IA et Phases Précoces en cancérologie

Modéré par : Marco Fiorini, Christophe Le Tourneau

Avec la participation de : Fabrice André, François-Henry Boissel, Michaël Duruisseaux, Xavier Alacoque, Franck Le Ouay

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Inserm
U981

université
PARIS-SACLAY

Digital Twins

Fabrice ANDRE

Gustave Roussy

Outline

- **Why do we need a switch on cancer classifications ?**
- First illustrations
- Frameworks
- Moving toward Digital Twins
- Issues

Comment

ANNE-CHRISTINE POUJOULAT/AFP/GETTY

Getting access to samples will become increasingly important as approaches for the molecular profiling of tumours improve.

The way we name cancers needs to change

Fabrice André, Elie Rassy, Aurélien Marabelle, Stefan Michiels & Benjamin Besse

Classifying metastatic cancers according to their organ of origin is hampering access to potentially life-saving drugs.

Over the past century, the two main approaches to treating people with cancer – surgery and radiation – have focused on where in the body the tumour is. This has led to medical oncologists and other health-care providers, regulatory agencies, insurance companies, drug firms – and patients – categorizing cancers according to the organ in which the tumour originated. Yet there is a growing disconnect between classifying cancers in this way and developments in precision oncology, which uses the molecular profiling of tumour and immune cells to guide therapies.

More than ten years ago, for example, investigators in the United States showed in a clinical trial that the drug nivolumab could improve outcomes for certain individuals with cancer[1]. In the trial – which included people with different 'types' of cancer (as conventionally defined), from melanoma to kidney cancer – nivolumab shrank some people's tumours by more than 30%, but it had little or no effect on the tumours of others.

Nivolumab targets PD1. This is a receptor of a protein called PD-L1, which helps cancer cells to escape attack from the immune system. Of the 236 trial participants whose tumours could be assessed, 49 responded positively

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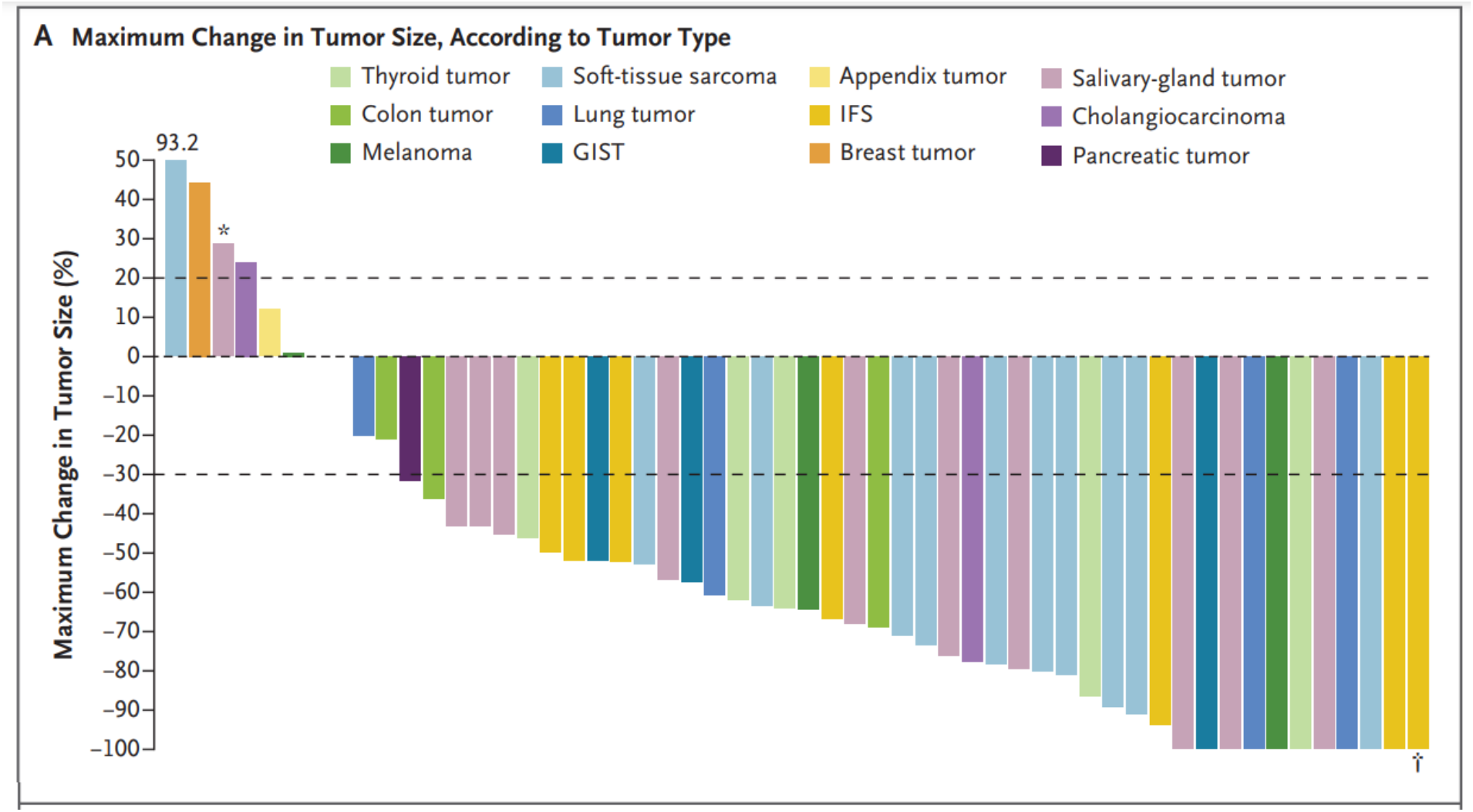
Exemple: larotrectinib in NTRK translocated cancers



Drilon, NEJM, 2018

Tumor agnostic approvals

Table 1. List of tumour-agnostic genomic alterations

Gene/Signature[a]	Alteration	Estimated prevalence (illustration of tumours with high prevalence of the alteration)	ESCAT score	Drug class matched	References
NTRK1/2/3	Fusions	80%-90% secretory breast cancer 15%-20% Spitzoid melanoma	IC	TRK inhibitors	Hong et al., *Lancet Oncol* 2020[2] Demetri et al., *Clin Can Res* 2022[3]
MSI-H/dMMR[a]	MSI-H/dMMR	15%-20% endometrial cancer 15%-20% gastric adenocarcinoma	IC	PD-1 checkpoint inhibitors	Marcus et al., *Clin Can Res* 2019[4]
RET	Fusions	7% thyroid papillary cancer 2% salivary gland cancer	IC	RET inhibitors	Subbiah et al., *Lancet Oncol* 2022[5] Subbiah et al., *Nat Med* 2022[6]
BRAF	Mutations (p.V600E)	40%-45% melanoma 5%-6% small intestinal adenocarcinoma	IC	BRAF inhibitors + MEK inhibitors	Subbiah et al., *Cancer Discov* 2020[7] Salama et al., *J Clin Oncol* 2020[8]
FGFR1/2/3	Fusions Mutations	20%-40% bladder cancer 3% glioblastoma multiforme 10%-20% urothelial carcinoma 10% endometrial cancer	IC	Pan-FGFR TKIs	Pant et al., *Lancet Oncol* 2023[9]
TMB-H[a]	TMB-H	30% neuroendocrine tumours 40% small-cell lung cancer	IC	PD-1/PD-L1 checkpoint inhibitors	Valero et al., *JAMA Oncol* 2021[10] Friedman et al., *Cancer Discov* 2022[11]

Mosele, Ann Oncol, 2024

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HOW COULD A TAXONOMY LOOK LIKE?

