Project Title

Developing clinic-omic surrogates for BRCAness and TP53 function to guide targeted therapeutic approaches in ovarian cancer

Names & Affiliation of Investigators:

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KolGOTrg
Kolkata Gynaecological Oncology Trials and Translational Research Group

Origin of Proposal

Ovarian cancer (OC):

- 3rd most common women's cancer in India (increasing:36,000/year with 30,000 deaths)
- Deadliest (75% recur, 30% survive 5 years)
- Costliest treatment
- 95% of HGSOC have p53 mutation: however, LOF or GOF mutation is predictor of survival (PI)

PARP inhibitors (PARPi): Single most important invention in targeted therapy in causing significant prolongation of survival in ovarian cancer both in frontline and recurrent settings as adjuvant/maintenance therapy (PI)
PARPi therapy costly: $\backsim 7000\ \mathrm{GBP/month}$

Homologous recombination deficient (HRD) cancers: PARP inhibitors work best in cancers with HRD **(also known as BRCAness**) due to synthetic lethality. 50% OCs are HRD: they are mostly platinum sensitive as well (PI)

Biomarker: Better **HRD assay**/biomarker stratification required to identify true responders to PARPi and justify cost-effectiveness/toxicity when resources are limited

Overarching Aim:

Develop a more precise biomarker strategy to predict true responders to PARP inhibitor therapy

Aim 1. Developing a clinic-omics surrogate for BRCAness (HRD)- Compare/combine Functional vs genomic and radiological approaches

Aim 2. Developing strategies to study p53 LOF/GOF and correlation with BRCAness

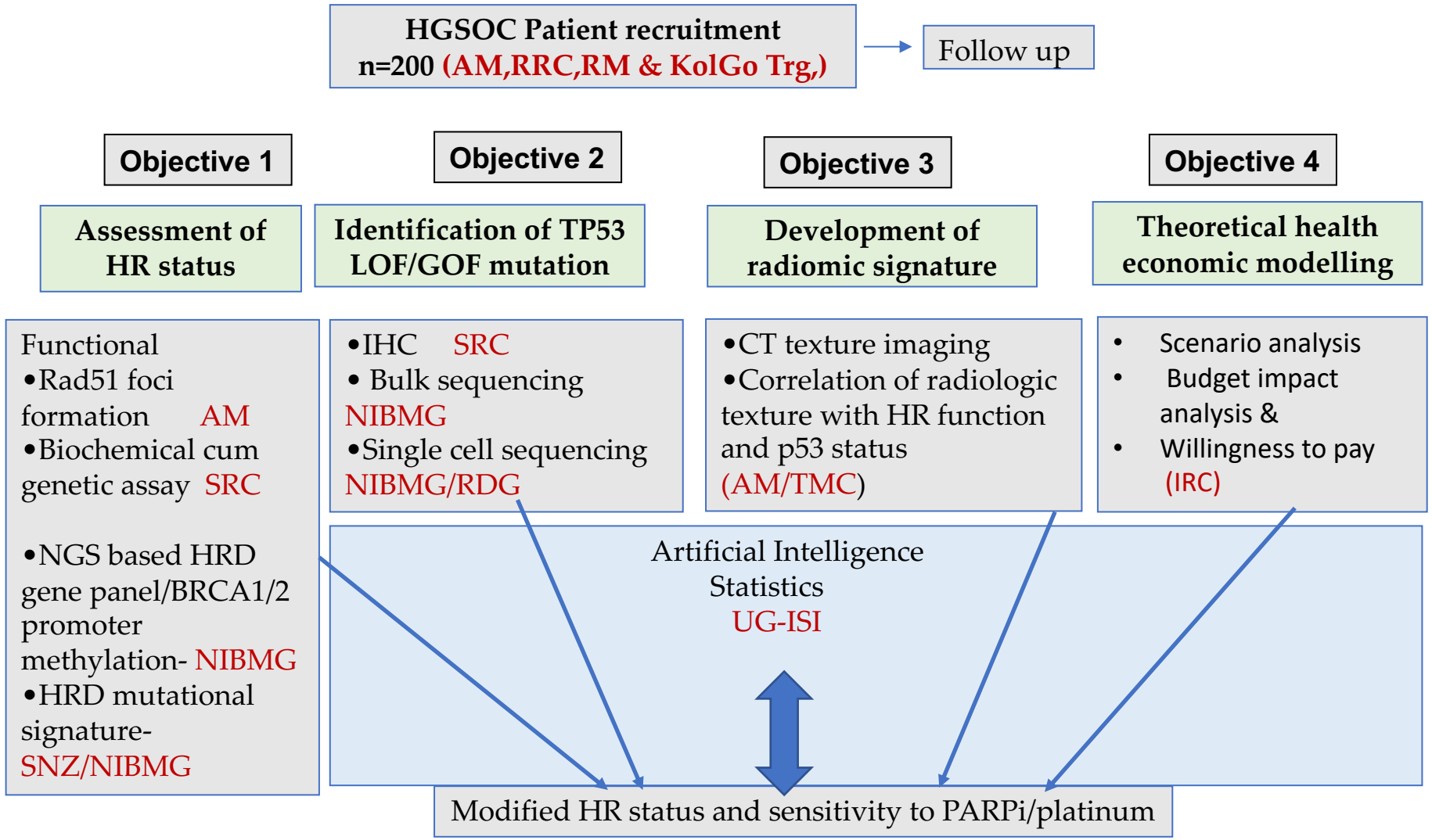
Aim3. Statistical modelling: Artificial intelligence (AI) based computational modelling of radiomics/genomics/functional(imaging) biomarker data and correlating with clinical observation

