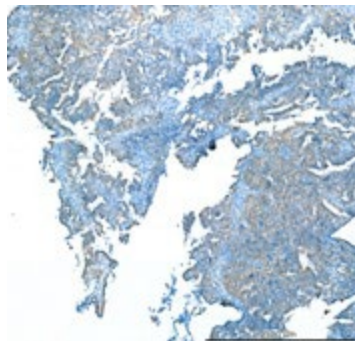
HGSC patient  
Diagnosis/  
Debulking



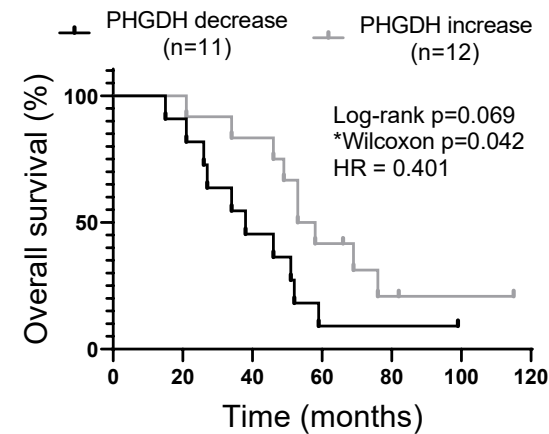
Primary



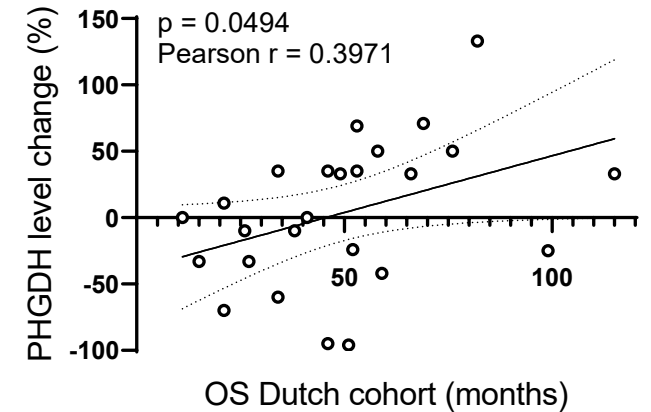
Recurrence



Cohort	Sample type	NACT	n	PHGDH change at recurrence	n (PHGDH change)
Dutch	Tumor	Mixed	25	Decrease	11
				Equal	2
				Increase	12



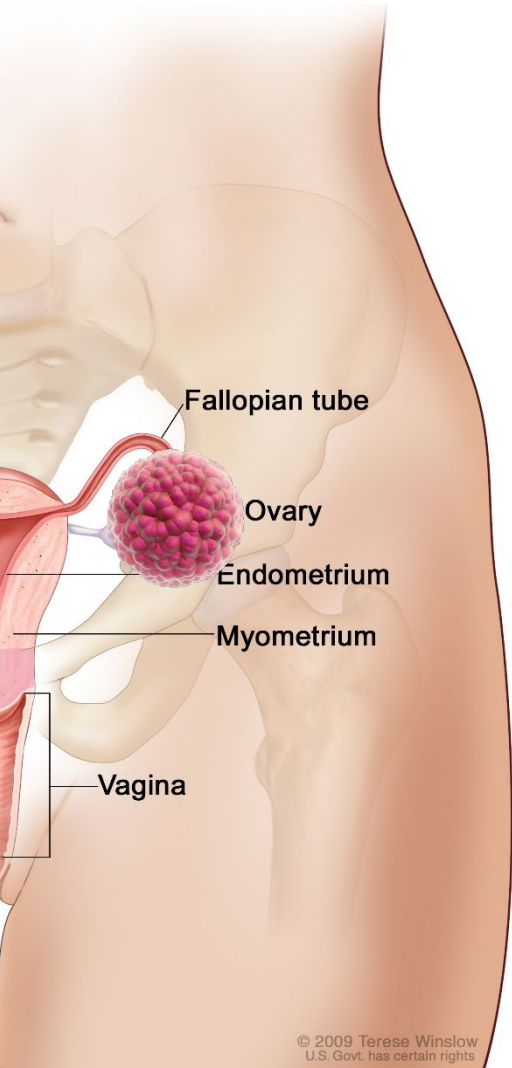
Median survival  
PHGDH decrease: 38.00 months  
PHGDH increase: 55.50 months





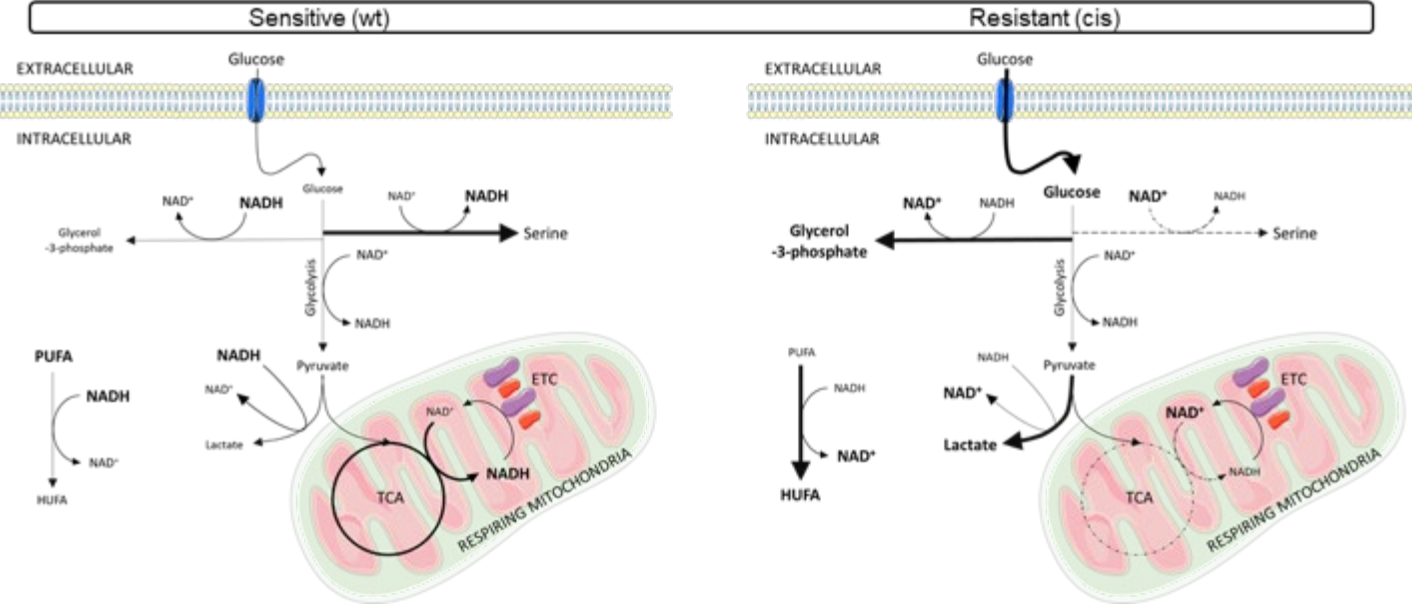
# Trace

Patient Derived Tumor Xenograft  
Platform

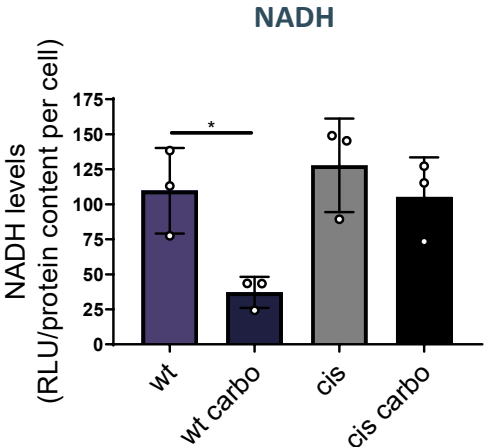
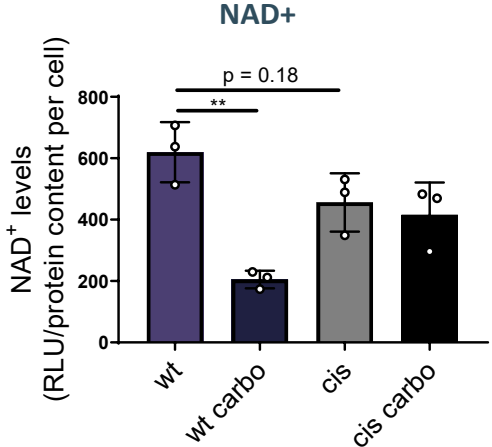
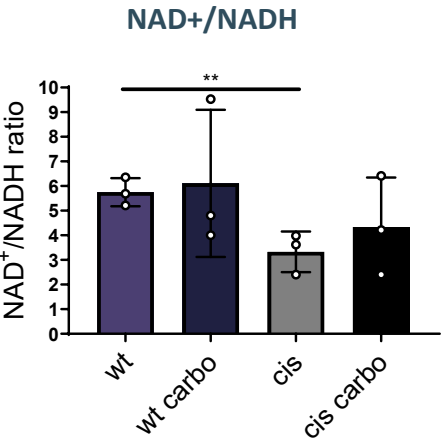