TUMOUR -AGNOSTIC

Targeting a driver molecular aberration defines the therapeutic effect, irrespective of tumour-specific biology

TUMOUR -MODULATED

Therapeutic effect on a targeted driver molecular aberration is modulated by the tumour-specific biology

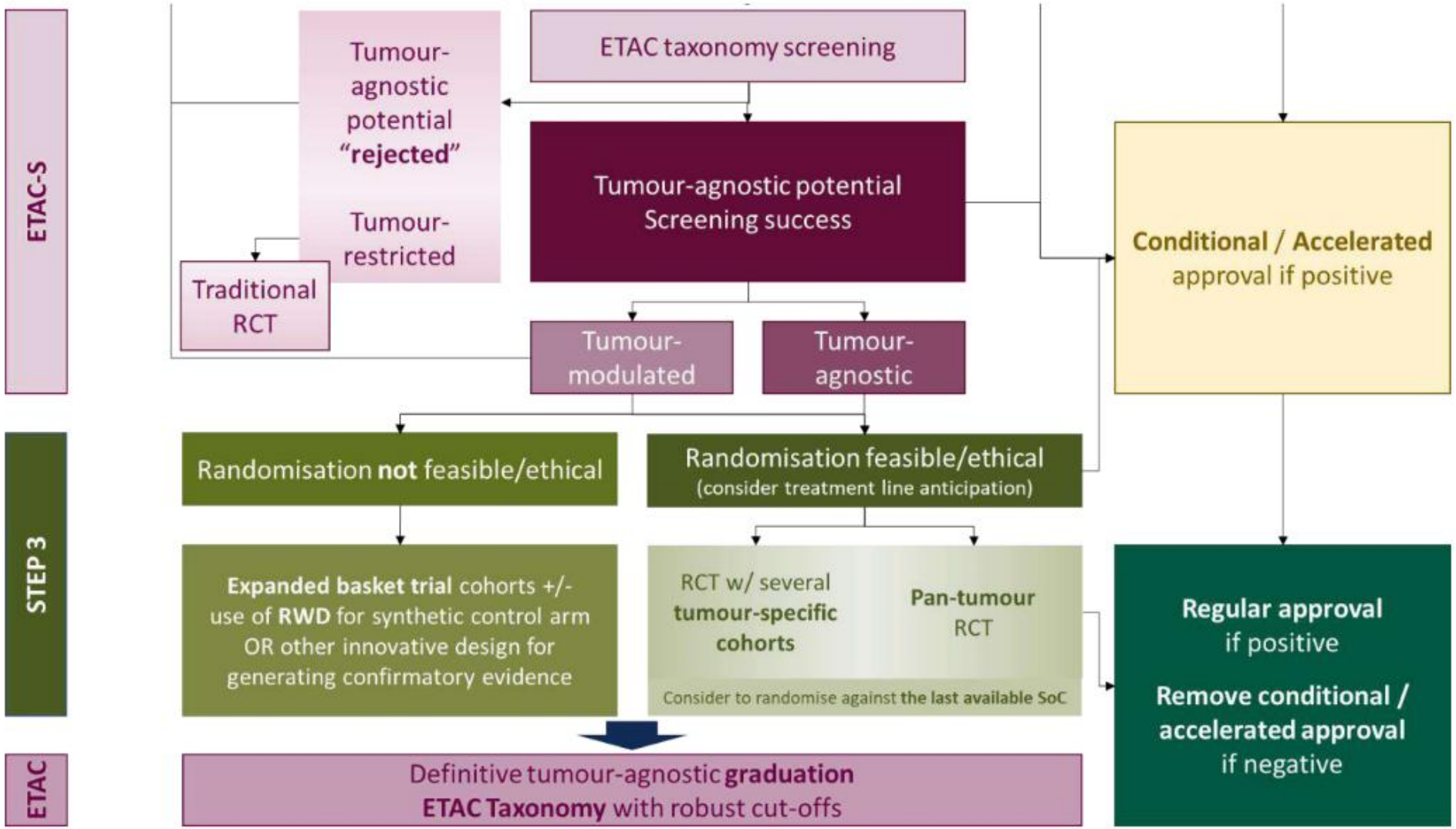
TUMOUR -RESTRICTED

Therapeutic effect on a targeted driver molecular aberration is only present in a tumour-specific biology context

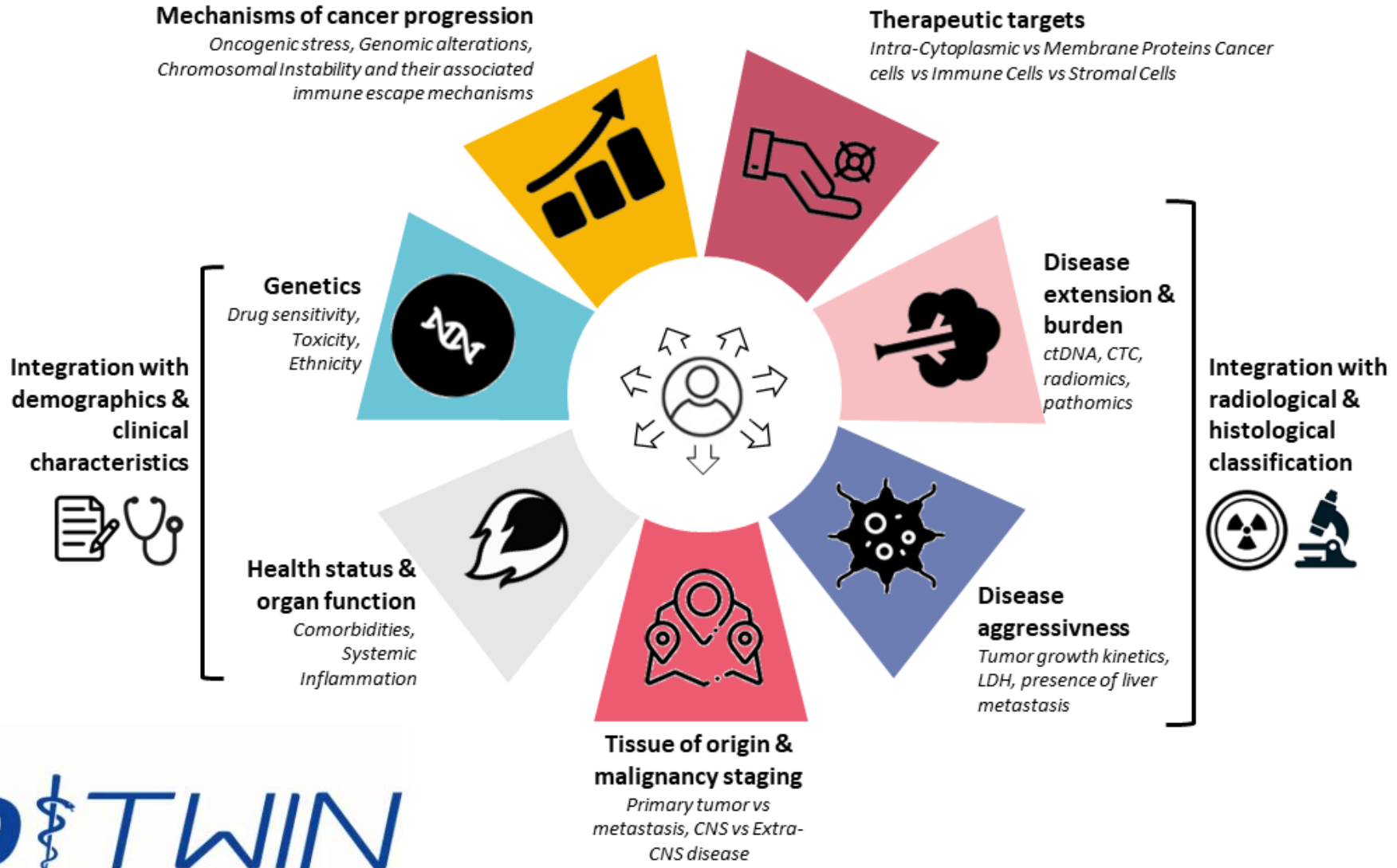
Organ icons are surrogates for tumour-specific biology

