Genomic Instability Metric (GIM) from OCA Plus

Annette Staebler, Isabell Götting, Franziska Otto, Falko Fend and Irina Bonzheim

27.09.2023

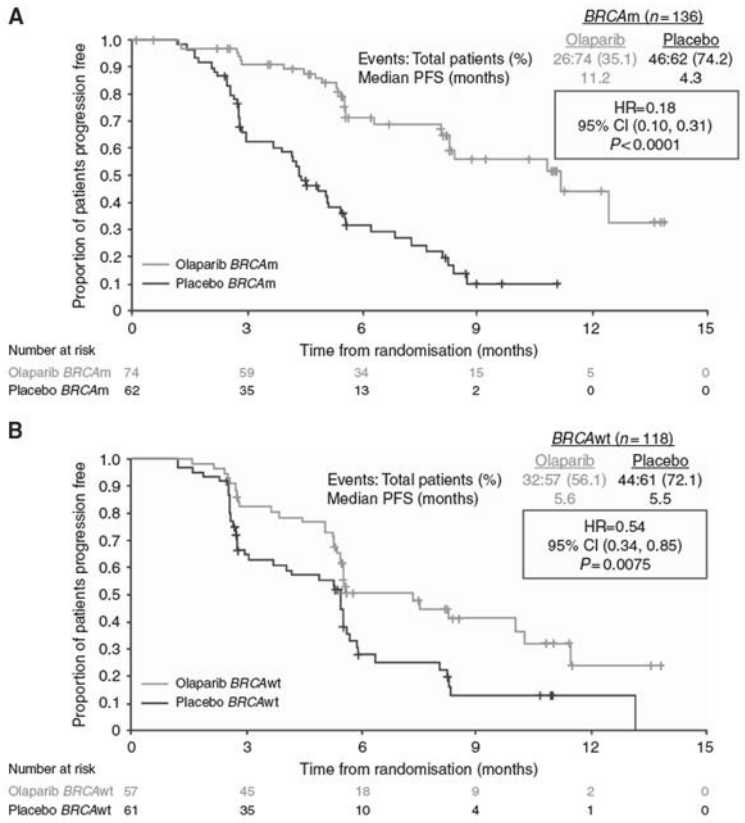
Universitätsklinikum Tübingen

Thermo Fisher Scientific and its affiliates are not endorsing, recommending or promoting any use or application of Thermo Fisher Scientific products by third parties during this seminar. Information and materials presented or provided by third parties as-is and without warranty of any kind, including regarding intellectual property rights and reported results. Parties presenting images, text and material represent they have the right to do so. Speaker was provided honorarium by Thermo Fisher Scientific for providing this presentation.

ThermoFisher SCIENTIFIC

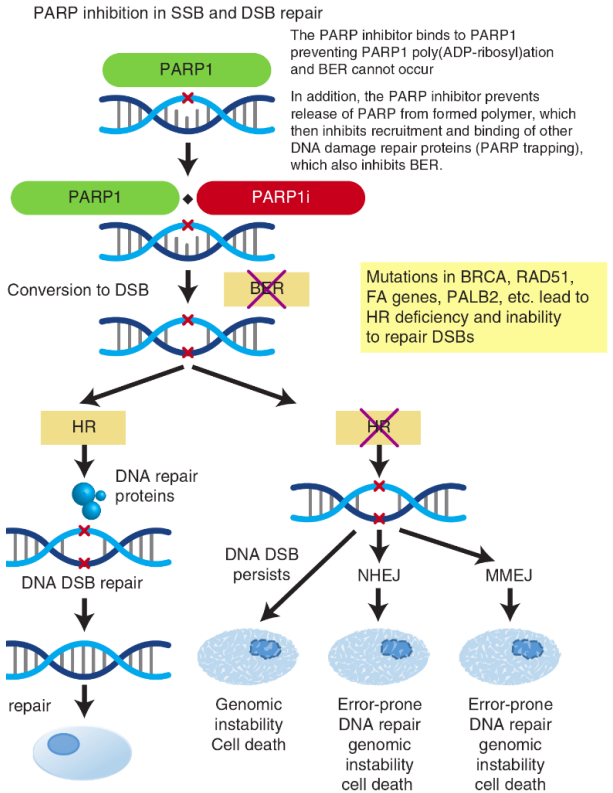
Background:
Homologous recombination deficiency (HRD) as a therapeutic target

