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The Geneva HRD test

Clinical validation on 469 samples from the PAOLA-1 trial

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Declaration of interests

- I declare that I have no conflicts of interests
- This study was partially funded by AstraZeneca, Cambridge, UK and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

The ENGOT HRD European Initiative (EHEI)

- The aim of this initiative is to evaluate HRD tests on a subset of the PAOLA-1 cohort in order to determine reliable and feasible HRD tests for routine AOC patient management
  - Comparison with the Myriad myChoice test and clinical endpoints from the PAOLA-1 trial
- Three phases
  - Selection of tests (December 2019)
  - Technical validation (85 BRCA wild type samples)
  - Clinical validation (384 samples)
- 6 laboratories participating in the clinical validation
  - France, Italy, Netherlands, Belgium, Germany (next talk!), Switzerland
- EHEI cohort
  - Only samples with high DNA quality
  - 33% of BRCA-mutated samples (29% in the full PAOLA-1 cohort)
  - Hazard ratio for disease progression of 0.64 (0.59 in the full PAOLA-1 cohort)
  - All 469 samples used for validation of the Geneva test

The Geneva HRD test

	Myriad myChoice Dx	Geneva test
Technology	NGS assay (proprietary)	SNP assay (ThermoFisher oncoscan)
Mutation detection	BRCA1/2	None
HRD phenotype	LST+LOH+TAI (GIS) (patented algorithm)	Normalized LST (nLST) (free software)
Min tumor content	20%	20%
Cost	~5000€	~350€ (reagents)
Accessibility	Material to be send to Myriad Genetics, USA	Send material to Geneva *or* To implement locally as LDT

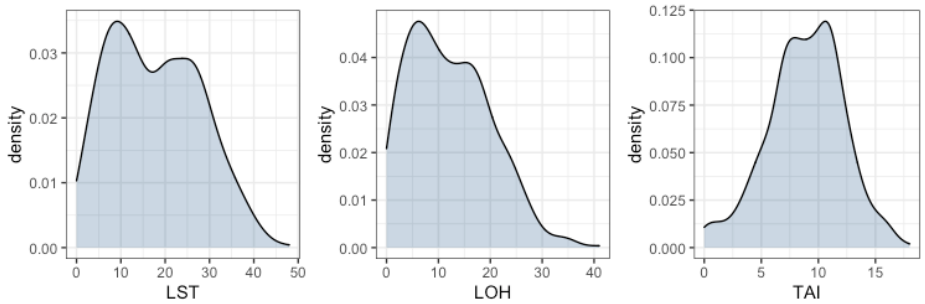
Source: TCGA data (457 HGOC and 112 TNBC)

Rationale behind the nLST biomarker

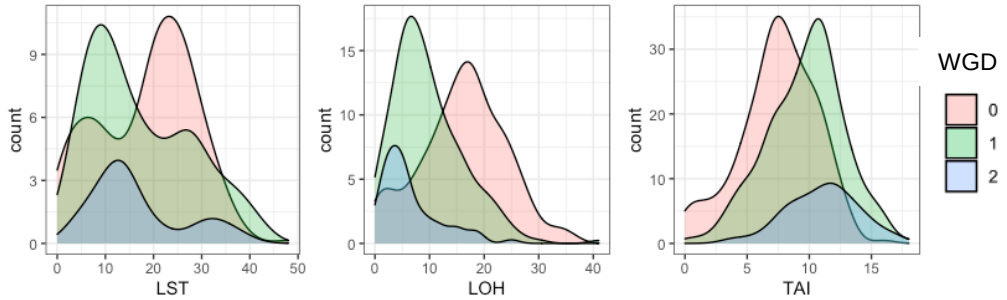
- The number of whole-genome doubling (WGD) events is a confounding factor when counting DNA alterations
  - 54% of HG OC have undergone a whole-genome doubling event (TCGA data)
- Of the three markers used by Myriad only the LST has a bimodal distribution when accounting for the number of doubling events
  - BRCA mutations are more rare in tumors with WGD
- Geneva test
  - Only use the LST and the WGD as biomarkers
  - Normalize (or shift) the number of LST in order to align the distributions with respect to the number of WGD events

$$\mathrm{nLST} = \mathrm{LST} - \frac{7}{2}\mathrm{WGD} \qquad \text{HRD positive if } \mathrm{nLST} \geq 15$$