▲ High therapeutic effect ▼ Moderate therapeutic effect ▼ No therapeutic effect

SCREENING FOR TISSUE AGNOSTIC POTENTIAL



Moving to personalized, biomarker-based oncology



3DS MEDTWIN

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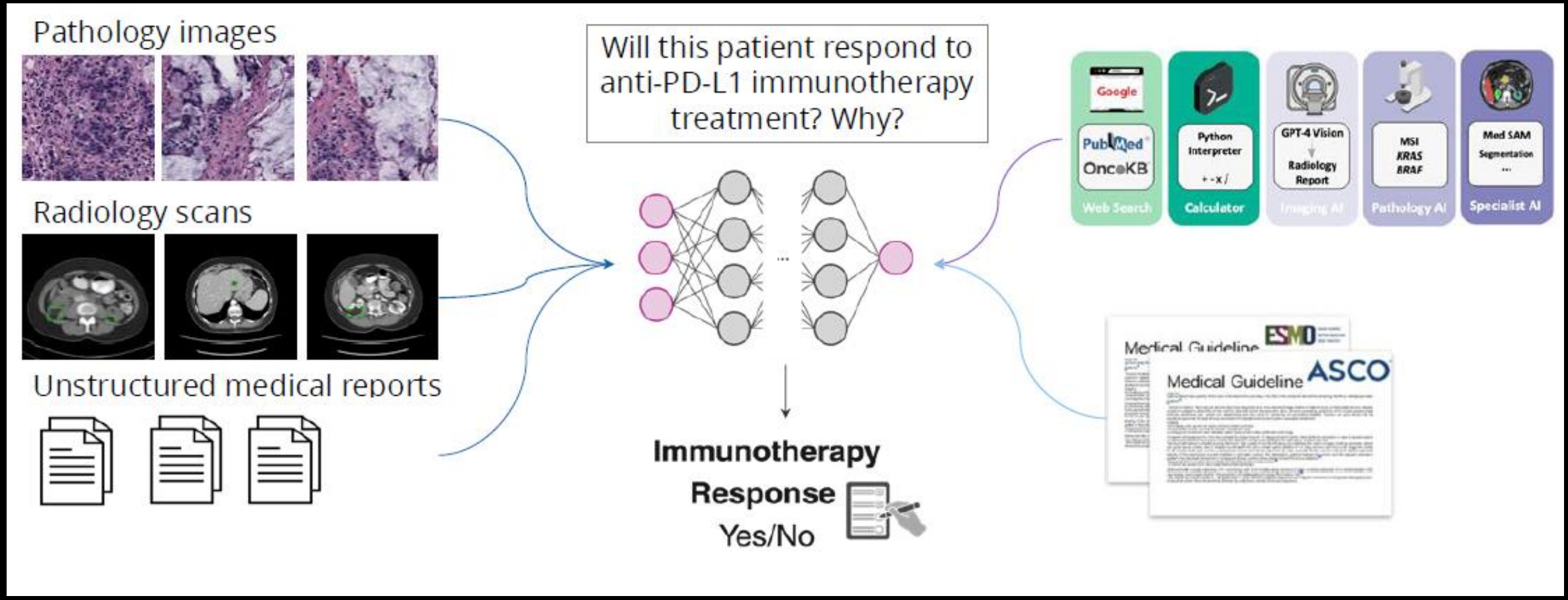
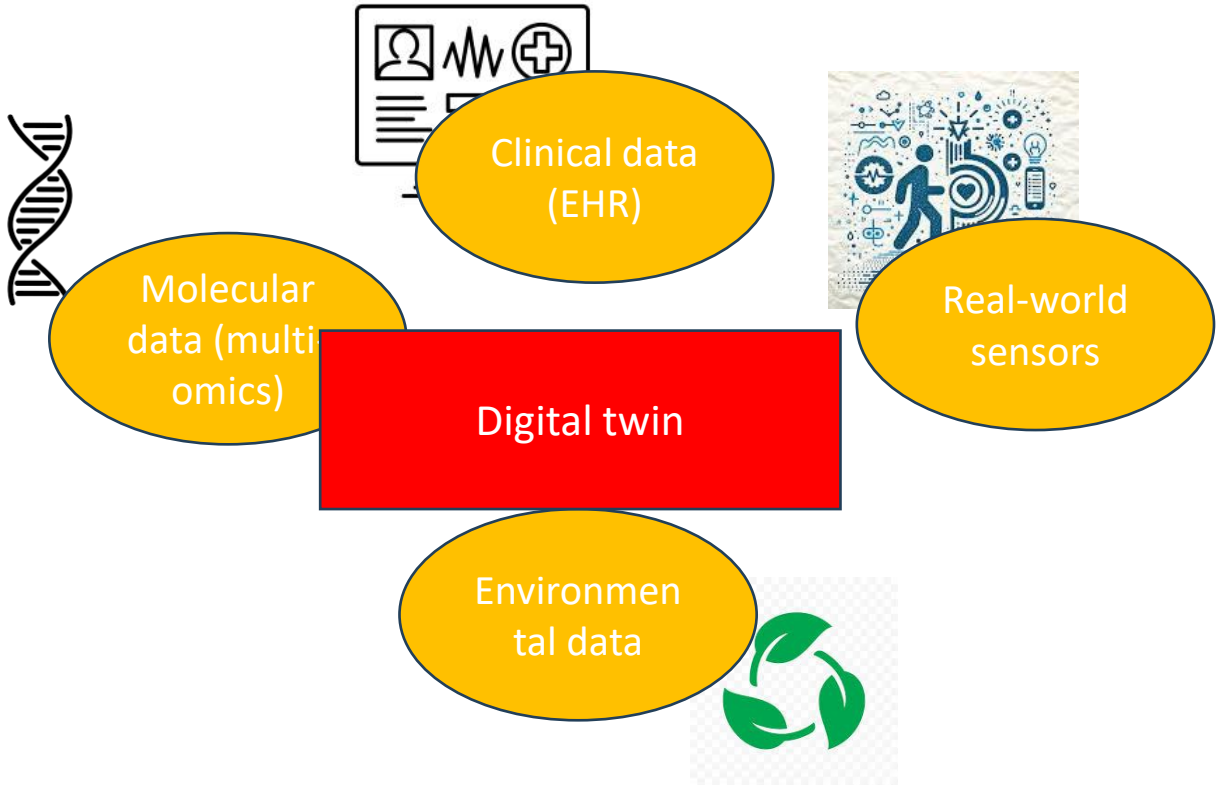
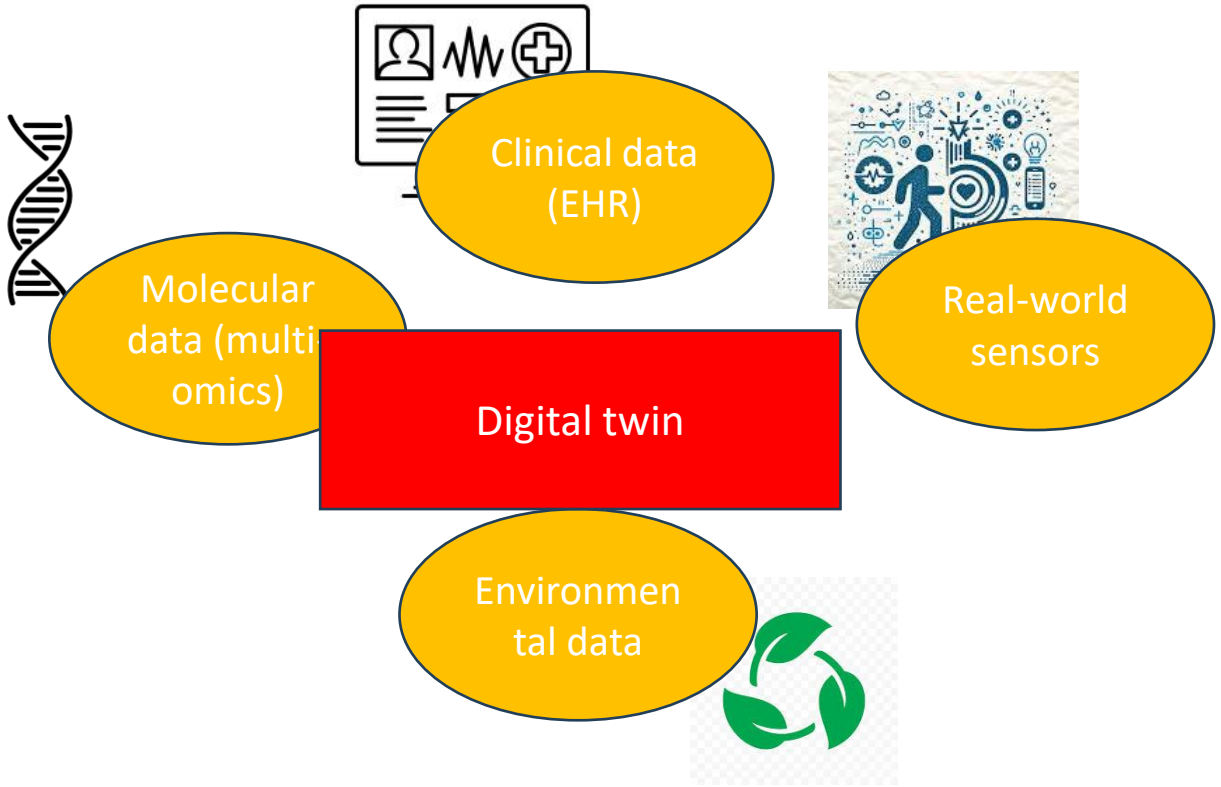
AI AGENTS FOR ONCOLOGY DECISION-MAKING