BRCAmut tumors respond better to PARPi



Ledermann, J. et al. 2014 Jul;15(8):852-61

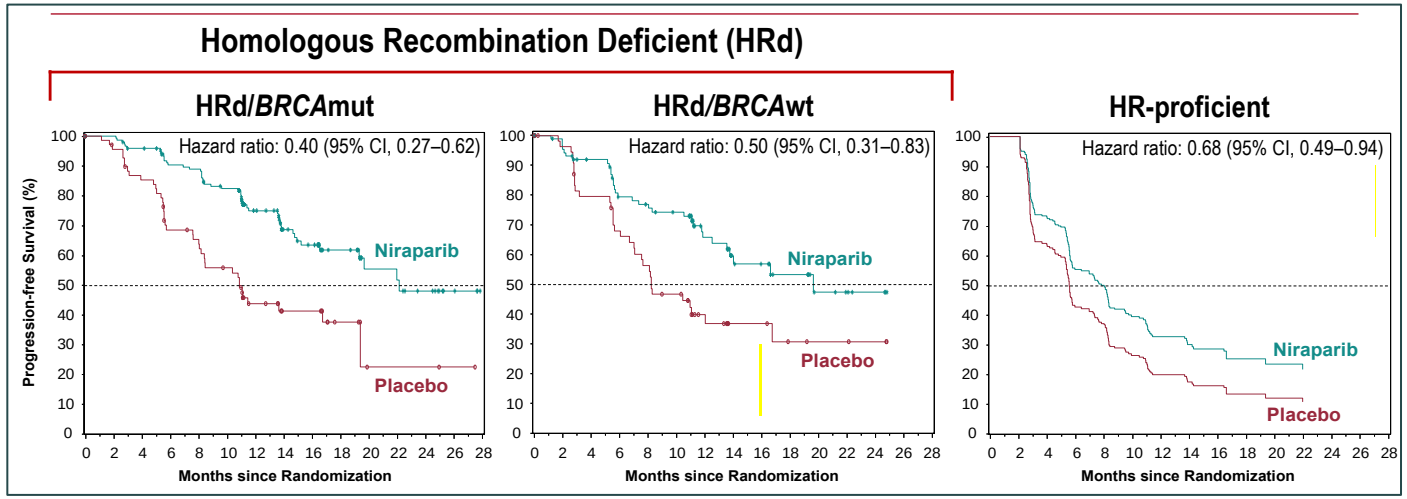
HRD leads to inability to repair double strand breaks



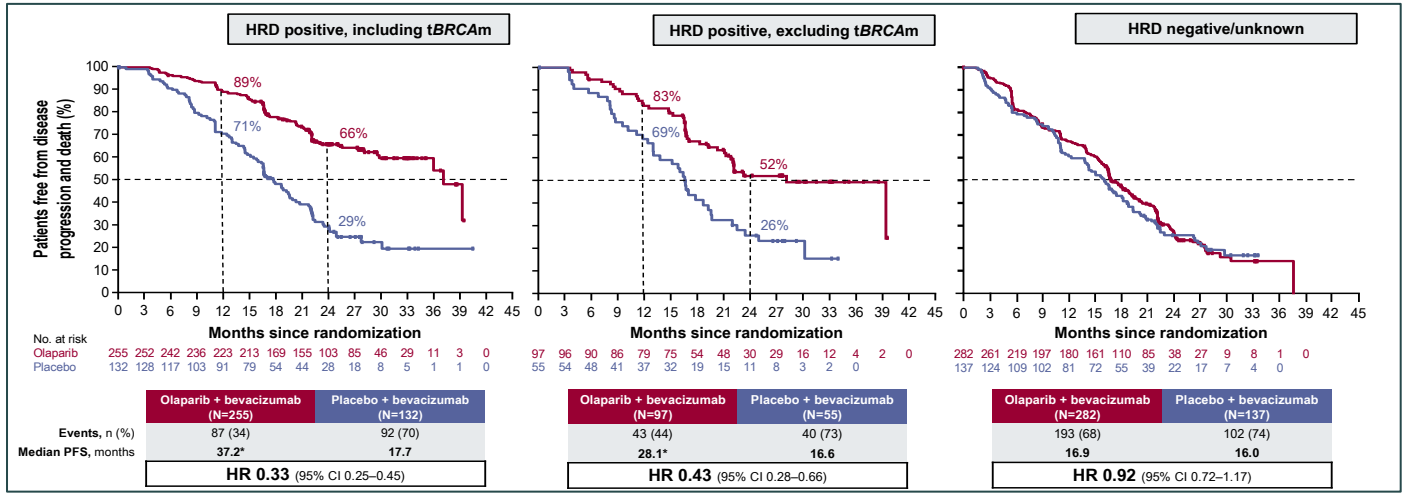
Konecny, G. E. et al. 2016 Nov 8;115(10):1157-1173