Tumor ID	Subtype	Grading	Patient therapy response
OVC001	Serous	Grade 3	Acquired resistance
OVC002	Serous	Grade 3	Acquired resistance
OVC003	Serous	Grade 3	
OVC004	Serous	Grade 3	
OVC005	Serous	Grade 3	Resistant
OVC007	Serous	Grade 3	
OVC015	Serous	Grade 3	Refractory
OVC020	Serous	Grade 3	Sensitive
OVC025	Serous	Grade 3	
OVC034	Serous	Grade 3	Relapse OVC020 sensitive
OVC012	Endometrioid	Grade 1	
OVC028	Endometrioid	Grade 3	
OVC031	Mesonephric	Grade 3	
OVC022	Neuroectodermal	Grade 3	

# Resistant cells sustain NAD+ recycling



Resistant cells downregulate serine biosynthesis as part of metabolic rewiring towards a NAD+ generating phenotype...



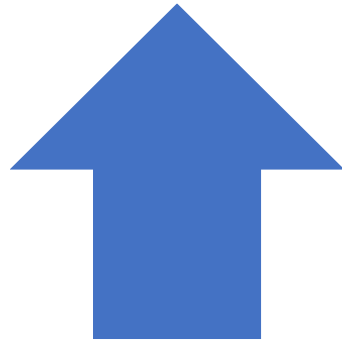
... yet decreased NAD<sup>+</sup>/NADH ratio and lower NAD<sup>+</sup> availability!



**NAD+ consumption  
(PARPs, sirtuins, CD38)**



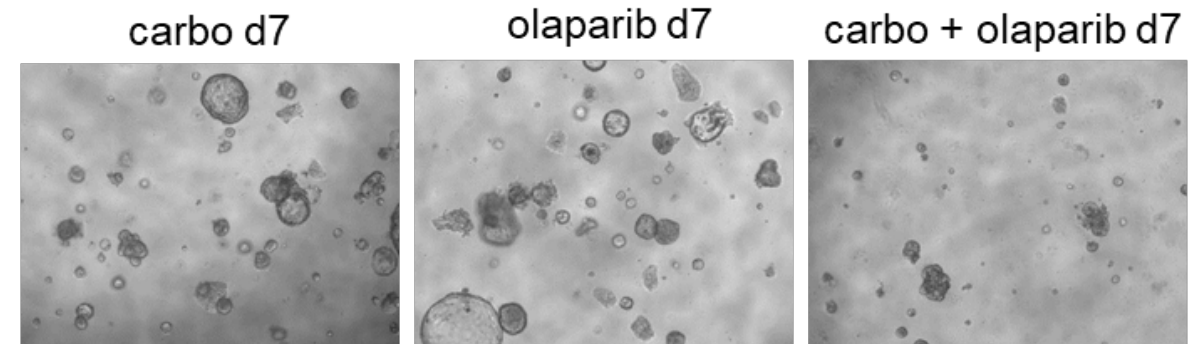
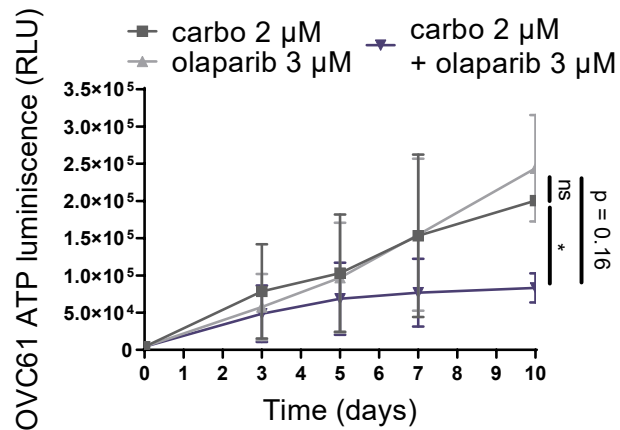
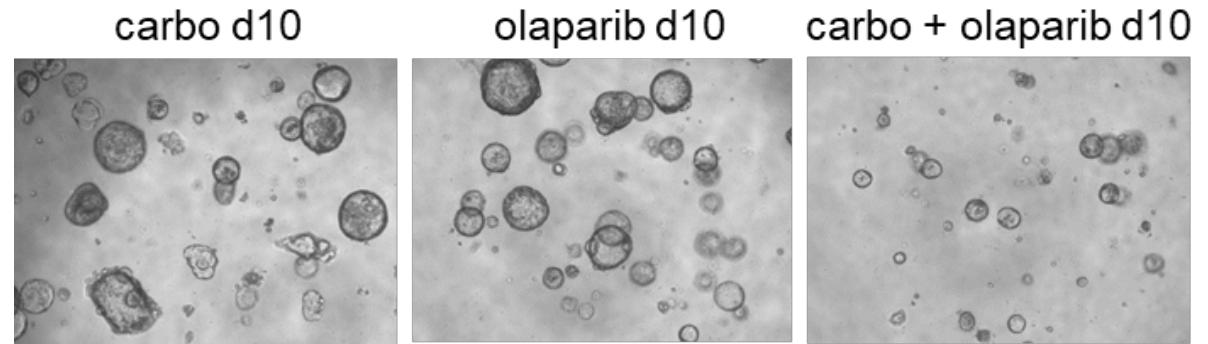
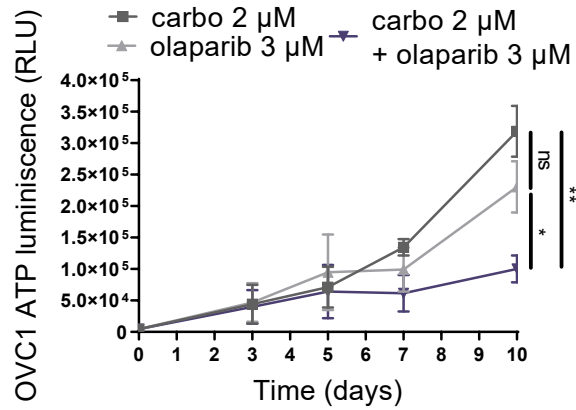
**NAD+ regeneration  
(oxidative reactions)**



**Are resistant cells consuming more NAD+ through PARPs?**

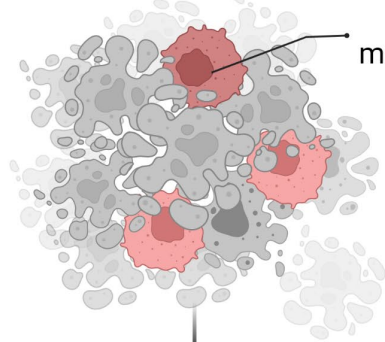
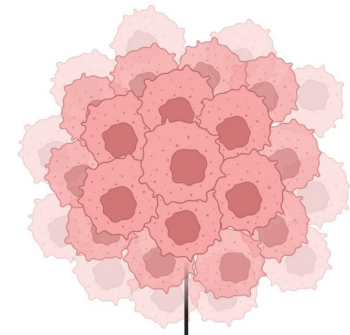
# Can platinum combined with PARP inhibitors be used to overcome platinum resistance?