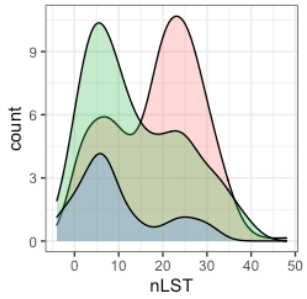
Distribution of LST, LOH and TAI



Distribution with respect to WGD



LST normalized for WGD

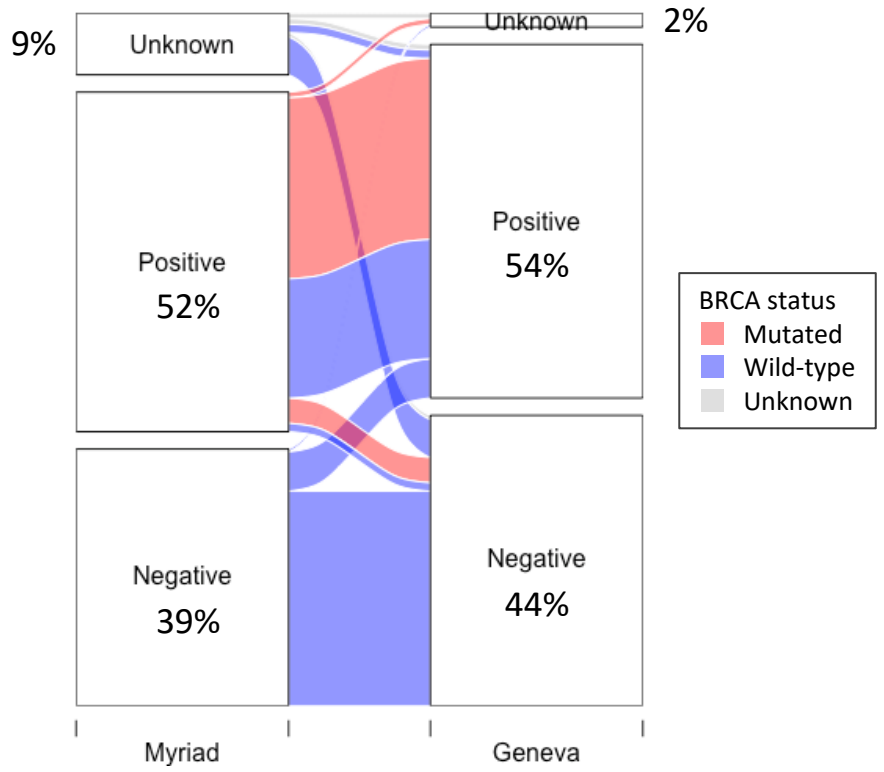


Analysis on TCGA data (457 HGOC and 112 TNBC)