BRCAmut and HRD as predictive markers for treatment with PARPi

PRIMA



PAOLA



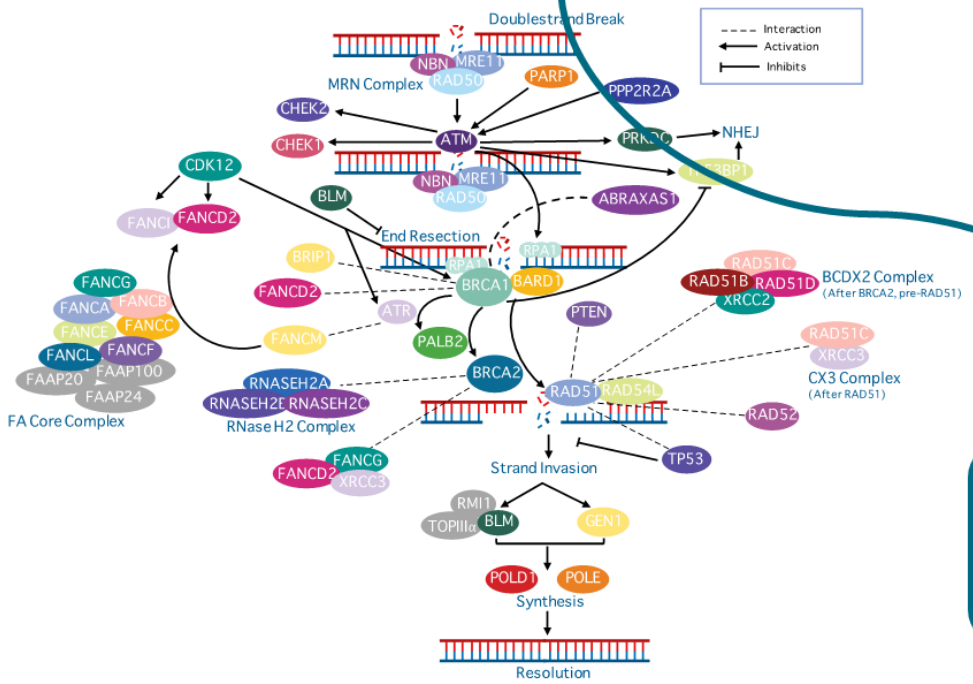
Gonzalez-Martin et al. N Engl J Med. 2019 Dec 19;381(25):2391-2402.; Ray-Coquard et al. N Engl J Med. 2019 Dec 19;381(25):2416-2428.