## ✓ PDX-derived organoid models



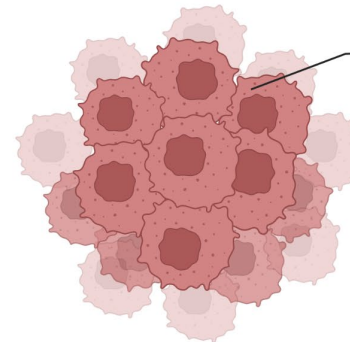
# HGSOC

1st line platinum treatment



Serine and NAD+ metabolic remodeling

2nd/3rd line platinum treatment



Acquired resistance

PHGDH ↓

PARP activity ↑

NAD+

In tumors with decreased serine synthesis after platinum exposure lowering PHGDH helps in sustaining PARP activity



Can combination of platinum and PARPi be beneficial in pre-treated resistant tumors with reduced serine synthesis?

After 7 years.....



nature communications

Article


<https://doi.org/10.1038/s41467-022-32272-6>

# Serine metabolism remodeling after platinum-based chemotherapy identifies vulnerabilities in a subgroup of resistant ovarian cancers

Received: 29 March 2022

Accepted: 19 July 2022

Published online: 05 August 2022

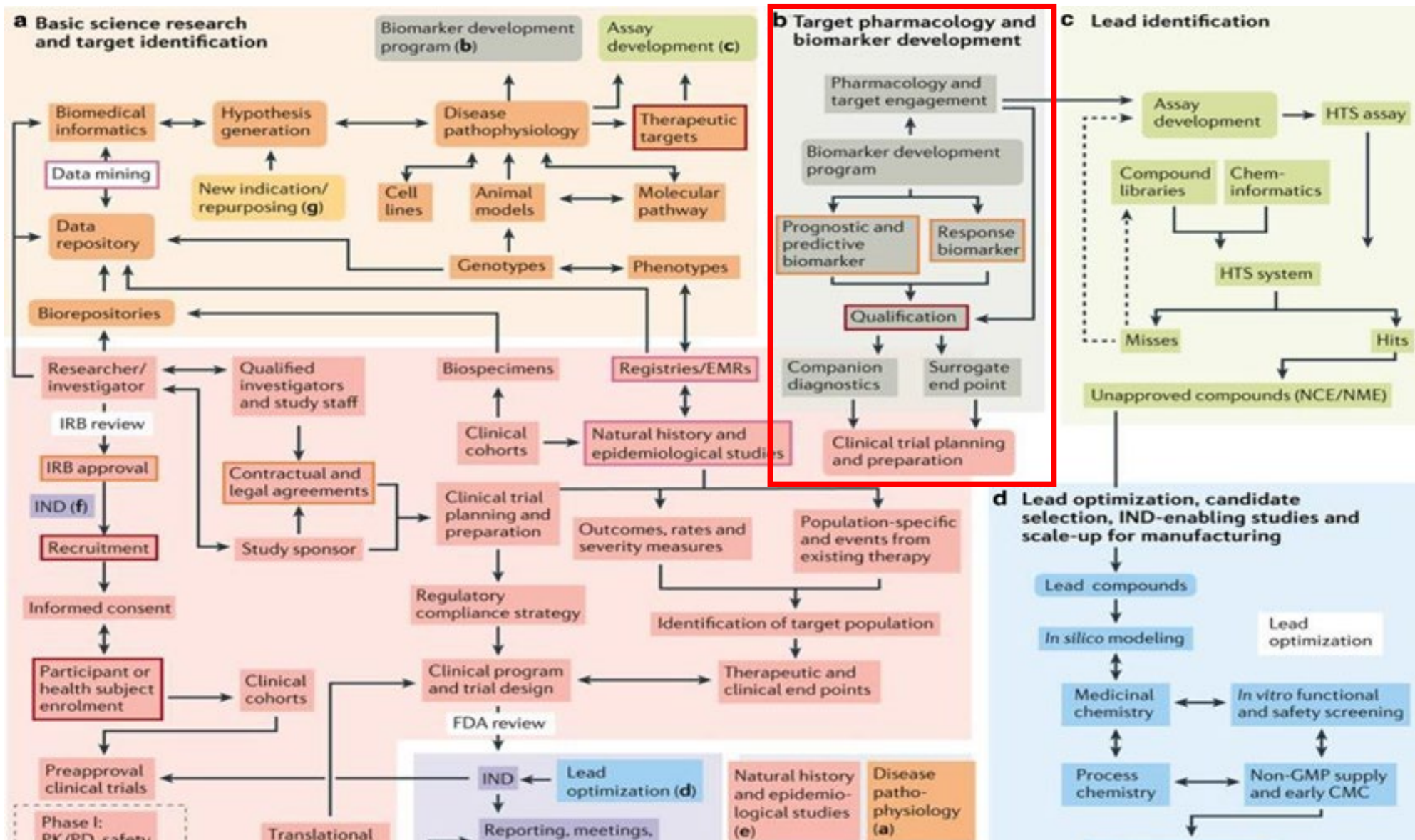
 Check for updates

Tom Van Nyen<sup>1,2</sup>, Mélanie Planque<sup>3,4</sup>, Lilian van Wagenveld<sup>5,6,7</sup>, Joao A. G. Duarte<sup>3,4</sup>, Esther A. Zaal<sup>8,9</sup>, Ali Talebi<sup>10</sup>, Matteo Rossi<sup>3,4</sup>, Pierre-René Körner<sup>2</sup>, Lara Rizzotto<sup>11</sup>, Stijn Moens<sup>1</sup>, Wout De Wispelaere<sup>1</sup>, Regina E. M. Baiden-Amissah<sup>1</sup>, Gabe S. Sonke<sup>12</sup>, Hugo M. Horlings<sup>13</sup>, Guy Eelen<sup>14</sup>, Emanuele Berardi<sup>15</sup>, Johannes V. Swinnen<sup>10</sup>, Celia R. Berkers<sup>8,9</sup>, Peter Carmeliet<sup>14,16,17</sup>, Diether Lambrechts<sup>18,19</sup>, Ben Davidson<sup>20,21</sup>, Retno Agami<sup>2,22</sup>, Sarah-Maria Fendt<sup>3,4</sup>, Daniela Annibali<sup>1,2,25</sup> & Frédéric Amant<sup>1,23,24,25</sup>

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# Biomarkers in Oncology: the opportunity

**Prognostic** - Predict survival

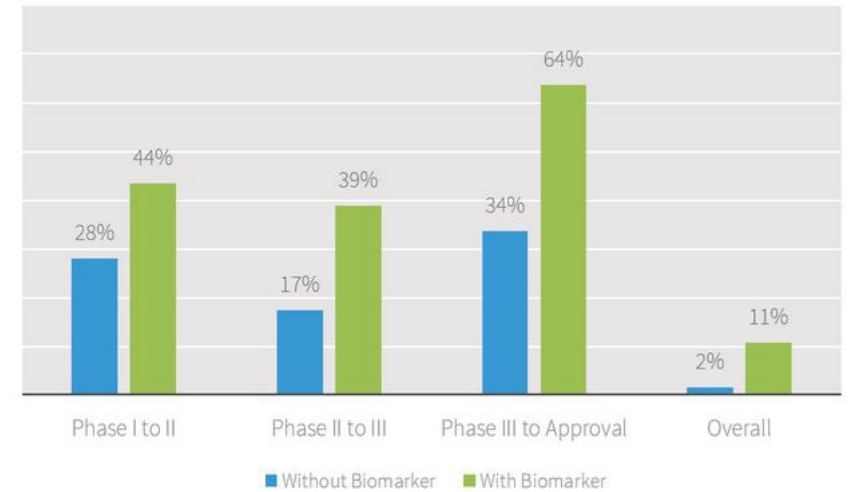
**Pharmacodynamics** - Assess drug safety and evaluate target engagement