Jakob Kather
Ferber et al., arXiv (2024)


Clinical data (EHR)
Molecular data (multi omics)
Digital twin
Real-world sensors
Environmen tal data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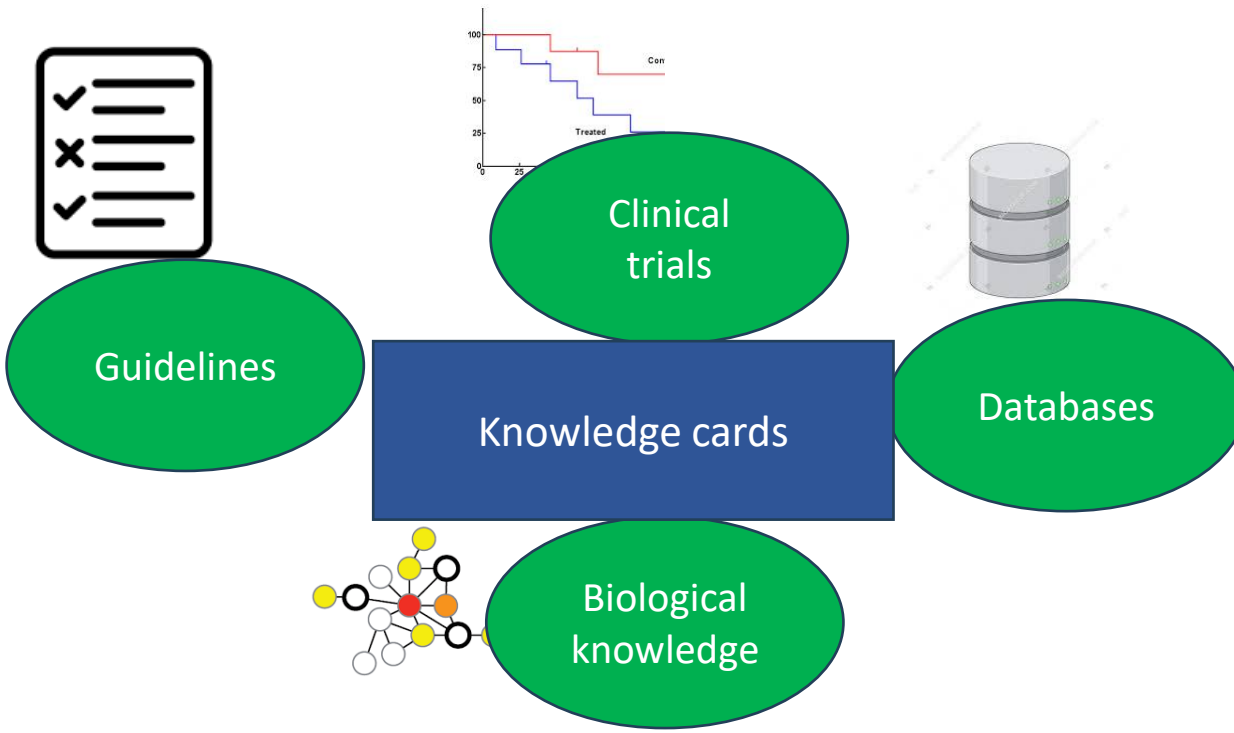
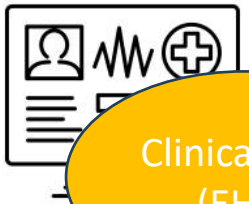

Guidelines
Clinical trials
Knowledge cards
Databases
Biological knowledge

Molecular data (multi omics)



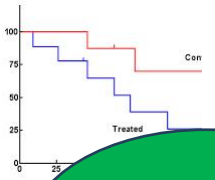
Clinical data (EHR)

Real-world sensors

Environmental data

Digital twin

Guidelines



Clinical trials

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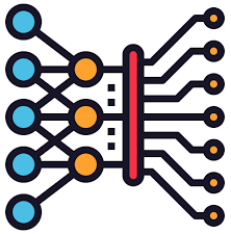


Comment construire des cartes de connaissance ?

