Preparing the future of Personalised Medicine: EP PerMed - **January 17-18, 2023**

Best practice of overcoming personalised medicine implementation barriers

JTC2019: RAD51predict, Patient stratification based on DNA repair functionality for cancer precision medicine

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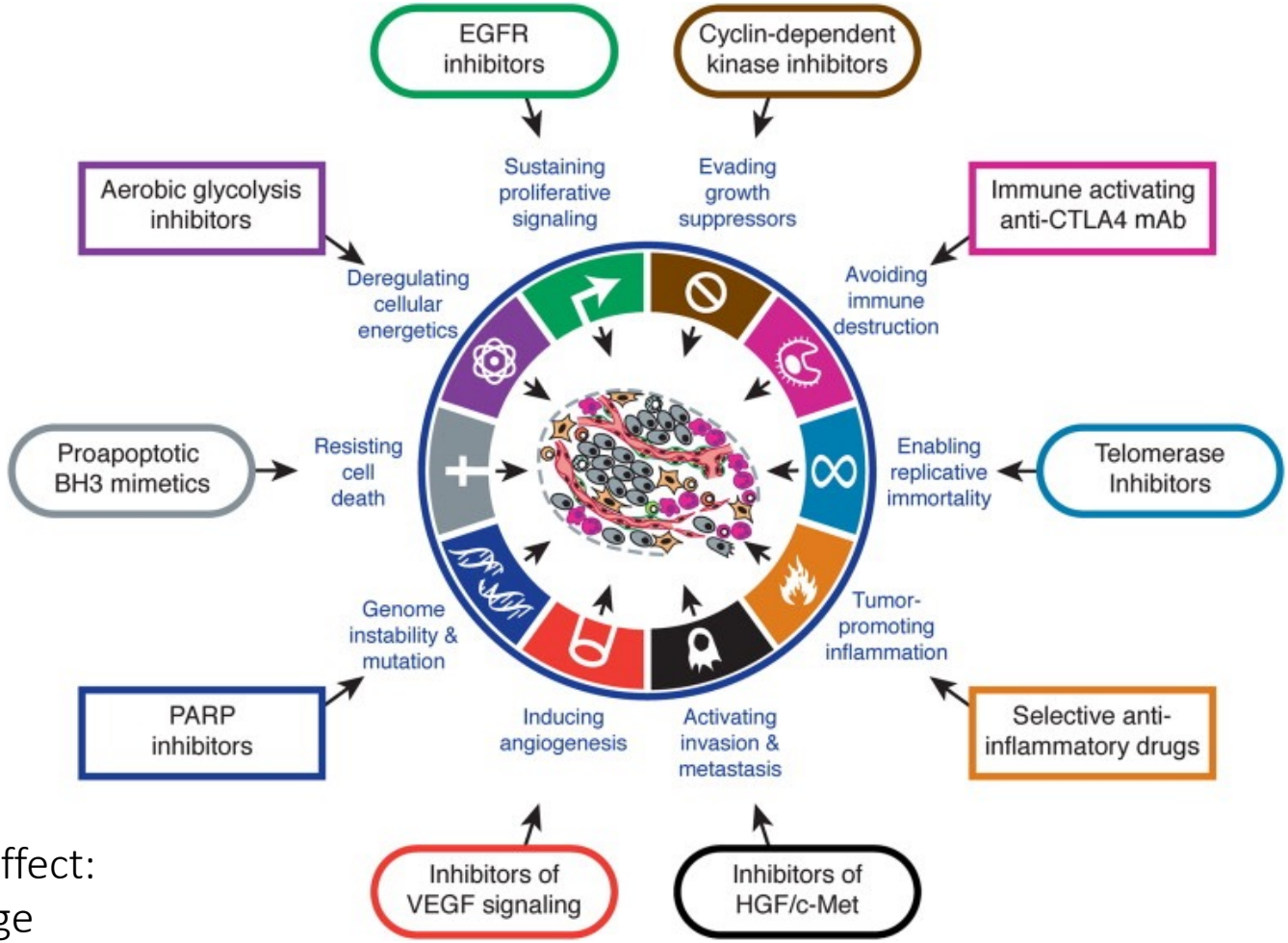
Content

- Background: disease, treatments and biomarkers
- JTC2019 project overview
- Precision Medicine Challenges
- Proposed solutions