Aim 4. Health economic analysis based on Scenario analysis, budget impact analysis, and Valuation of health through willingness to pay (WTP) for predicted PARP inhibitor and platinum response in biological subgroups:

- HRD-p53 LOF
- HRD-p53 GOF
- HRC-p53 LOF
- HRC-p53 GOF

Question

The most pertinent question is how one can accurately stratify HGSOC patients based on homologous recombination repair and TP53 mutational status for precise and cost-effective treatment options and outcomes (response to platinum-based therapy or PARP inhibitors)



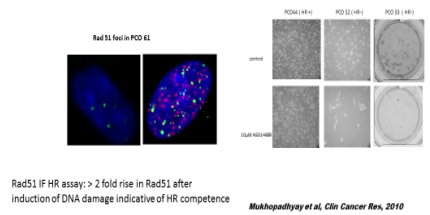
Aim 1. Developing a clinic-omics surrogate for BRCAness (HRD): Previous and ongoing work: Bench → Clinic → Bench

Compare/combine Functional vs genomic and radiological approaches: Background work and scope for the project

HR Functional Assays: PI - AM

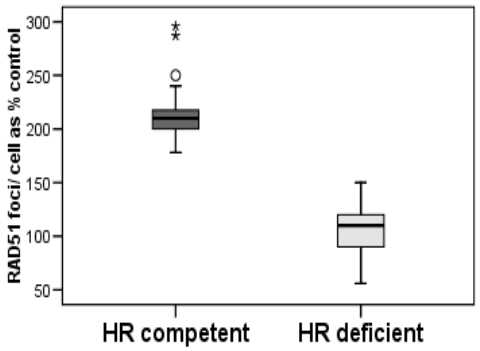
(Mukhopadhyay et al . CCR 2010; Cancer Res 2012; & .JNCI, 2010; PloS One 2014)

The Rad51 assay is possible in primary culture cells



Rad51 IF HR assay: > 2 fold rise in Rad51 after induction of DNA damage indicative of HR competence