Interrogation des cartes de connaissance

A moyen terme, est ce qu'une IA
Pourra predire a partir d'une alteration moléculaire pour laquelle peu de connaissances existent ?

Comment les interroger ?

Exemple simple de système d'interrogation des cartes de connaissance:
ESCAT: ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS

A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

J. Mateo[1], D. Chakravarty[2], R. Dienstmann[1], S. Jezdic[3], A. Gonzalez-Perez[4], N. Lopez-Bigas[4,5], C. K. Y. Ng[6], P. L. Bedard[7], G. Tortora[8,9], J.-Y. Douillard[3], E. M. Van Allen[10], N. Schultz[2], C. Swanton[11], F. André[12*] & L. Pusztai[13]

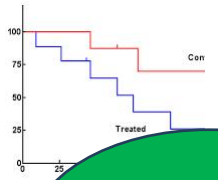
OBJECTIVE: To assist clinicians and patients to prioritize precision medicine strategies more likely to impact positively in patient outcome

Mateo et al, Ann Oncol 2018

Genomic data:

Digital twin

TP53 mutant
FGFR1 amplification
BRCA mutation



OlympiaD….

Clinical trials

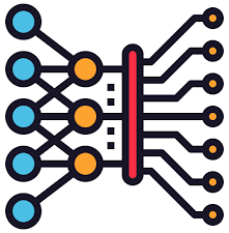
Guidelines

Databases

Knowledge cards

ESMO breast

Biological knowledge



ESCAT

TP53 mutant : NT
FGFR1 amplification: IV
BRCA mutation: I

Treatment:
PARP inh

SCIENTIFIC STRATEGY:

FROM UNIDIMENSIONAL ANALYSES TO COMPREHENSIVE ASSESSMENT OF BIOLOGY IN EACH PATIENT

Uni-dimensional Analyses
using patient samples, molecular profiling, datasciences = knowledge map

Epigenetics | Clonality | Myeloid cells | Natural Killer | Microbiome | Metabolism | Exposure | Persistent Tumor cells

Therapeutic targets + Outcomes predictors for Disease models and Impactful clinical questions

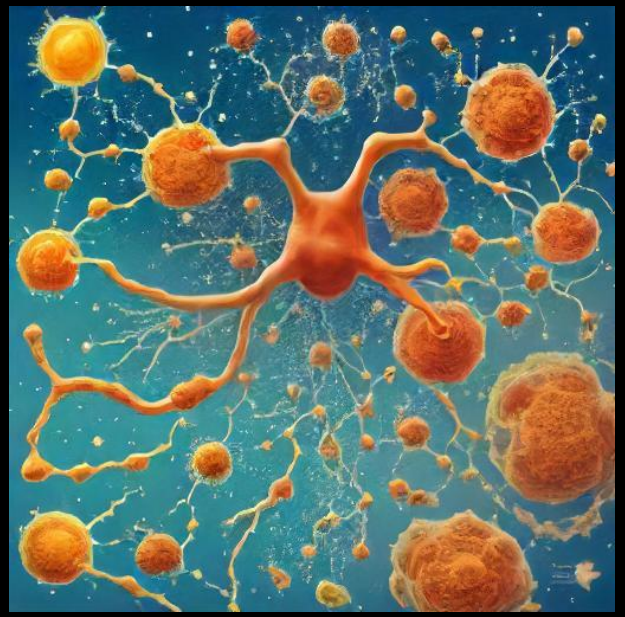
Technologies & Applied mathematics for
comprehensive assessment of biological mechanisms in each patient longitudinally