**Predictive** - Identify patients more likely to benefit from a treatment

**Surrogate** - Predict outcome given the response to therapy

**Monitoring** - Monitor disease progression or therapeutic efficacy

Probability of Clinical Trial Success

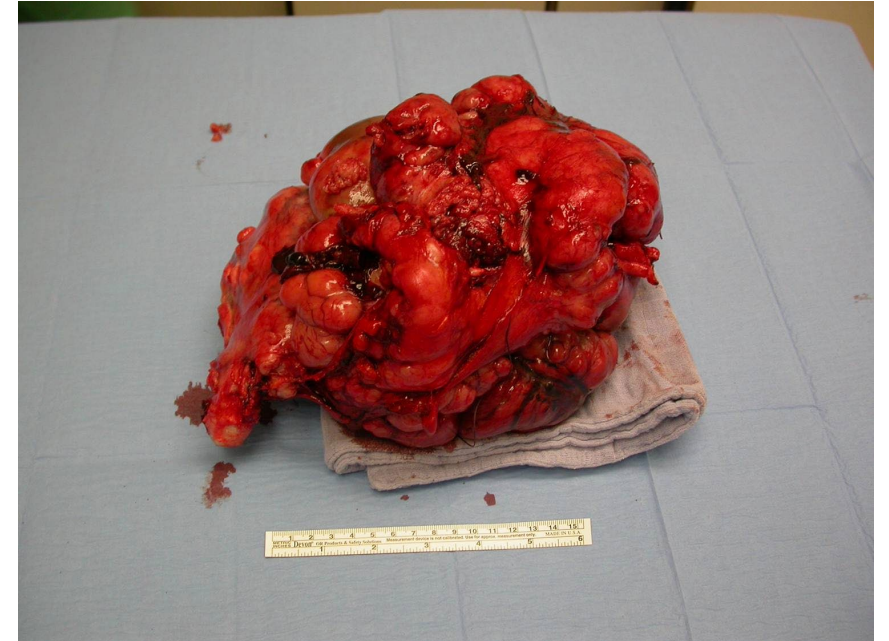


Biomarkers		Phase 1 to Phase 2			Phase 2 to Phase 3		
		Total phase transitions	POS <sub>1,2</sub> , %	(SE, %)	Total phase transitions	POS <sub>2,3</sub> , %	SE, %
Oncology	No biomarker	9349	28.0	(0.5)	4773	17.4	(0.5)
	With biomarker	1136	43.5	(1.5)	742	38.8	(1.8)
	All	10 485	29.7	(0.4)	5515	20.3	(0.5)

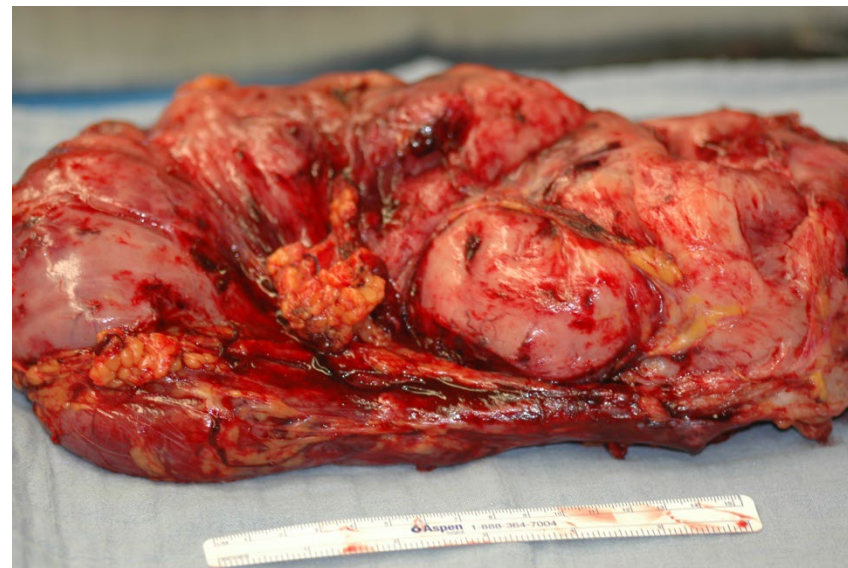
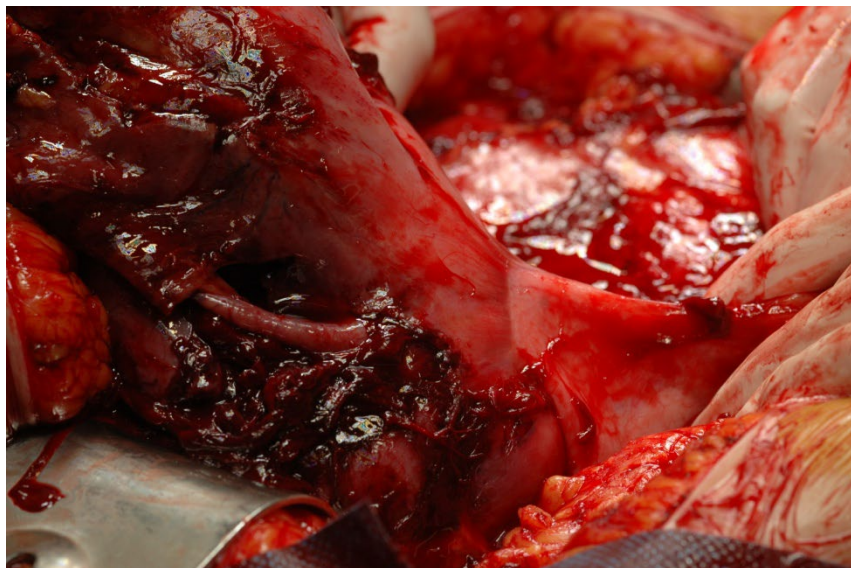
From Wong CH et al, Biostatistics 2019

# Uterine leiomyosarcoma (uLMS)

- Smooth muscle tumor of the uterus
- Incidence rate of **0.4-0.9/100 000** women
- High inter- and intratumoral heterogeneity
- Propensity for early hematological dissemination
- 5-year overall survival **57%** stage I to **16%** stage IV



# *Secondary debulking: peroperative findings*



# Clinical trials uLMS

- Only **9** ongoing clinical trials on uterine leiomyosarcomas

- To put in perspective: **3,509** ongoing clinical trials on breast cancer

9 Studies found for: **Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation** Studies | uterine leiomyosarcoma

Applied Filters:  Recruiting  Not yet recruiting  Active not recruiting  Enrolling by invitation

Not enough studies found? Try these search suggestions: [+](#)

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Apply Clear

Status

Recruitment ⓘ :

- Not yet recruiting
- Recruiting
- Enrolling by invitation
- Active, not recruiting
- Suspended
- Terminated
- Completed
- Withdrawn
- Unknown status†

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	<input type="checkbox"/>	Active, not recruiting	<a href="#">Nivolumab Alone or in Combination With Ipilimumab in Treating Patients With Advanced Uterine Leiomyosarcoma</a> <a href="#">Has Results</a>	<ul style="list-style-type: none"><li>Metastatic <b>Leiomyosarcoma</b></li><li>Unresectable <b>Leiomyosarcoma</b></li><li><b>Uterine Corpus Leiomyosarcoma</b></li></ul>	<ul style="list-style-type: none"><li>Biological: Ipilimumab</li><li>Other: Laboratory Biomarker Analysis</li><li>Biological: Nivolumab</li></ul>	<ul style="list-style-type: none"><li>Brigham and Women's Hospital Boston, Massachusetts, United States</li><li>Dana-Farber Cancer Institute Boston, Massachusetts, United States</li></ul>
2	<input type="checkbox"/>	Active, not recruiting	<a href="#">Olaparib and Temozolomide in Treating Patients With Advanced, Metastatic, or Unresectable Uterine Leiomyosarcoma</a>	<ul style="list-style-type: none"><li>Stage III <b>Uterine Corpus Leiomyosarcoma</b> AJCC v8</li><li>Stage IIIA <b>Uterine Corpus Leiomyosarcoma</b> AJCC v8</li><li>Stage IIIB <b>Uterine Corpus Leiomyosarcoma</b> AJCC v8</li></ul>	<ul style="list-style-type: none"><li>Drug: Olaparib</li><li>Drug: Temozolomide</li></ul>	<ul style="list-style-type: none"><li>Mayo Clinic Hospital in Arizona Phoenix, Arizona, United States</li><li>Stanford Cancer Institute Palo Alto Palo Alto, California, United States</li><li>University of Colorado Hospital Aurora, Colorado, United States</li><li>(and 12 more...)</li></ul>