Mukhopadhyay et al, Clin Cancer Res, 2010

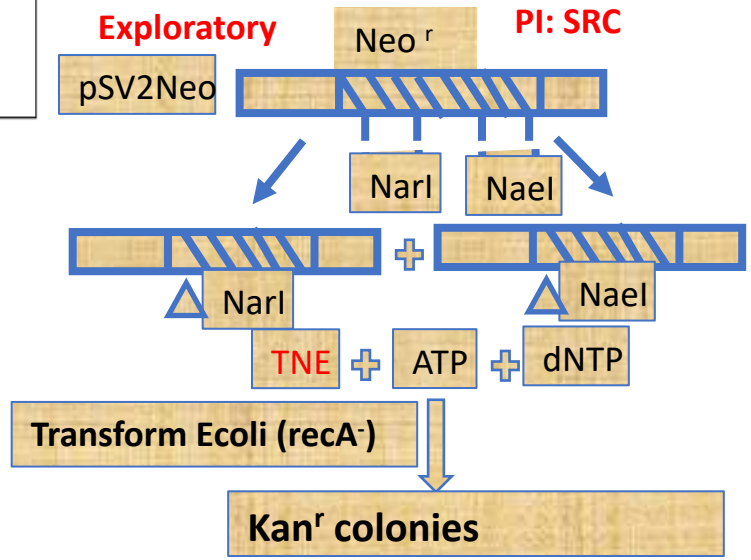


	HRC (24)	HRD (26)	
Complete /optimal cytoreduction	62.5%	80.8%	
CA 125 at presentation (median)	427	2079.50	0.007*
Serous Histology	62.5%	92.3%	0.035*
Platinum Sensitive	16.7%	53.8%	
Sensitivity to PARPi	0/24	24/26 (92.8%)	<0.001 **
OS 12 months(death)	41%	15%	

50% EOC are HRD

Development of other HRD assays- Panel/LOH used in clinical trials

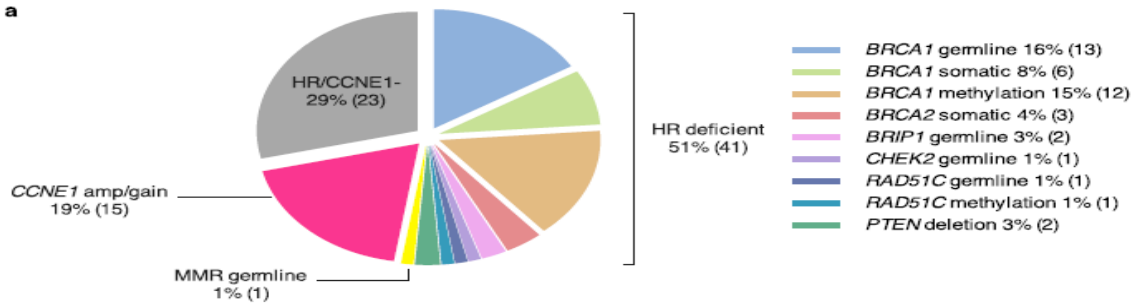
Exploratory **PI: SRC**



HR Genomic Assays: PI - NIBMG

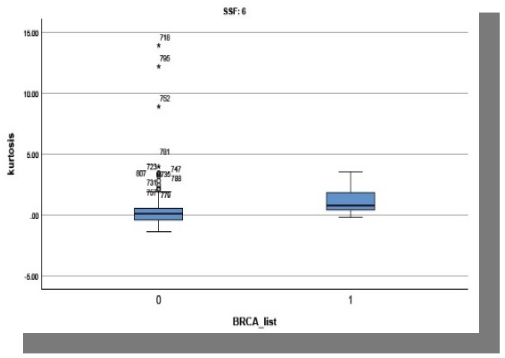
- HR gene panel +/LOH (Clinical Trials on PARPi- inconsistencies)
- BRCA promoter methylation analysis
- Genomic mutational signature (Signature 3)

from whole genome sequencing - *Serena Nick Zainal (Collaborator)*



HGSOC genomic features (TCGA 2011)

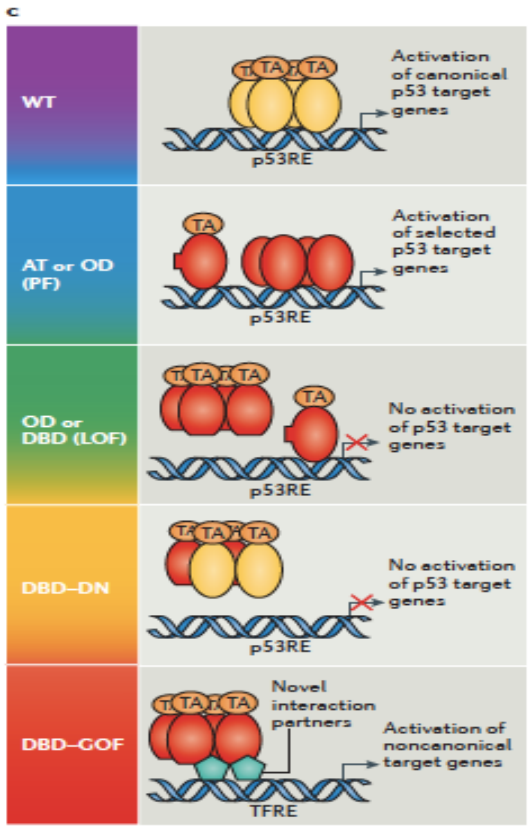
Developing a radiomic signature (CT texture) for BRCAness and P53 function: Pilot data (PI: AM)