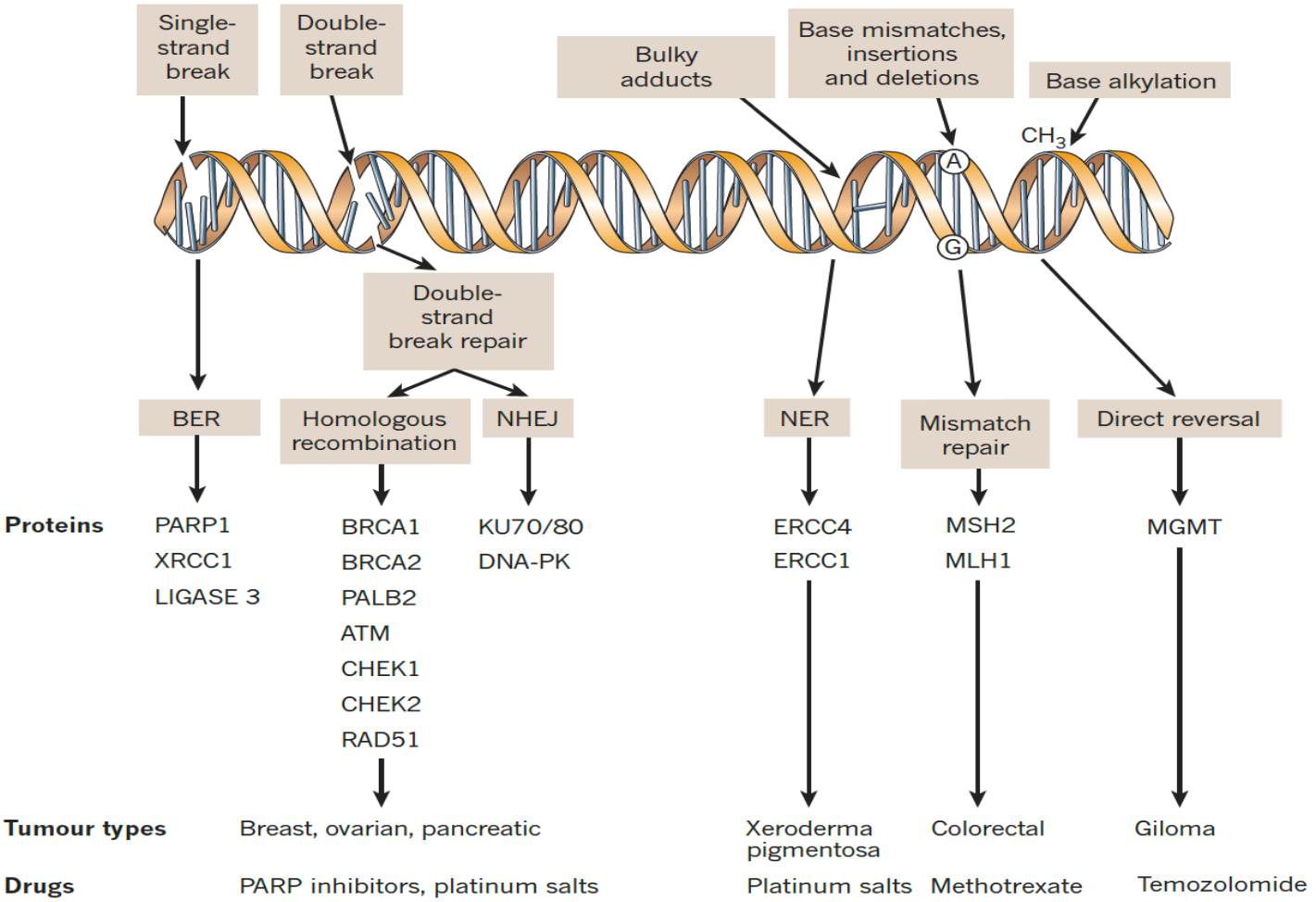
Genomic instability is a hallmark of cancer