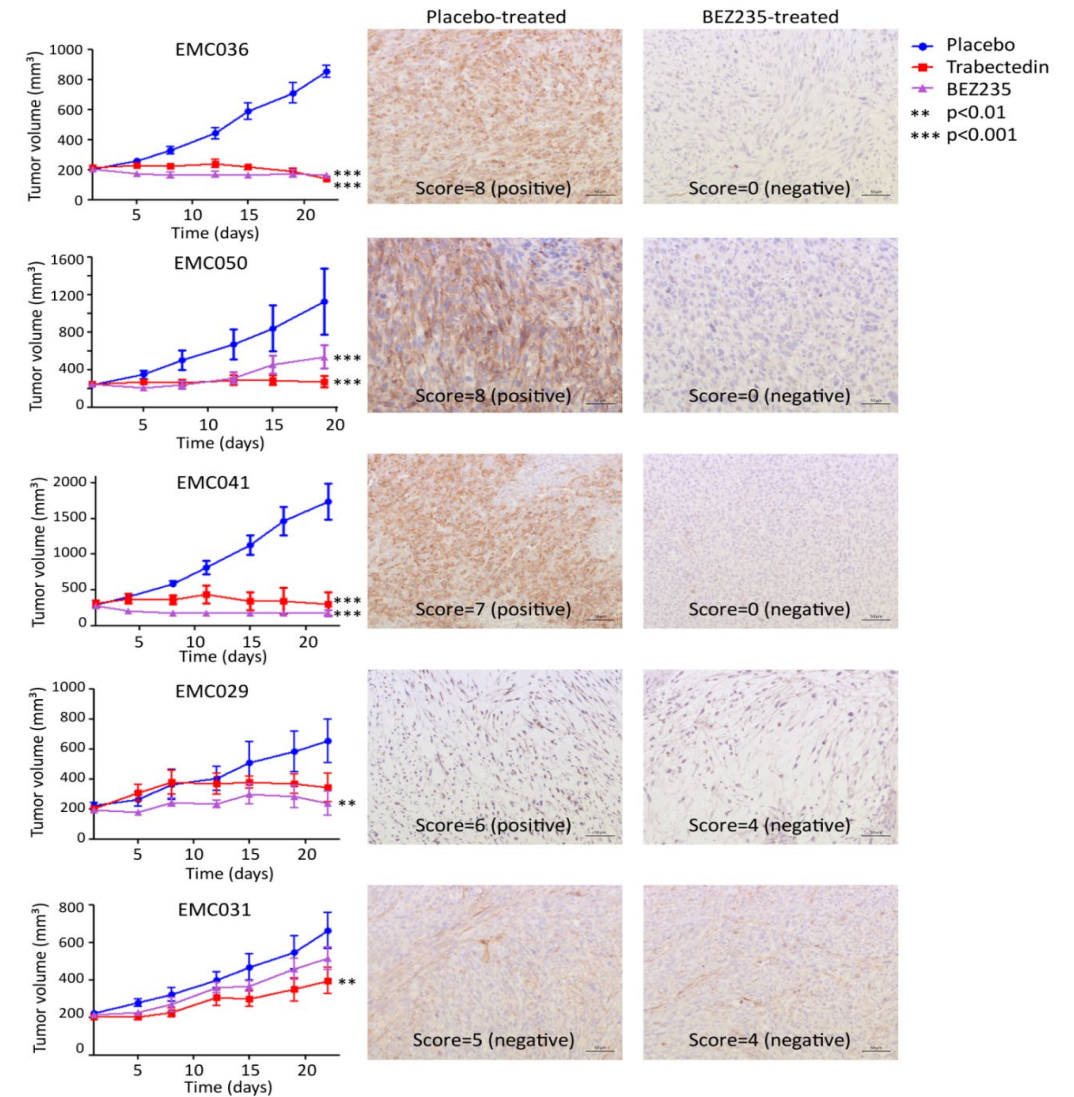
# Available uLMS PDX models

Model	Tumor used for implantation	Stage at diagnosis	Age at diagnosis	Previous treatment	Treatment after surgery	PFS (months)	OS (months)
EMC036	Primary uterine tumor	Ib	55	none	unknown	3,5	5
EMC050	Primary uterine tumor	IV	59	Tamoxifen and radiotherapy for other cancers	unknown	0 <sup>a</sup>	3
EMC041	Primary lung metastasis	IVb	61	none	Response to chemotherapy but progression pancreatic cancer	0 <sup>a</sup>	13 <sup>b</sup>
EMC029	Abdominal recurrence	Ib	58	none	Response to radiotherapy	23	>58
EMC031	Abdominal recurrence	/	62	No response to doxorubicin	none	15	30

# Dual PI3K/mTOR inhibition is effective in p-S6-positive LMS PDX models



- Treatment of uLMS PDX models with PI3K/mTOR inhibitors
- **Responding models** are phospho-S6<sup>s240</sup> **positive**, **non-responding** models phospho-S6<sup>s240</sup> **negative**
- **Phospho-S6<sup>s240</sup>** as a biomarker for response to PI3K/mTOR inhibitors



Model	Response to BEZ235	p-S6 <sup>S240</sup> mean score placebo-treated tumors	p-S6 <sup>S240</sup> status placebo-treated tumors
EMC036	Decrease in tumor volume	7,8	positive
EMC050	Decrease in tumor growth	7,7	positive
EMC041	Decrease in tumor volume	7,0	positive
EMC029	Stable tumor volume	6,3	positive
EMC031	No response	5,1	negative

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Maladies



## PI3K/mTOR Inhibitors May be Effective Against Some Uterine Sarcomas

2/23/2017

PHILADELPHIA — The protein P-S6S240 may serve as an indicator of poor prognosis for patients with a hard-to-treat type of uterine sarcoma called leiomyosarcoma, and preclinical data suggest that patients whose tumors have this protein may respond to PI3K/mTOR inhibitors, according to a [study](#) published in *Clinical Cancer Research*, a journal of the American Association for Cancer Research.

“Uterine sarcomas have generally been underexplored due to their rareness; nevertheless, they behave aggressively and are difficult to treat, resulting in a high clinical need,” said Frédéric Amant, MD, PhD, a professor at the Leuven Cancer Institute in Belgium and at the Netherlands Cancer Institute in Amsterdam.

“We wanted to generate a clear view on the presence of targetable proteins in all subtypes of uterine sarcomas, with the aim of improving treatment options for these patients,” Amant said.

His team also investigated whether any of the targetable proteins might be potential biomarkers for predicting clinical outcomes.