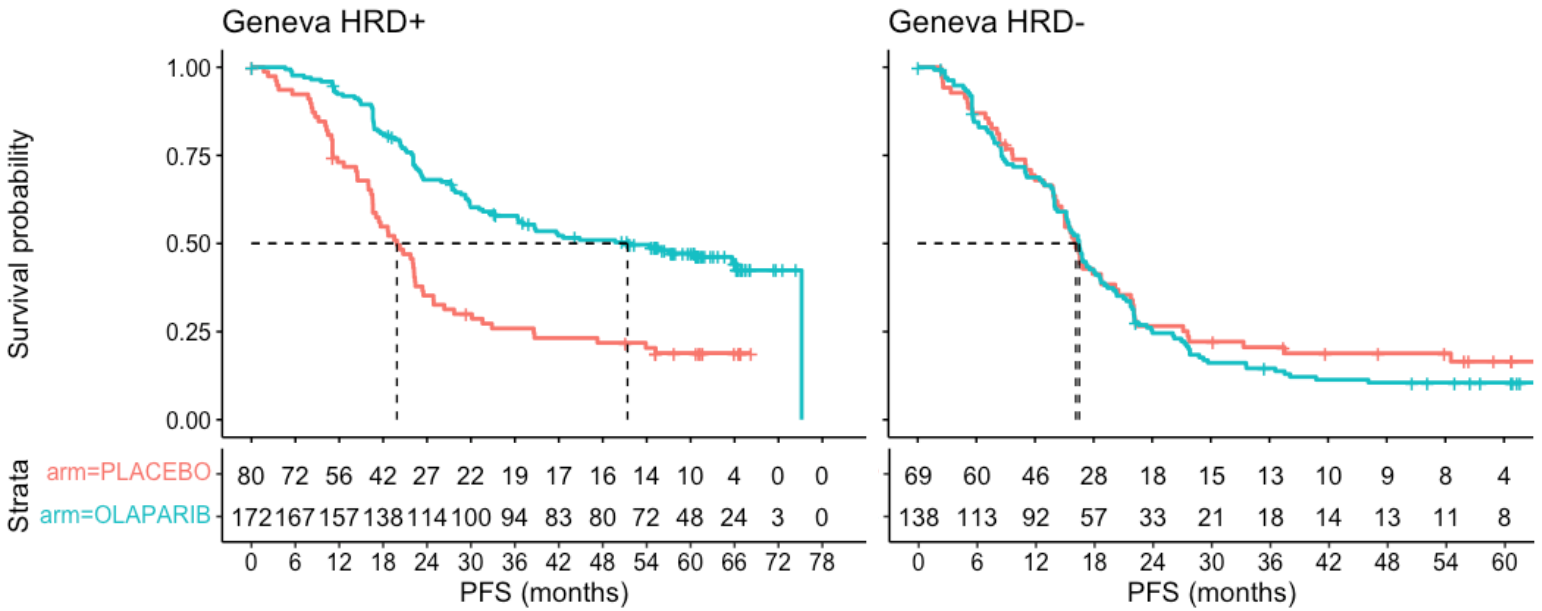
Comparison of the Geneva test with Myriad MyChoice

- High concordance between the two tests
  - Pearson's correlation coefficient at 0.88 between the nLST score and Myriad GIS
  - Positive and negative agreement value of 85% and 74%
- Higher positivity rate and lower failure rate for the Geneva test
- In the BRCA-wt subpopulation the differences are even larger
  - Positivity rate of 38% vs 29%
  - Failure rate of 1% vs 14%

- This suggests that more advanced OC patients might have the opportunity to benefit from PARPi when tested with the Geneva test compared to Myriad