Combined effect:
-DNA damage
-DNA repair defects
-failure to stop cell cycle

Hanahan & Weinberg, *Cell* 2011

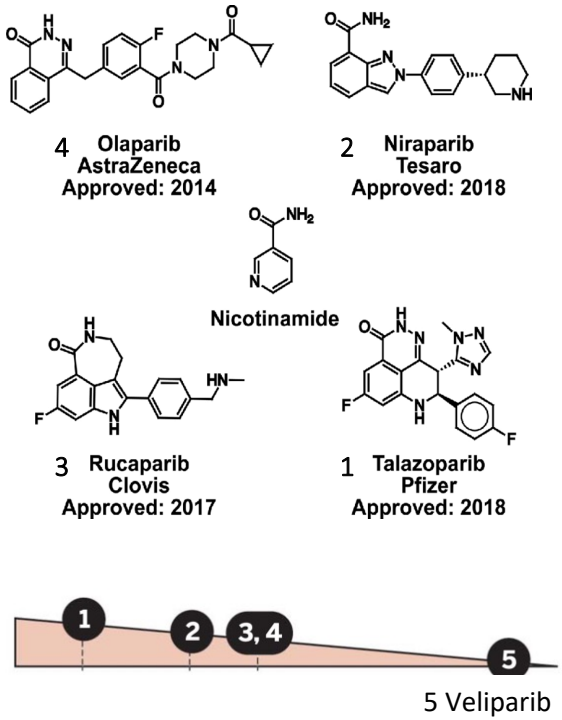
DNA repair deficiency in cancer



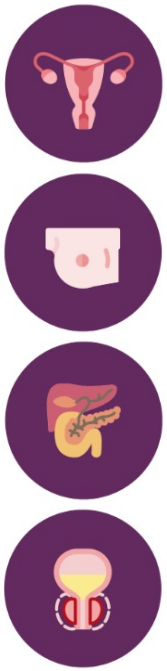
Lord & Ashworth, *Nature* 2012

PARPi and biomarkers

Approved PARPi

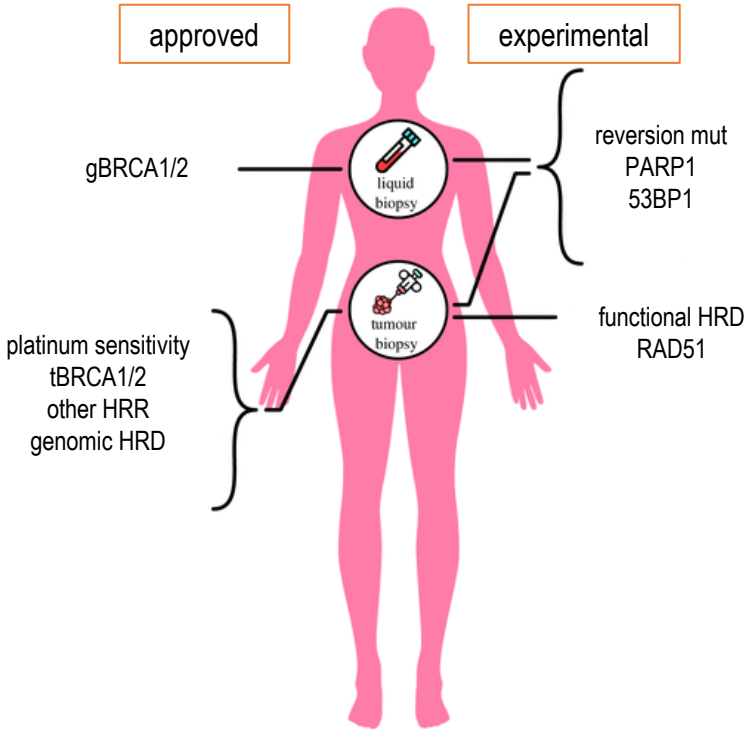


Cancer types



Monotherapy
Maintenance

Biomarkers for PARPi



Spiegel et al, DNA Repair. 2021
Adapted from Lord & Ashworth, Science 2017
Adapted from Wicks et al, Open Biol. 2022