# Alternative inhibitors

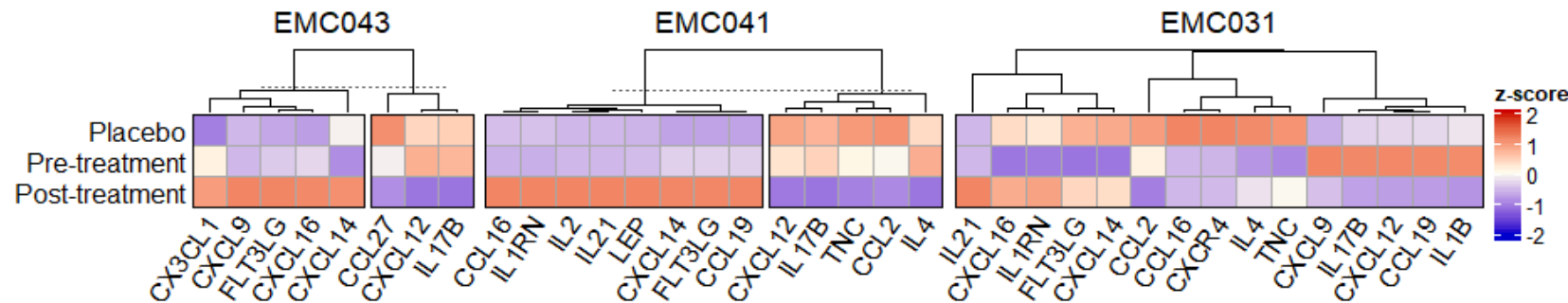
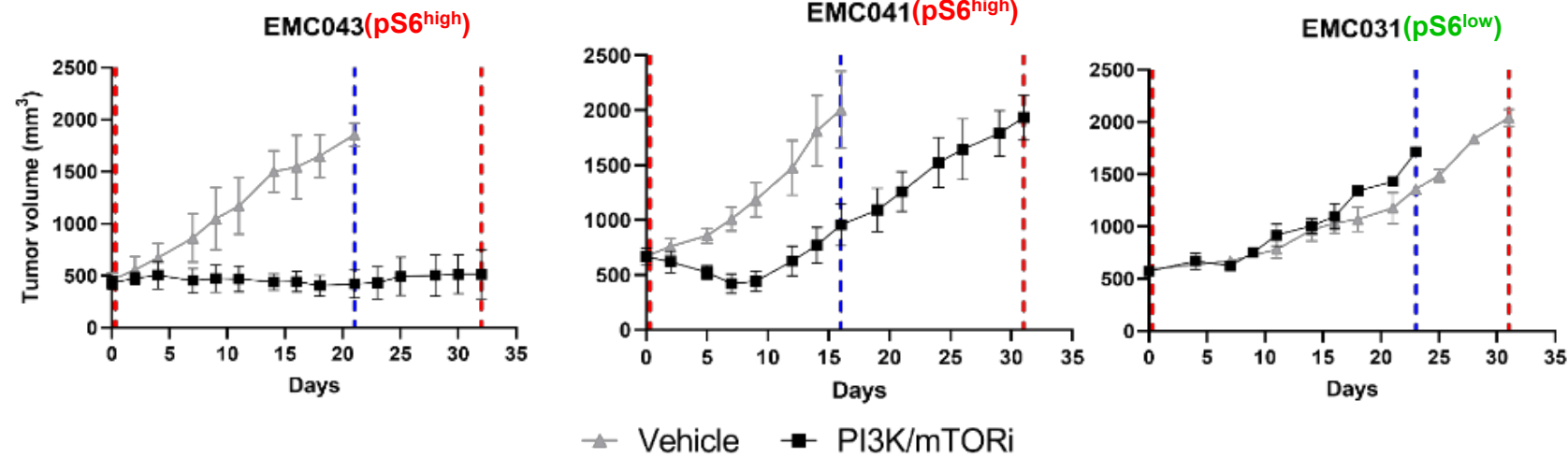
- Dactolisib (BEZ235) discontinued by Novartis due to toxicity in clinical trials



- Alternatives with better toxicity profiles:
  - Sapanisertib: mTORC1/2 inhibitor
  - Alpelisib: PI3K $\alpha$  inhibitor

# Pro-inflammatory transcriptional profile after PI3K/mTOR inhibition

PI3K $\alpha$  inhibitor  
(Alpelisib)  
+  
mTORC1/2 inhibitor  
(Sapanisertib)

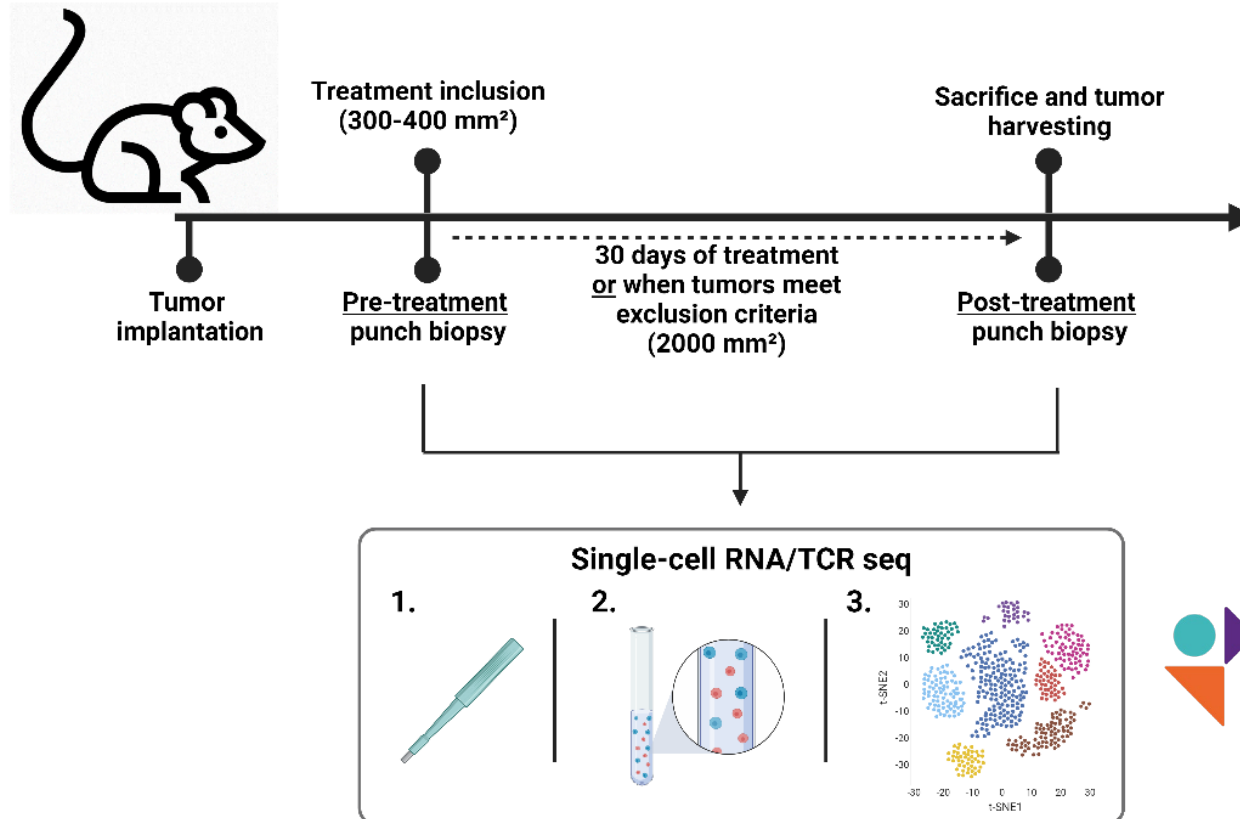


Bulk RNA seq

# Humanized uLMS PDX models



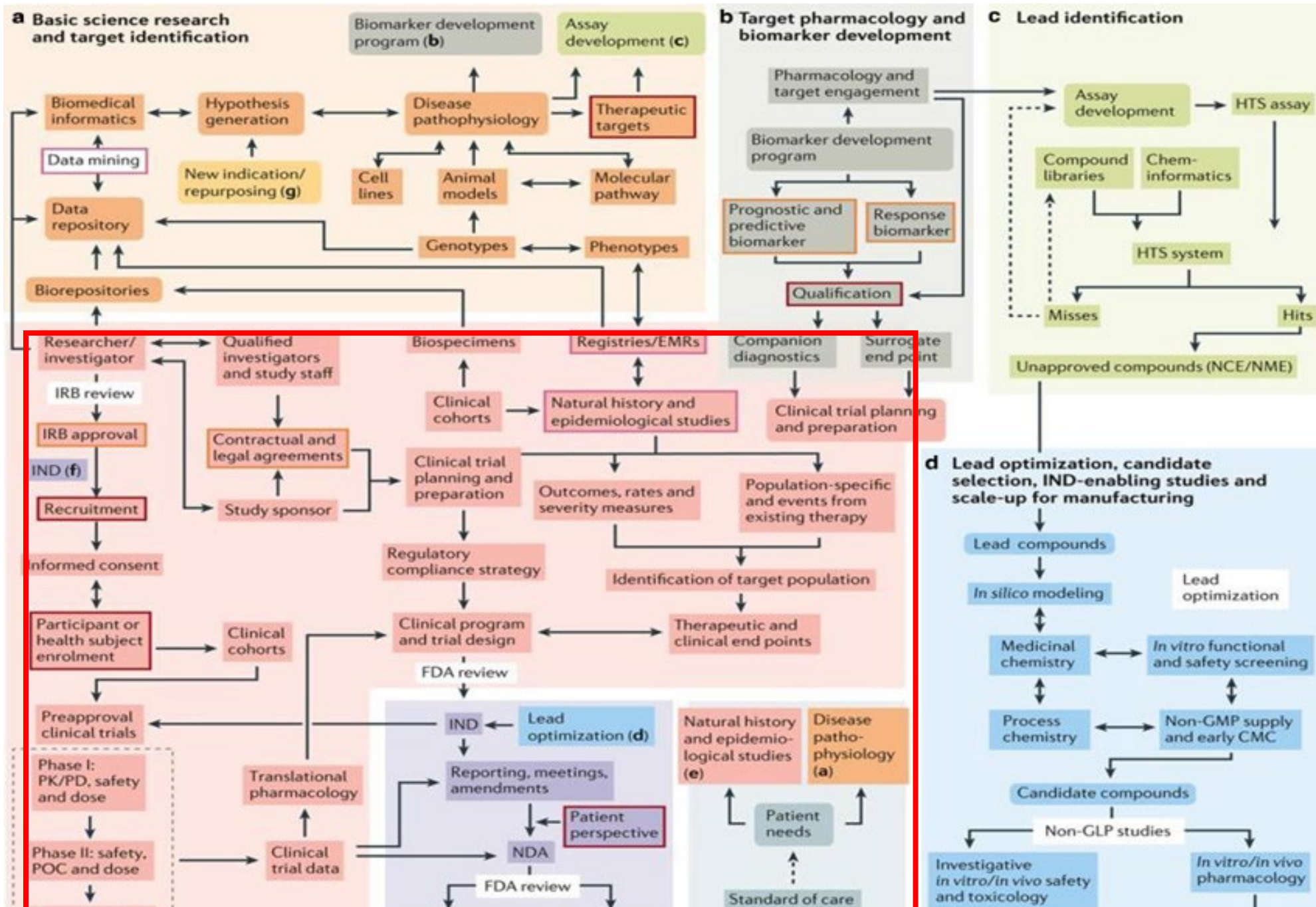
# Exploiting humanized PDX models to study the TME