BRCA wt tumours tend to have more heterogenous architecture (unpublished)

AI based modelling may refine HRD assay

AIM 2 : Study of TP53 genotypes In HR stratified HGSOC tumours

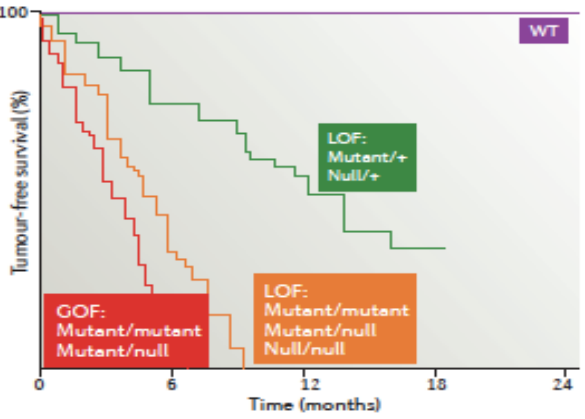


Rational:

- >96% HGSOC tumors harbor *TP53* mutation
- Tumors with *TP53* mutations show chemoresistance
- Mutant p53 proteins show functional heterogeneity
- Mouse tumors bearing different *TP53* genotypes exhibit survival difference
- wt and mut p53 crosstalk with HRR- P53BP1 determines HR-NHEJ switch/ mechanism for PARPi resistance

Objectives:

- Single cell sequencing/ other validation to stratify p53 loss of function and gain of function subgroups in clinical cohorts
- CT texture imaging of p53 loss of function and gain of function subgroups
- Does p53 loss or gain of function affect functional BRCAness and response to PARPi- ex vivo model

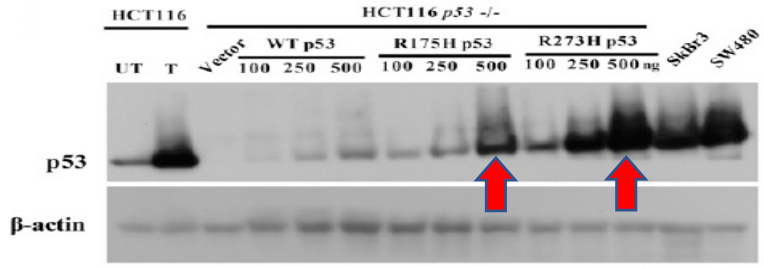


K. Sabapathy, Nat Rec Clin Oncol 15:13-30 (2018)

Work plan:

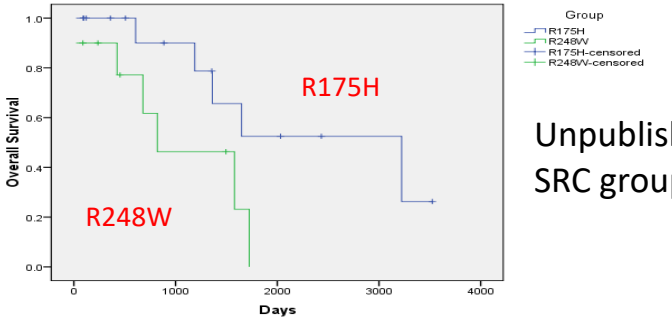
- Single cell sequencing of *TP53* gene
- Single cell RNA-sequencing
- Single cell ATAC-sequencing
- Bulk *TP53* exon sequencing
- Immunohistochemistry of p53
- CT texture analysis: p53 LOF/GOF subgroups
- Molecular analysis p53-HRR crosstalk

Background and ongoing work

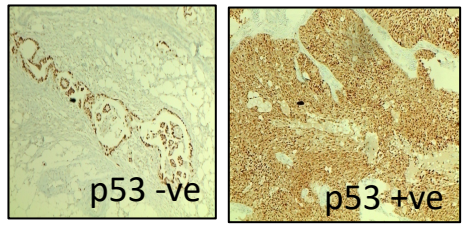


Datta A et al EMBO Rep 18:2030-2050. (2017)