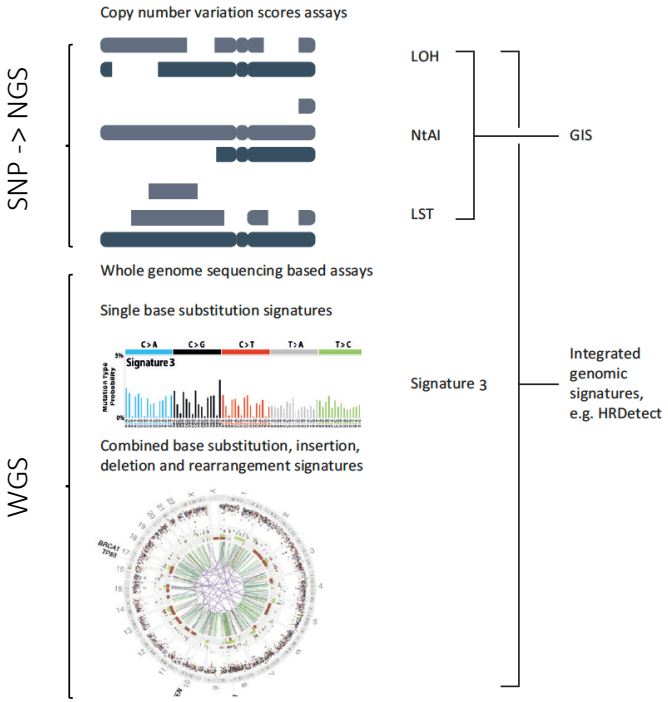
gBRCA1/2, germline BRCA1/2; tBRCA1/2, tumor BRCA1/2; HRR, homologous recombination repair; HRD, homologous recombination deficiency

PARPi and biomarkers

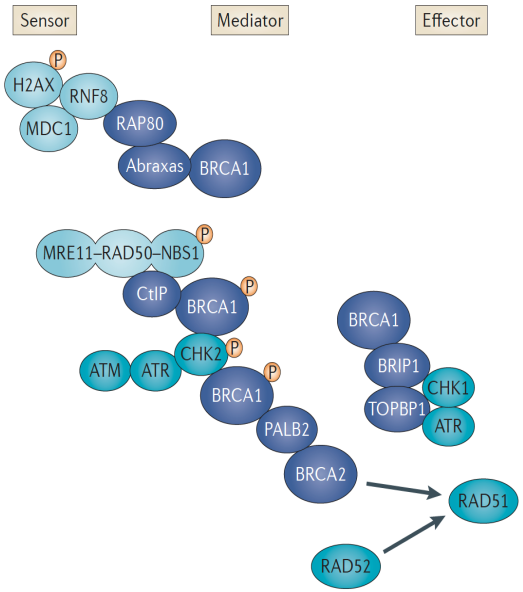
Cause of HRD
HRR-gene alterations

BRCA1	*FANCL*
BRCA2	*FANCN/PALB2*
ATM	*BARD1*
RAD51B	*CHEK1*
RAD51C	*CHEK2*
RAD51D	*CDK12*
RAD54L	*PPP2R2A*
FANCJ/BRIP1	

Consequence of HRD
Genomic scars



Current status of HRD
Functional tests



HRR, homologous recombination repair;
SNP (arrays), single nucleotide polymorphism (array);
NGS, next generation sequencing;
WGS, whole genome sequencing