# Table of contents

1. Inspiration and plan of action
2. Importance of reliable preclinical models
  - Serine metabolism: a novel biomarker and tool for P-res OC?
3. Biomarker development
  - PI3K/mTOR pathway inhibition in uLMS
4. **Value of clinical samples originating from clinical trials**
  - **PAOLA-1 trial: academically laboratory-developed HRD test**





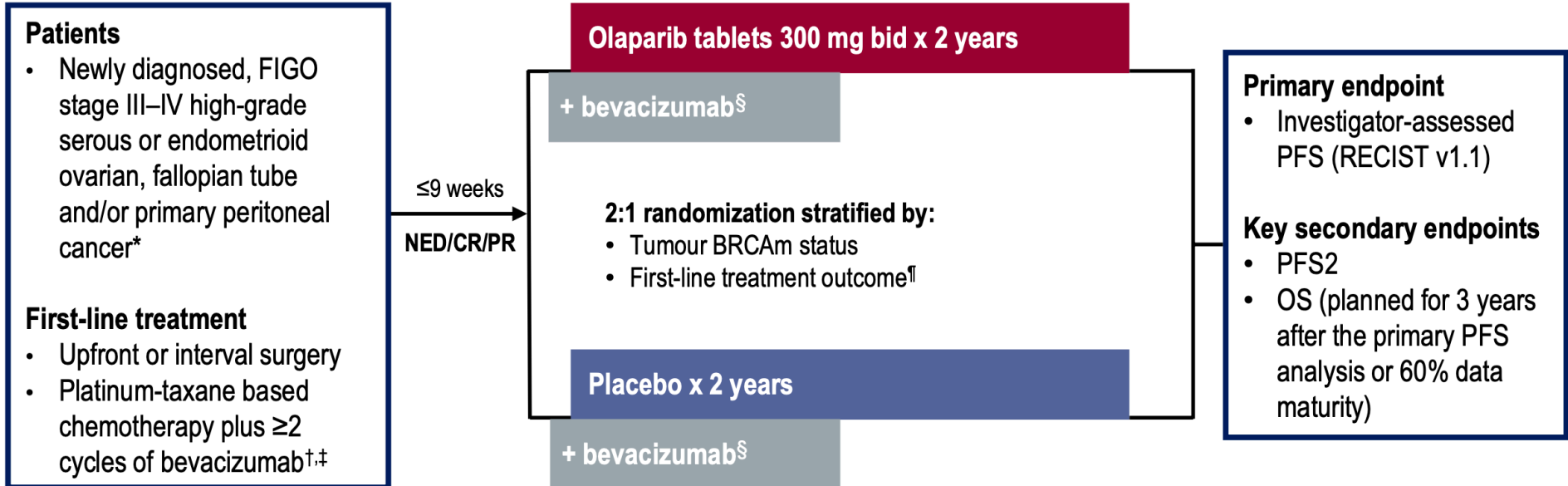
# Advantages of biopsies derived from clinical trial

- Prospective collection
- Cohort with common clinical criteria, cfr inclusion criteria
- Same/Similar/known cancer treatment
- Standardisation re sampling, collection, storage
- Complete baseline clinical data
- Complete follow up data

# PAOLA-1 trial design



FFPE  
biopsy collection  
diagnosis/debulking



\*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a gBRCAm; <sup>‡</sup>Patients must have received  $\geq 4$  and  $\leq 9$  cycles of platinum-based chemotherapy; <sup>§</sup>Patients must have received  $\geq 3$  cycles of bevacizumab with the last 3 cycles of chemotherapy, apart from patients undergoing interval surgery who were permitted to receive only 2 cycles of bevacizumab with the last 3 cycles of chemotherapy; <sup>¶</sup>Bevacizumab 15 mg/kg every 3 weeks for a total of 15 months, including when administered with chemotherapy; <sup>¶</sup>According to timing of surgery and NED/CR/PR. bid, twice daily; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; gBRCAm, germline BRCA mutation; NED, no evidence of disease; PBC, platinum-based chemotherapy; PFS2, time from randomization to second progression or death; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.

# Importance of sufficient tumor tissue collection



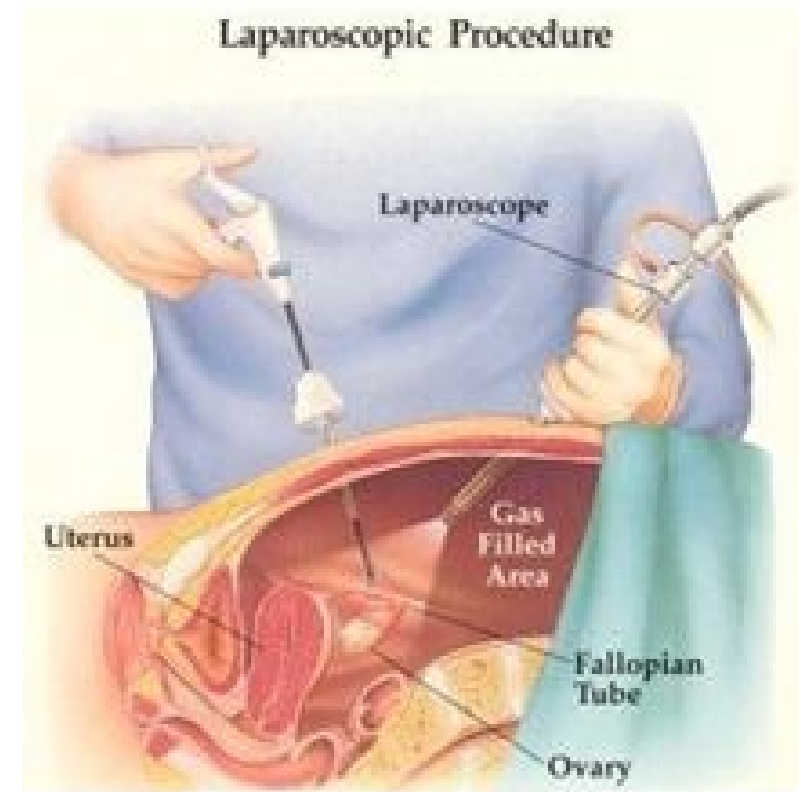
## Myriad MyChoice tissue requirements:

- Tumor > 5x5mm, and
- $\geq 20\%$  tumor cellularity

## FoundationOne CDx:

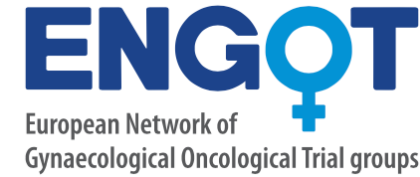
- Minimum 25mm<sup>2</sup> surface area of tumor cells, and
- $\geq 20\%$  tumor cellularity

Sample/test failures



Good biomarkers need to be easily measurable in biological fluids/clinical samples  
But if the sample size is too small → it will increase testfailure rates

ENGOT-Gineco HRD initiative shared FFPE samples from PAOLA-1 for translational research \*



**Goal:** to identify a new, reliable and feasible academic HRD test

**Method:**

All samples were first tested with Myriad myChoice in the scope of the PAOLA-1/ENGOT-ov25 trial.