TCGA-HGSOC



Unpublished SRC group



Optimising P53 IHC staining n HR stratified tumours

AI based modelling can refine TP53-HR stratification

PI: SRC, AM, SSG, UG, JDS. Collaborator: RDG

Aims 3: Economic Analysis (PI – IRC)

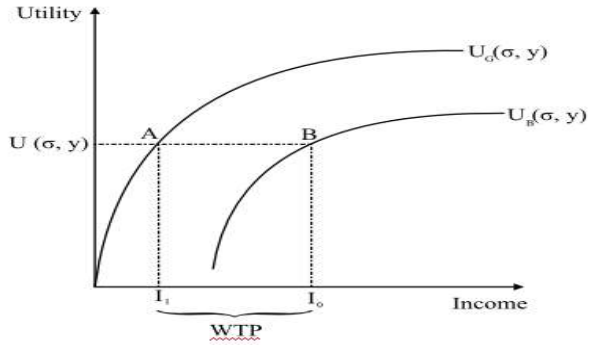
An economic analysis is proposed in 3 steps to investigate the rationale for the biomarkers preceding to the PARPi therapy in terms of its benefits and costs .

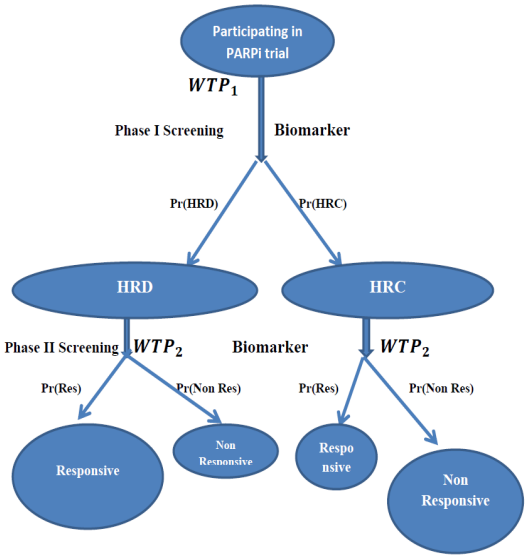
1. Scenario analysis for biomarker driven 3 stratification levels of OC patients in terms of PARPi therapy (**1**.HRD- p53 LOF & HRC-p53 LOF, **2**.HRD-p53GOF, & HRC-p53 GOF and **3**.Control Group.) .

2. Budget impact analysis for examining efficacy of PARPi to the targeted OC patients.*

3. Sequential Valuation of health under bio markers towards targeted PARPi therapy. ⟹

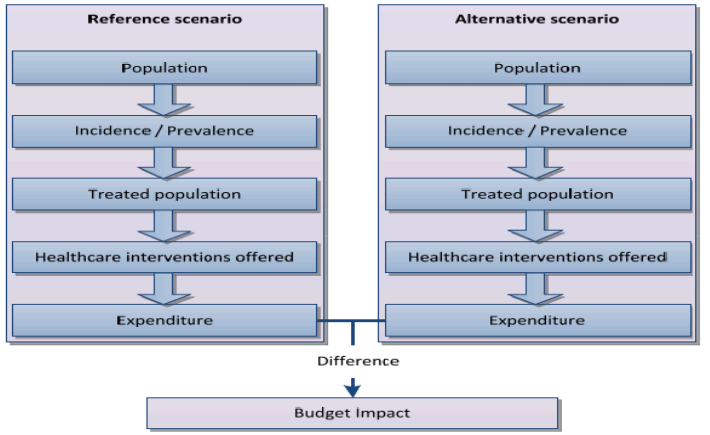
Estimation of average WTP of OC patient for a likely reduction in mortality due to the intervention of PARPi.





We propose to do an experimental survey of 200 OC patients who will receive the biomarkers and 100 OC patients in the control group. Given that health is not directly purchased in the market, for the objectives 1, we propose the patients' valuation of health through Stated Preference Method (or *CVM*) by analysing patients' WTP. The maximum amount of payment will be identified by using double bounded payment card method. We will then apply MLM method for interval regression to estimate the mean WTP and further explore the influence of different predictor variables.