Static

Dynamic

Adapted from Miller et al, Annals of Oncology 2020

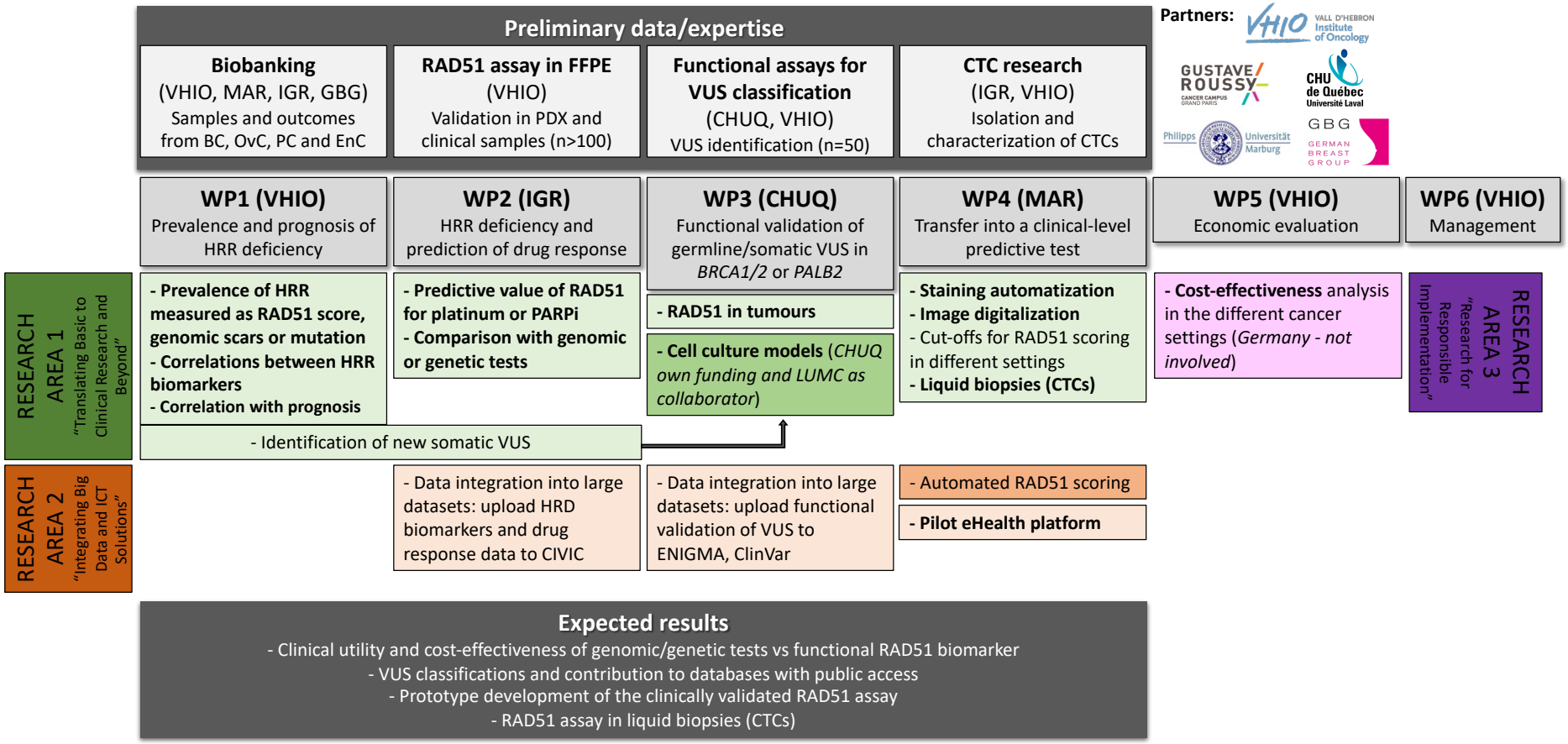
Project overview

Advance the development and clinical validation of RAD51predict as a diagnostic test to personalize anti-cancer treatment

In the present proposal, we aim to:

1) Establish the **prevalence of functional HRR deficiency (HRD)** and its **prognostic and predictive values** for personalized treatment with platinum salts and PARPi in BC, OvC, PC and EnC, using the RAD51 immuno-assay and genomic assays
2) Perform an **economic evaluation** of selecting patients for PARPi treatment based on the RAD51 assay, genomic assays, or the current selection criteria
3) Provide **functional validation of germline/somatic genetic variants of unknown significance (VUS)** using patient´s data, cell lines and assessment of HRR markers in the tumour
4) Integrate functional HRD data into existing **public genomic databases**
5) Transfer the **RAD51 assay** into a clinical-level test: development of multiplexed protocols, automatization of image analysis, and real-time monitoring in circulating tumour cells (CTCs)