SOME PERSPECTIVES

Consultation with digital twin

Synthetic data for clinical trials

Insights into biology of cancer



AI-generated images

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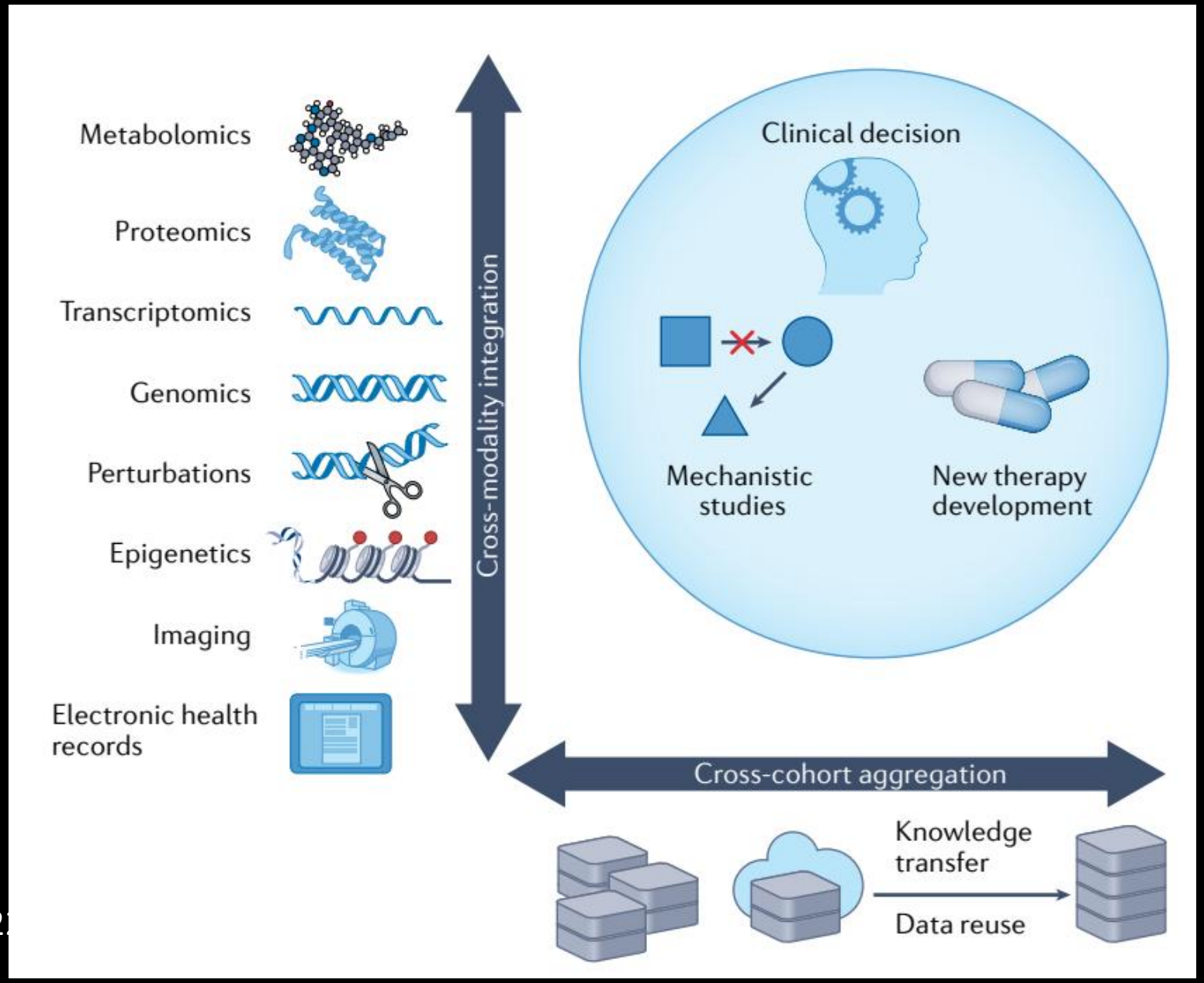
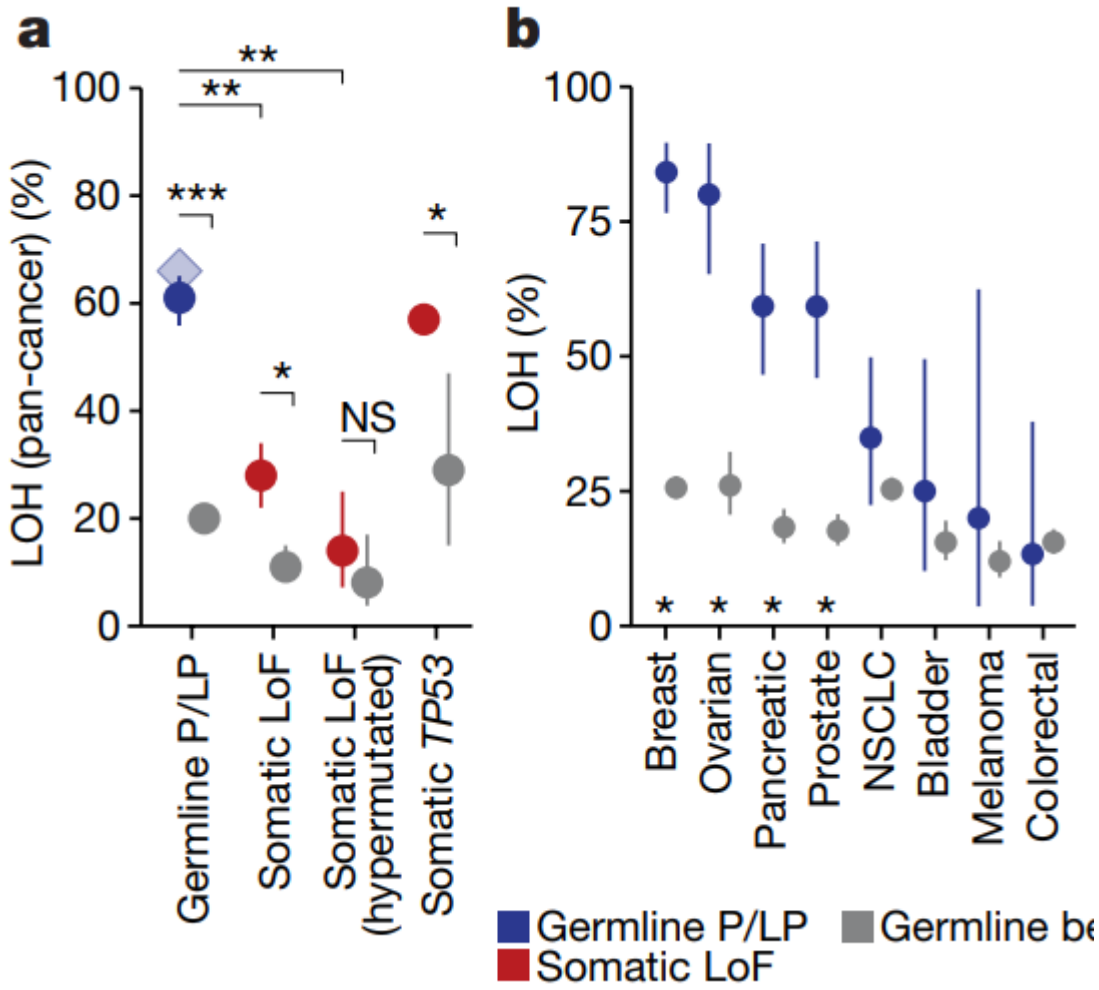
DATA AGGREGATION AND INTEGRATION



Jiang, Nat Rev Cancer, 202

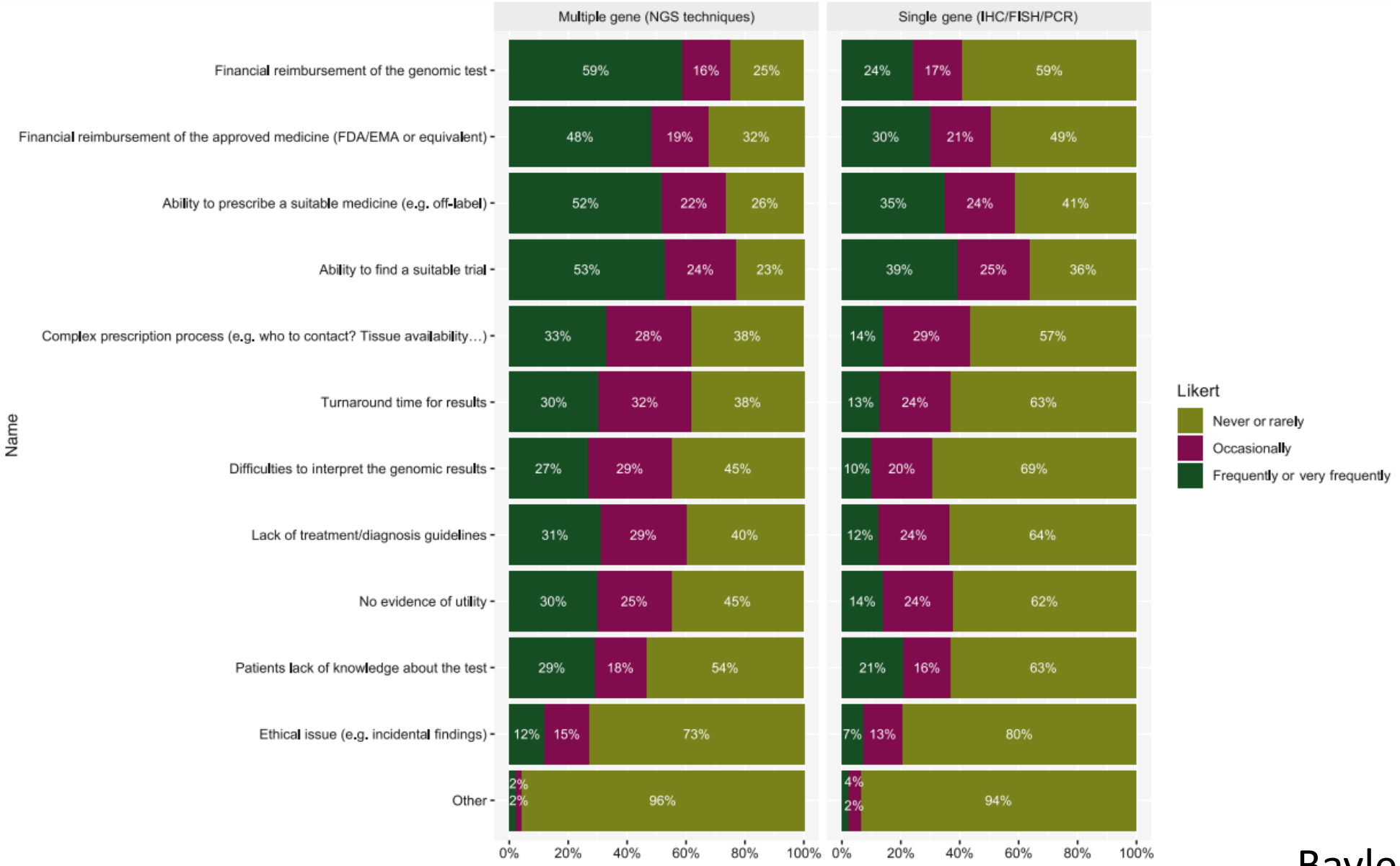
Defining the optimal biological variable, illustration with BRCA