Results on PAOLA-1 updated PFS



Full PAOLA-1 cohort

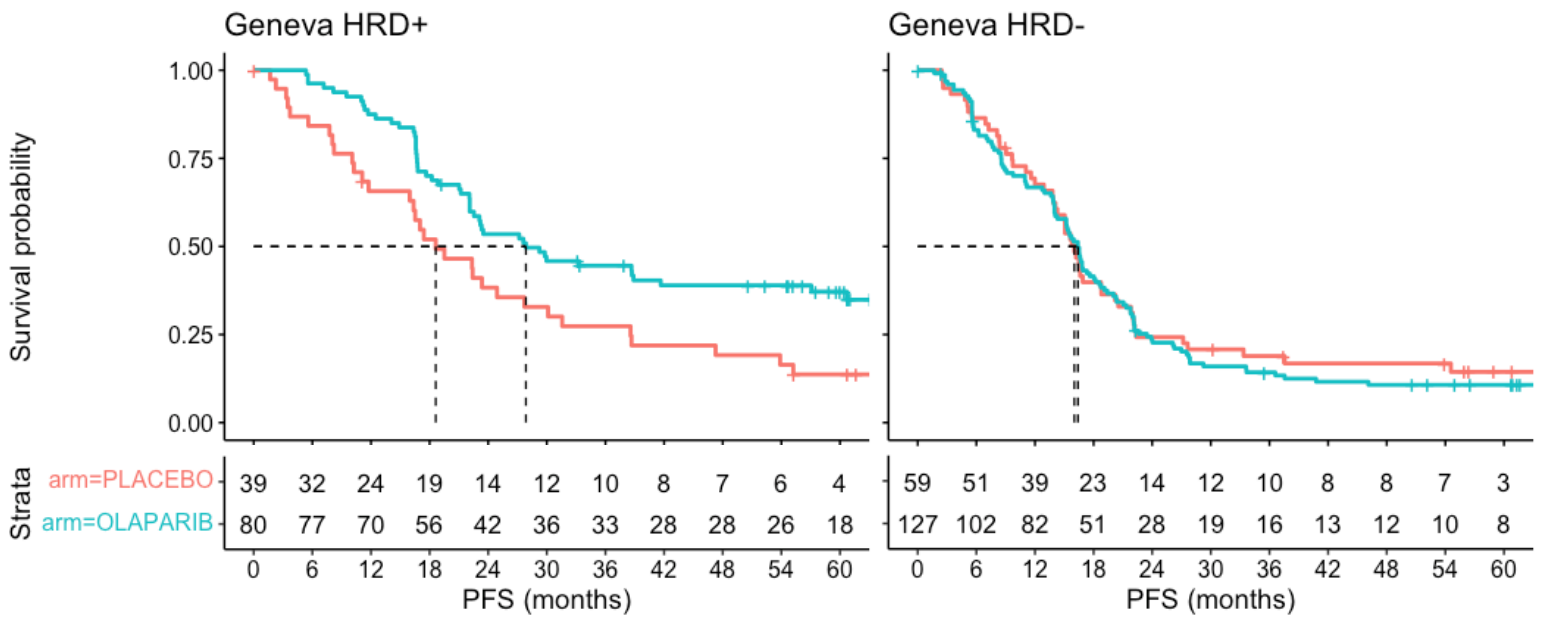
HRD positive	Geneva N=252	Myriad N=242	Myriad N=387
Median (months)			
- Olaparib+Bev	51.4	57.1	46.8
- Placebo+Bev	19.9	20.1	17.6
Hazard ratio (95% CI)	0.41 0.30-0.57	0.41 0.29-0.57	0.41 0.32-0.54

HRD negative	Geneva N=207	Myriad N=183	Myriad N=277
Median (months)			
- Olaparib+Bev	16.5	16.8	16.6
- Placebo+Bev	16.2	16.5	16.2
Hazard ratio (95% CI)	1.10 0.81-1.50	1.10 0.76-1.50	1.01 0.77-1.33

- The Geneva test is very similar to the Myriad myChoice test with respect to the progression-free survival
  - Identical hazard ratios