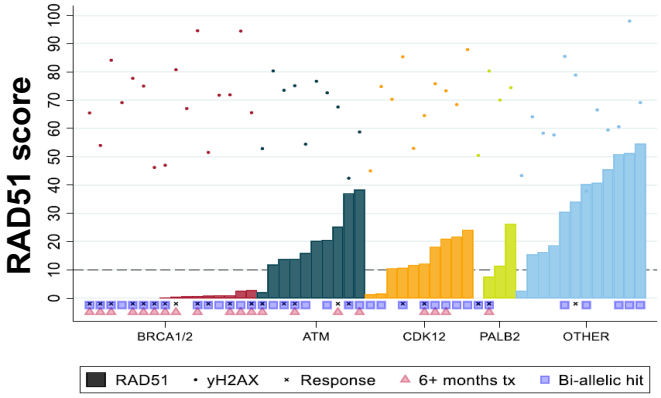
Scientific Work Packages



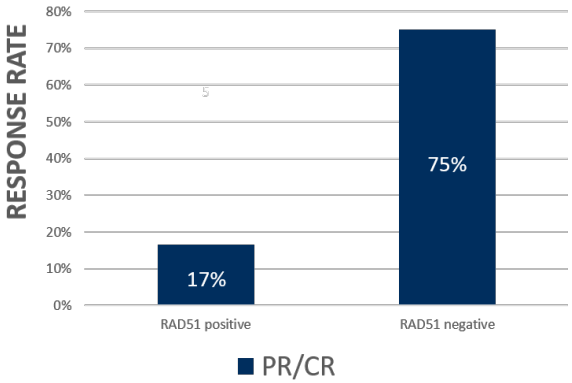
Scientific Outcomes

WP1 (VHIO)	WP2 (IGR)
Prevalence and prognosis of HRR deficiency	HRR deficiency and prediction of drug response

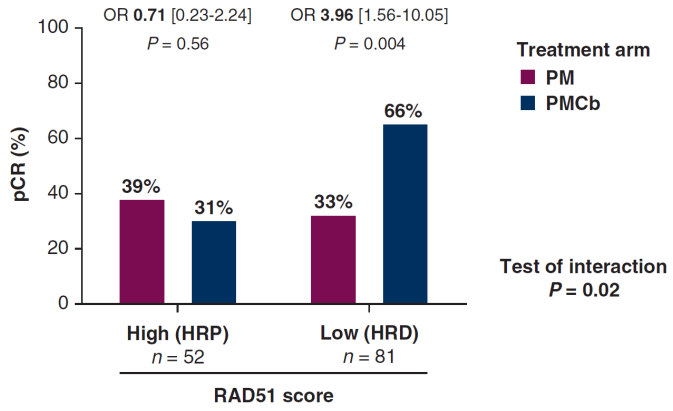
High concordance of RAD51 with biallelic mutations in mCRPC (*Can Disc* 2021)

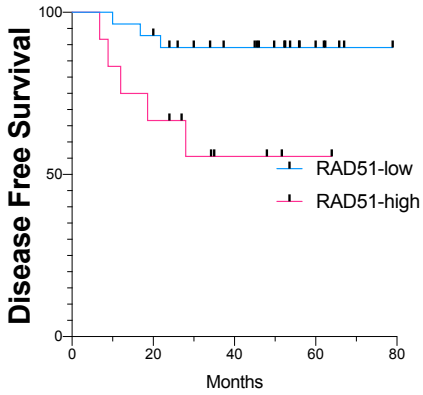


High response rate in HGSOC with BRCA1/2 mutation and HRD by RAD51 (*under review*)



In TNBC, RAD51 score predicts platinum response and DFS independently of pCR (*Annals of Onc* 2022 and ESMO 2022)

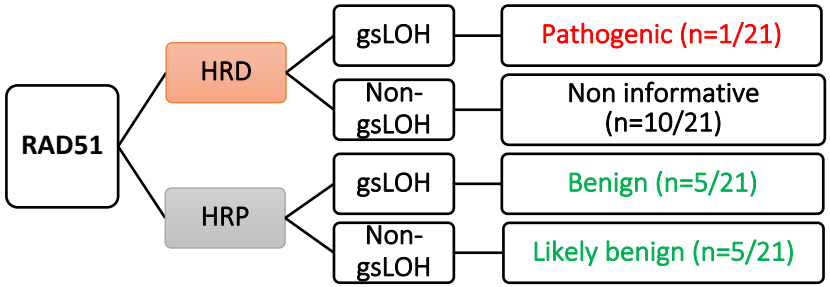




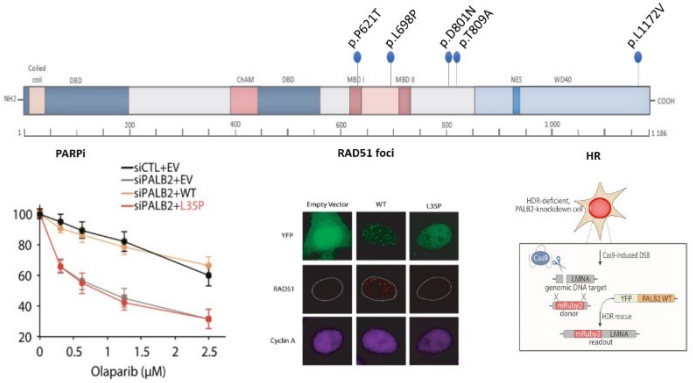
Scientific Outcomes

WP3 (CHUQ)