Tumour lineage shapes BRCA-mediated phenotypes

Philip Jonsson[1,2,3], Chaitanya Bandlamudi[1], Michael L. Cheng[4,7], Preethi Srinivasan[5], Shweta S. Chavan[1], Noah D. Friedman[2,3], Ezra Y. Rosen[4], Allison L. Richards[1], Nancy Bouvier[1], S. Duygu Selcuklu[1], Craig M. Bielski[1,2,3], Wassim Abida[4], Diana Mandelker[5], Ozge Birsoy[5], Liying Zhang[5], Ahmet Zehir[5], Mark T. A. Donoghue[1], José Baselga[4,8], Kenneth Offit[4], Howard I. Scher[4], Eileen M. O'Reilly[4], Zsofia K. Stadler[4], Nikolaus Schultz[1,3], Nicholas D. Socci[1], Agnes Viale[1], Marc Ladanyi[2,5], Mark E. Robson[4], David M. Hyman[4,6], Michael F. Berger[1,5,6]*, David B. Solit[1,2,4,6]* & Barry S. Taylor[1,2,3,6]*

Availability of molecular tests



Bayle, Ann Oncol, 2023

Change disease representation

Patient perception of cancer driven by its complexity and including biology

- "I have a *HER2*-positive cancer located in the breast"
- "My tumor is hormone-receptor positive and has a specific mutation called *PIK3CA* and is primary located in the breast" "Both of our cancers are located in the breast but are different tumors!"
- "My cancer responds well to oral therapy; this is why I need to take them everyday and discuss side effects with the care team and seek for available strategies close to home to manage them"
- "I should not compare my history to other because each cancer is unique, and the complexity of each case is different"

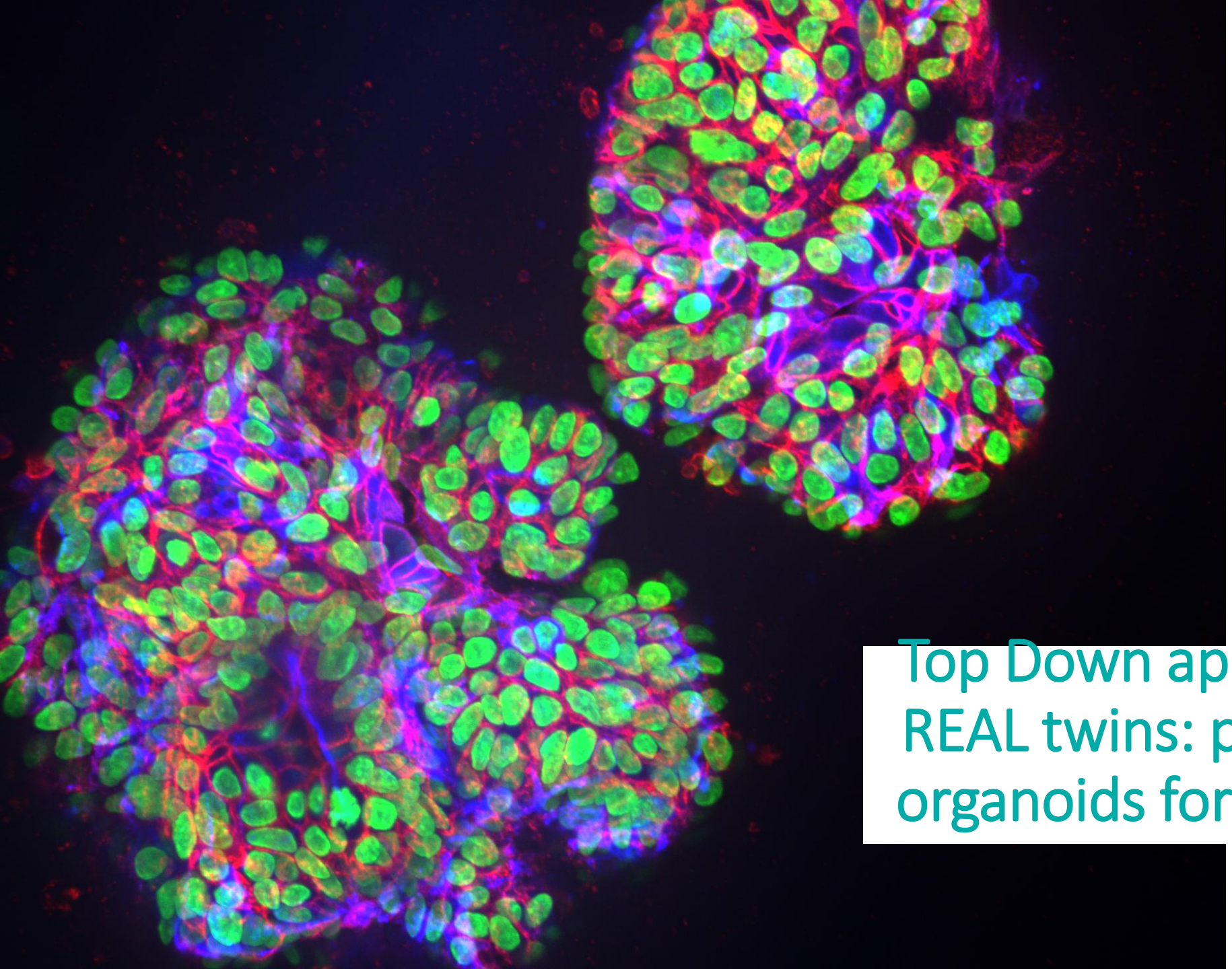
- "My tumor has a specific mutation that does not respond well to usual care. The best treatment for me is a novel clinical trial in a complex cancer center"
- "Oh, I see… Mine although located in the same organ as you has all the characteristics that respond well to standard treatment, this is why I can be treated close to home
- "I discussed with my doctor the pros and cons of the treatment options and which side effects would be acceptable for me in my daily life"