* We may access data from patients on clinical trials of PARPi during the course of the study period to perform actual cost-effectiveness/QALY studies and the same for platinum sensitivity



Existing/ ongoing work:

- HEPTROC (Health Economic analysis of primary treatment of ovarian cancer) and SOCQER-IND (QOL) study in Ovarian cancer with the KolGo Trg group
- WTP studies through PhD studentships and NCAER-NDIC(BMGF grants)

Expected outcome : #1

1. Refining HRD assays/models for better risk/response stratification: (need of the hour-topical)
- Reduce clinical and financial toxicity
- Reduce PARPi resistance

2. Deriving cost-effective treatment options/ assessment of novel economic models like WTP- affect public funding strategies for a costly but highly effective therapy

3. Develop future Clinical trials

4. Correlation between TP53 genotypes and prognosis

Expected outcome #2: (PI: UG)
Developing AI based models for biomarker stratification

Overall goal

reduce observational oversights

screen against errors of omission

have a time- and cost-effective solution for rapid diagnosis

generate new insights to advance the existing treatment procedure

AI tasks

1. **Predicting BRCAness in HGSOC patients from CT scan images**
- Automatic segmentation of tumor from CT images
- Machine learning approach based on hand-engineered features
- Deep learning framework
- Decision based on machine generated attributes

2. Designing a non-invasive predictive model to determine sensitivity to PARP inhibitor
- Image level classification of responsive and non-responsive cases
- Decision based on all available omics data (at genomic, radiomic and socio-economic level)
- Biomarker detection-To correlate radiographic imaging features with biological data

3. Recurrence prediction using patient's omics and historical data of previous patients

Expected outcome #3: Broader collaboration

- Developing/consolidating a clinical academic group in Gynecological cancer
- KolGo- GCIG (Gynecological Cancer Intergroup) collaboration: access to broader groups as a proof of concept leading to trials with translational end points/N=1 studies: will be presented in 2020 GCIG Chicago Meeting
- Validate results in larger datasets from clinical trials
- Apply knowledge to other cancers with HRD and potential for PARPi therapy
- Cohort of 200 OC women with bio-repository: Pilot data – resource for future related studies/ participation in OTTA (ovarian tumour tissue analysis consortium) and OCAC
- Encourage young scientists/clinicians/clinician-scientists
- Foster future collaborations and grant applications

Challenges/ barriers

- **Recruitment**
- **HRD assay**

Some aspects are exploratory

- **p53 workplan**

Some aspects are exploratory

- **AI based study**
- Requirement of large amount of annotated data by deep learning systems remains an issue
- Weak state of the art for AI in ovarian cancer treatment
- **Economic analysis**

- **Project management**

Plan to overcome

- **KolGo Trg group collaboration (pre-existing experience of working together as a research group)**
- **WGS based assay may be a better gold standard rather than panel based genomic assay based on recent clinician consensus (October 2019)-cost**
- **Existing collaboration with GIS PI (TMEOC study in ovarian cancer) and ICMR HSMC clearance for tissue transfer to GIS for a limited no. of samples. If in-vivo work required later for mechanistic study, we have an established IP mouse model (ID8/ID8-p53 mut/ID8-p53-BRCa1 mut) at IISER**
- **(i) Machine learning approach will help to work on hand-engineered features and this initial diagnosis system may help in annotating more data;(ii) Data from other types of cancer may be used to have a pre-trained ; (iii) AI model which will be retrained on available data for the present problem (fine tuning) AI applications for cancer imaging of other types might help to design suitable architecture for ovarian cancer analysis**
- **Due to the non availability of data related to post PARPi therapy, the economic analysis has to be partly based on imputation of the benefits (mortality gains) and costs documented in the literature, drawn from the experience of the developed countries. Moreover the exercise on the valuation of health benefits (through Stated preference method) which is proposed to be based on hypothetical scenarios of expected health gains (under the different stratifications), will be grossly contingent on the cognitive ability of the patients. So eliciting the correct valuation through the process of bidding game is a challenge- accessing actual clinical trial datasets may help; parallel PARPi trials are planned**
- **Research Governance, audit, risk management, SOP, Intellectual property, Publication strategy, regulatory aspects- periodic review**