Functional validation of germline/somatic VUS in *BRCA1/2* or *PALB2*



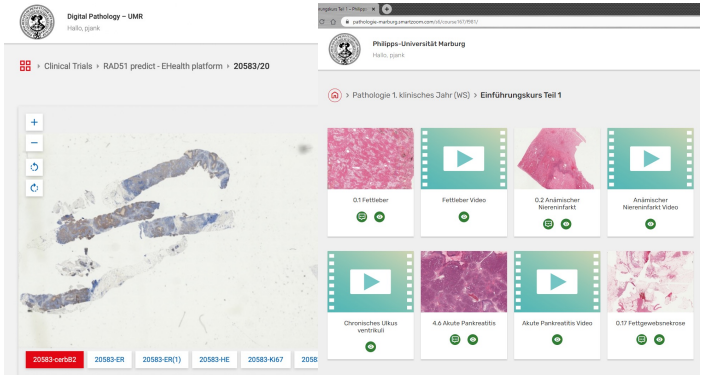
Knock-down PALB2 in Hela cells complemented with PALB2 VUS



WP4 (MAR)

Transfer into a clinical-level predictive test

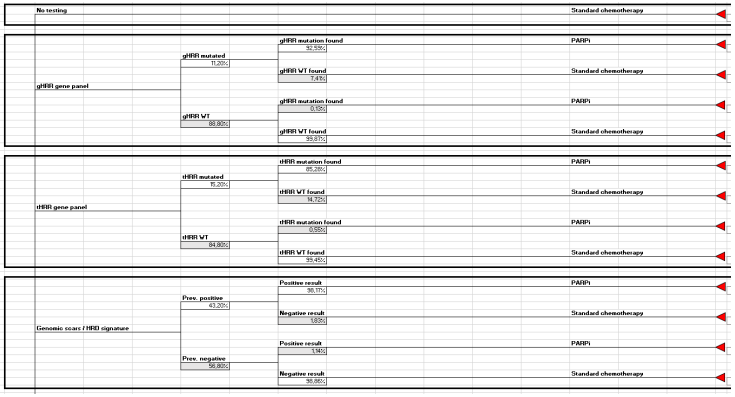
eHealth and learning platform



WP5 (VHIO)

Economic evaluation

Decision tree and model inputs



Personalised Medicine Challenges (diagnostic)

Technical

- Development of lab-based test beyond standard techniques
- Data collection, storage, sharing, and integration with health records

Level of evidence

- Preclinical validation
- Retrospective and prospective clinical trials

Economic

- Development of diagnostic-level / commercial test
- Prospective clinical trials (cost of drugs)

Regulatory

- Need of high-level expertise
- EU-IVD regulation

Social

- Incorporating biomarker information into clinical care
- Cost of the assays and drugs

Technical

Challenge	Solution
Immunofluorescence requiring specific microscope settings that are not available in routing diagnostic laboratories	centralised test in trained centers interlaboratory validation
Optimising the test from solid tumour to liquid biopsies (CTCs)	develop new protocols
Manual vs automated scoring	digital pathology
Histology-based assay in the era of genomics	provide comparative results to genomic biomarkers
Data storage and sharing: research vs local hospital vs international partners	different data storage structures

Level of evidence

Challenge	Solution
Preclinical evidence recapitulating cancer heterogeneity	patient-derived models (n>100)
Demonstrating clinical evidence	access to clinical cohorts with annotated outcome (clinical trials)
Design of prospective clinical trials	team up with cooperative groups and pharma

Economic

Challenge	Solution
High cost of biomarker validation with prospective clinical trials	team up with pharma
High cost of development of a diagnostic-level / commercial test	strong IP
	license to a diagnostic company
	support from an interested pharma company
	spin-off with venture capital

Regulatory

Challenge	Solution
Need of high-level expertise EU-IVD regulation	Include experts and training in the project

Social

Challenge	Solution
Economic analysis: lack of real-world clinical evidence	Add data from prospective trials

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Questions?