Subgroup PFS analysis on BRCA wild-type

BRCA status given by Myriad myChoice

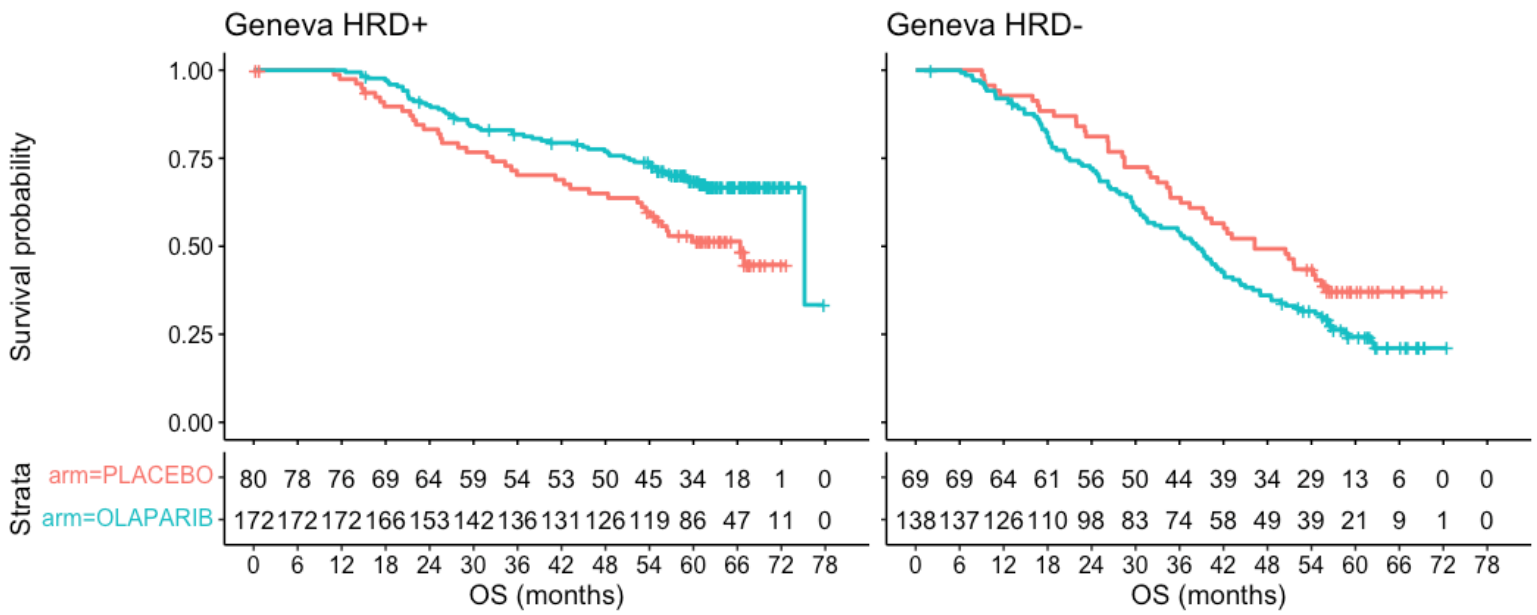


HRD positive	Geneva N=119	Myriad N=91
Median (months)		
- Olaparib+Bev	27.9	38.9
- Placebo+Bev	18.6	17.6
Hazard ratio (95% CI)	0.54 0.35-0.84	0.44 0.26-0.73

HRD negative	Geneva N=186	Myriad N=183
Median (months)		
- Olaparib+Bev	16.4	16.8
- Placebo+Bev	16.0	16.5
Hazard ratio (95% CI)	1.10 0.76-1.50	1.10 0.76-1.50

- With the Geneva test, the HR is less impressive than with the Myriad test but more patients are HRD positive
- The Geneva test is predictive of response in the BRCA-wt subpopulation

Results on PAOLA-1 OS



Full PAOLA-1 cohort

HRD positive	Geneva N=252	Myriad N=242	Myriad N=387
5-year OS			
- Olaparib+Bev	69%	68%	
- Placebo+Bev	51%	52%	
Hazard ratio (95% CI)	0.56 0.37-0.85	0.60 0.39-0.90	0.62 0.45-0.85

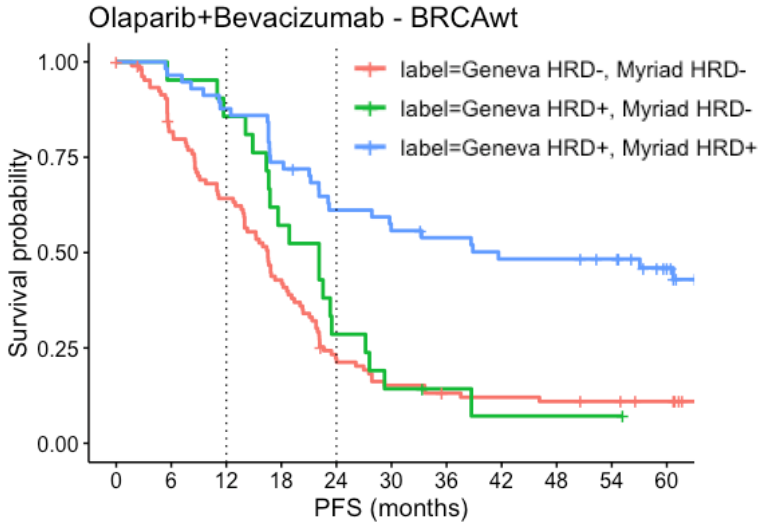
HRD negative	Geneva N=207	Myriad N=183	Myriad N=277
5-year OS			
- Olaparib+Bev	24%	27%	
- Placebo+Bev	37%	35%	
Hazard ratio (95% CI)	1.40 1.00-2.10	1.20 0.83-1.80	1.19 0.88-1.63