- "We knew that this could happen and allowed us to plan ahead"
- "Yes, and knowing all this allowed us to participate in advocacy and research initiatives, that can also help others facing a similar situation"

Consequences:

- Trust in the healthcare system and research
- Improved research participation and representation
- Rationale use of healthcare resources
- Better adherence to treatment plans
- Increased participation in their care (self-management, shared decision making, advocacy)

Changing cancer representations toward comprehensive portraits to empower patients in their care journey, Franzoi, Ann Oncol, 2023

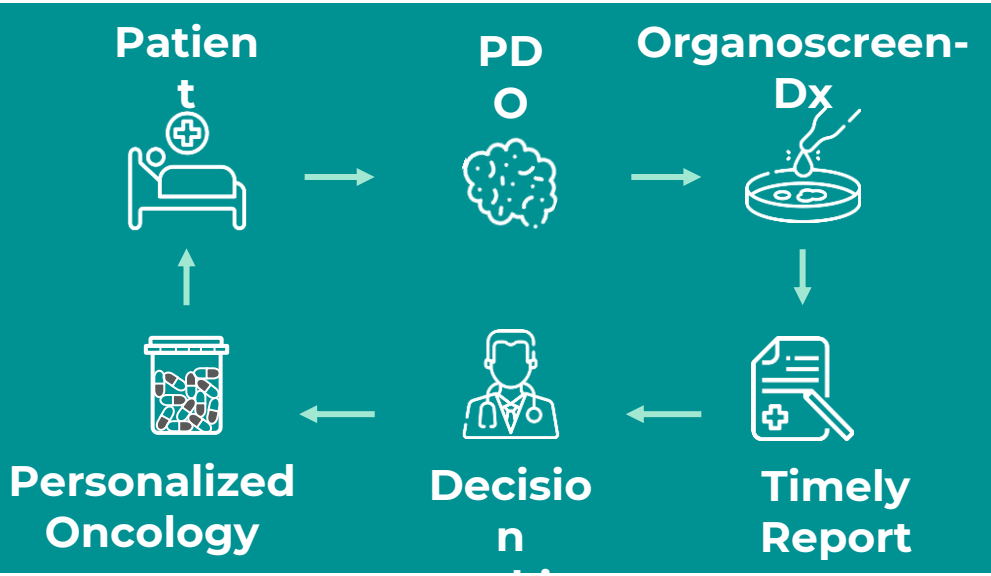


Top Down approacheds and REAL twins: patient-derived organoids for diagnostic use

ORGANOTREAT Clinical trial

	Phase :	Organ :	Patients
ORGANOTREAT-01	I/II	CRC	60 (GMI)
ORGANOTREAT-02R	III	PDAC	314
ORGANOTREAT-02R	III	CRC	582
ORGANOTREAT-02	II	Other	...

PI/Clinic: Pr Michel Ducreux
PI/Scientific: F. Jaulin



Interventional trial

ALL solid tumors, >1000 patients

Acknowledgments

Patients!

Julien Vibert
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Maud Kamal
Daphné Descarpentries
Fanny Jaulin
Alice Boilève
Clara Béchet

Nicolas Pecuchet
Guillaume Lefebvre
Laurent Naudin
Baptiste Demurger

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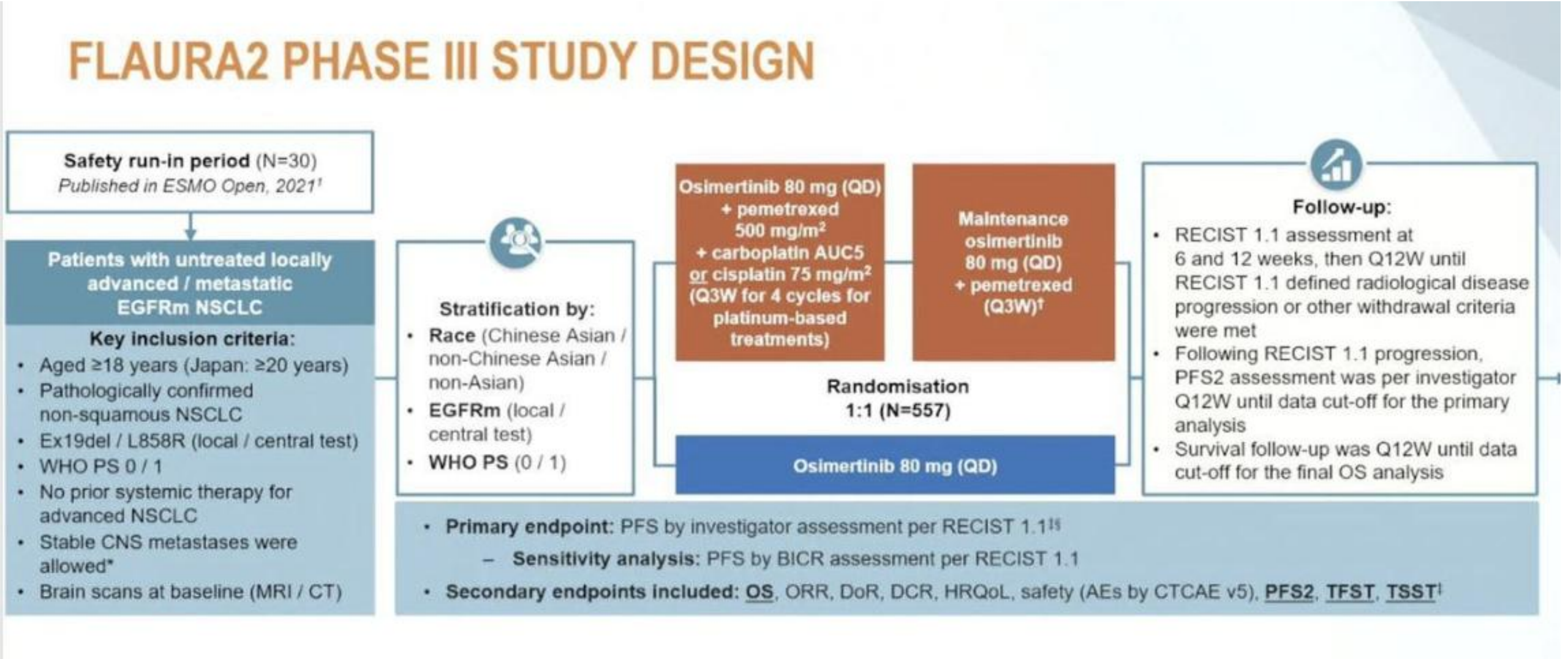
Cas d'étude: essai de phase III FLAURA2 et modèle ISELA2

@MDuruisseaux



Janne et al., WCLC 2023