Remaining FFPE-derived DNA of 468 samples was shared with 6 European academic centers.

**Leuven HRD testing in correlation with PFS in PAOLA-1 trial vs Myriad myChoice PLUS status (“Myriad test”)**

# Leuven HRD test

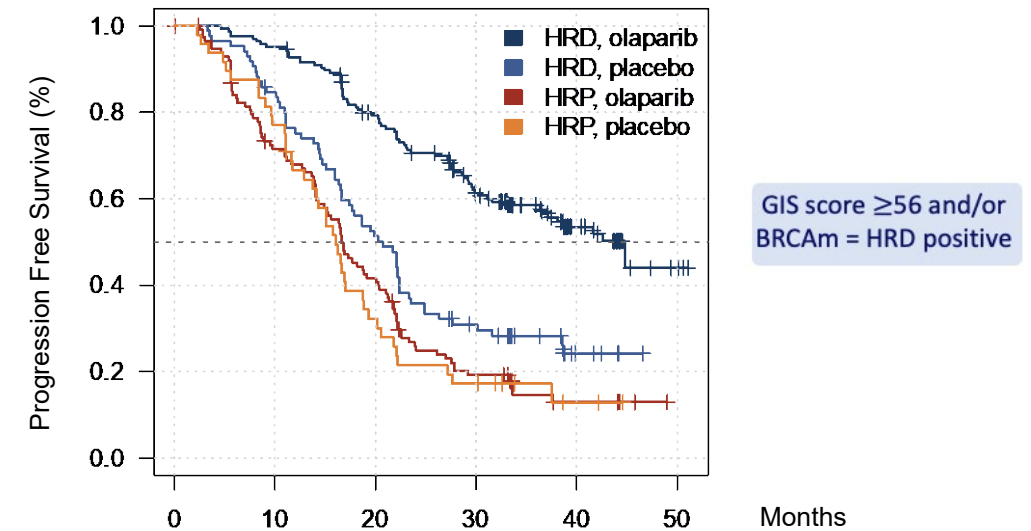
## Academic laboratory-developed HRD test

- Development on biobank ovarian cancer samples
- Based in components: LOH + TAI + LST
- Capture-based probe design for targeted sequencing developed at University Leuven
  - HRD genome-wide SNP panel at 40-100x coverage
  - HRR gene panel incl coding exons for *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*, *BARD1*, *PALB2*, *BLM* and *TP53* at 300-400x coverage
- Paired-end sequencing: Novaseq 2x150

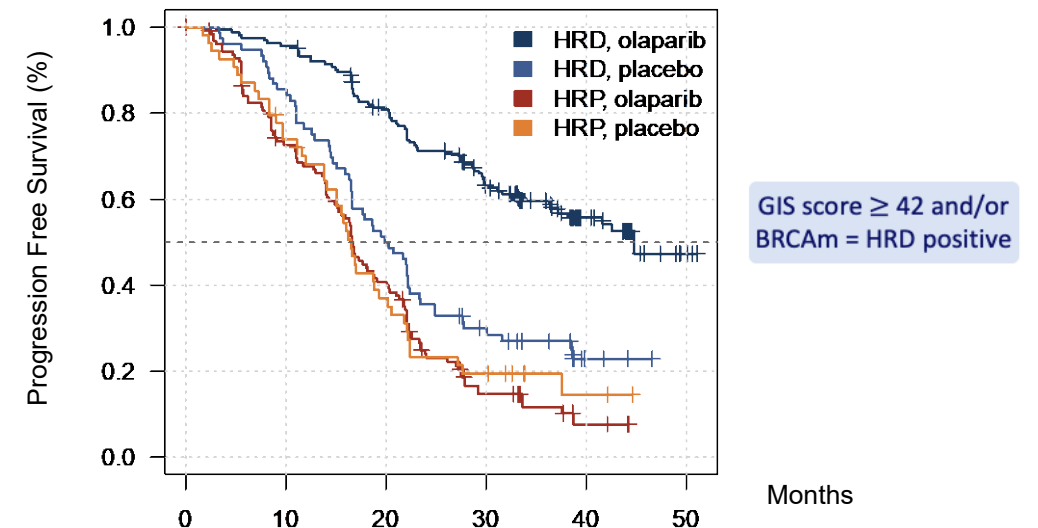
## Results on PAOLA-1 samples ENGOT HRD initiative<sup>1</sup>

- Leuven HRD test showed a similar impact of olaparib on PFS as Myriad myChoice PLUS test
- Subgroup analysis confirmed the PFS benefit with olaparib:
  - In all Leuven HRD positive tumors
  - In all Leuven HRD positive BRCAwt tumors

## Leuven HRD status versus PFS in PAOLA-1 (n=468)



## Myriad myChoice HRD status versus PFS in PAOLA-1 (n=468)



## Snapshots of the ups and downs of graduate life

Free-text comments in *Nature's* survey of graduate researchers worldwide detailed the downsides — and a few of the upsides — of their day-to-day lives at work. Comments have been lightly edited for length and clarity, and, when necessary, translated into English.

We really need to stop running like crazy people to be the first, the best, the one with the most publications. We need to focus again on the true end goal: finding solutions for problems to help people, patients, our world. Stop competing, start collaborating. It's up to us to stand on the barricades!  
*PhD student, Belgium.*

I think the PhD system is exploitive of graduate students. Horrible situations just get swept under the rug. After filing an official complaint regarding harassment, it took more than six months to receive a response that basically said, "We will do nothing as this professor has tenure." What a ridiculous system that is so stacked against students. It is turning bright young scientists

into depressed and anxious people.  
*PhD student, Switzerland.*

The intellectual stimulation and positive impact of my peers are the only reasons I've got through the PhD. Nearly everyone I know has had mental-health issues as a result of their studies. Nobody in power values the process of actually doing good science, only getting high-impact publications.  
*PhD student, United Kingdom.*

Every lab I've ever been in has been terribly managed, with multiple lab members doing nothing or flailing because of lack of attention from senior staff. After seeing what I've seen, I fully think that academic research is broken and needs major overhauls.  
*PhD student, United States.*

I was always interested in pursuing an academic career, but my supervisor killed this desire by expecting far too much, pushing me into burnout last year, and by not supporting me when I got started again.  
*PhD student, Belgium.*

PhD students at my institution take on lots of (non-voluntary, non-paid) mentoring of undergraduates, master's and even younger PhD students. Yet, we are given no training, support or guidance at all. I wish this contribution by PhD students was more widely recognized.





## OVER ONS

### /FILOSOFIE

Planteenbos wil met vrijwilligers lokaal werken aan natuur en milieu door bossen aan te planten die opengesteld zijn voor bezoekers.



### /TEAM



#### STEFANIE ALBERS

Voorzitter Stefanie, 42 jaar, woont in De Pinte. Ze was er vanaf de allereerste brainstorm bij en doet wat voorzitters doen: het overzicht behouden, zorgen dat het vooruit gaat en mensen aan het werk zetten.



#### FRÉDÉRIC AMANT

Frédéric, 53 jaar, woont en werkt in Amsterdam als gynaecoloog-oncoloog. Zijn woorden: 'Natuurbehoud is cruciaal, niet alleen voor de volgende generaties, maar ook voor mijn mentale en fysieke balans.'

**Take home message**  
**the map of TR resembles the map of the human central metabolic pathways**