- The Geneva test seems slightly superior to the Myriad myChoice test with respect to the overall survival
  - In particular in the HRD negative population where Olaparib treatment yields a worse outcome

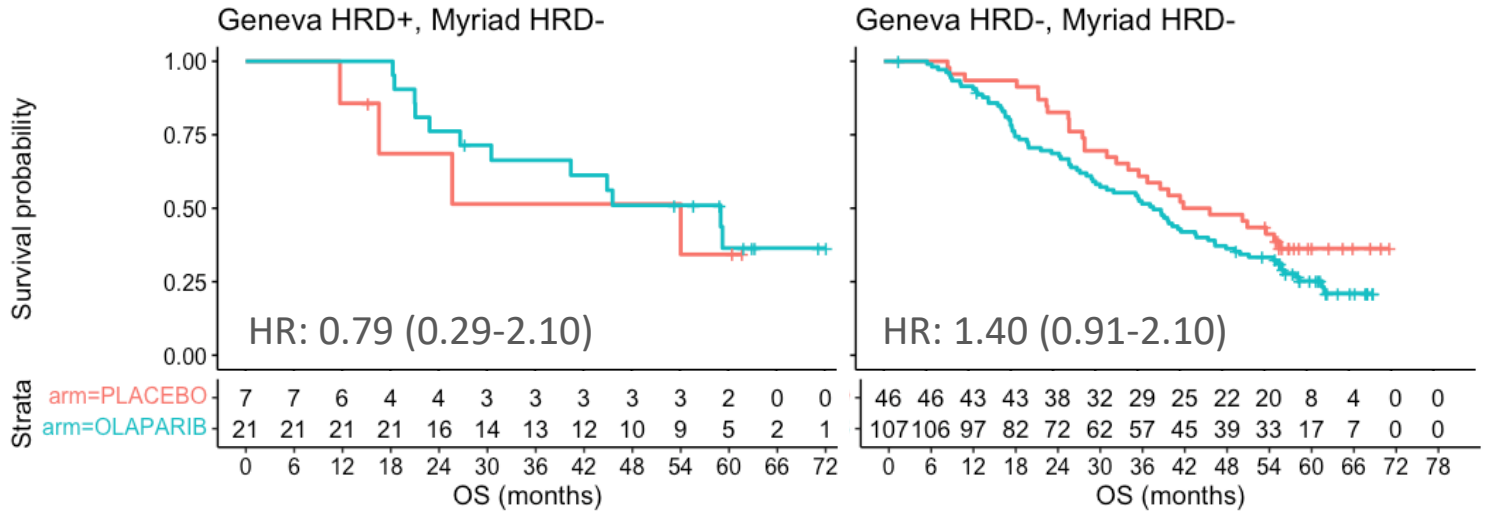
Discordant samples in the BRCA-wt subpopulation

- 6 samples were Geneva negative and Myriad positive
- 28 samples were Geneva positive and Myriad negative
  - Most of these are borderline nLST positive/GIS negative
  - These patients relapse earlier but benefit from Olaparib treatment (no statistical significance)
  - Representative of population with partial HR activity? (E.g. hypomorphic BRCA mutations)

Comparison on PFS



Comparison on OS (Myriad HRD negative subgroup)



Conclusion

- **The Geneva test is a viable alternative to the Myriad myChoice assay**
  - High concordance between the nLST score and the Myriad GIS
  - Lower failure rate
  - Reduced costs
  - Easily implementable by your own laboratory (free software)

- **Among the Myriad HRD negative patients, there is an «HRD-low» category identified by the Geneva test**
  - I.e. a subpopulation with HR deficiency who benefit from PARPi but with a smaller magnitude
  - To validate on a larger cohort

HUG Hôpitaux Universitaires Genève

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THANK YOU!