How to measure HRD

CAUSES

Inactivation of genes in the HRR pathway

e.g., *BRCA1, BRCA2*



CONSEQUENCES

Genomic Scarring

e.g., Loss of Heterozygosity (gLOH)

Genomic Instability Score (GIS)

Genomic Integrity Index (GI Index)

Genomic Scar Score

Genomic Instability Metric (GIM)

Homologous Recombination Deficiency

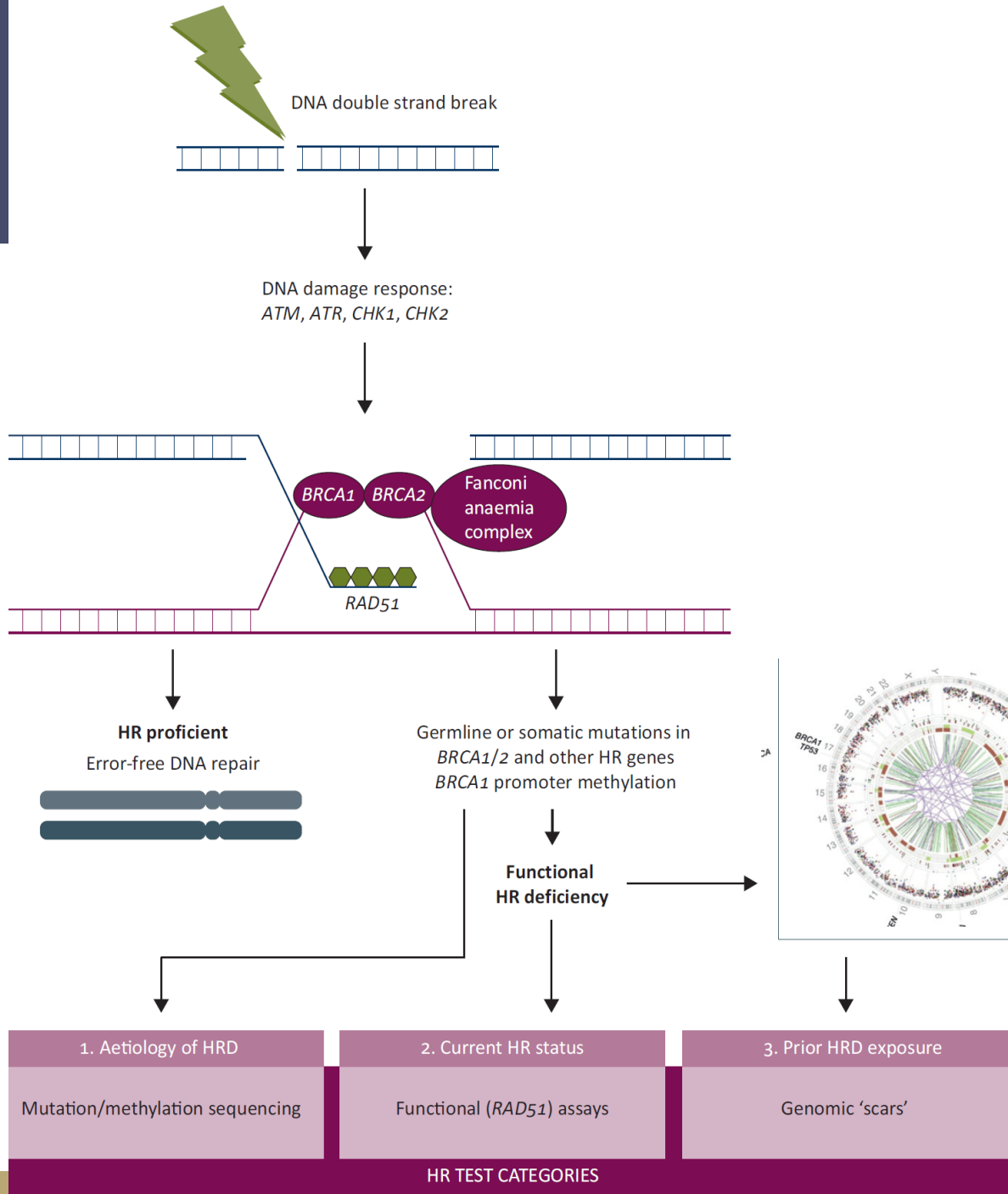
Common testing methods

ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer.

Recommendations:

- All patients with high-grade ovarian cancer should be tested for germline and/or somatic BRCA1/2-mut at diagnosis [I, A].

- Testing for HRD is recommended in advanced high-grade cancers [I, A].



Miller, R. E. et al. 2020, Annals of Oncology 31:1606-1622
González-Martín A. et al. 2023, Annals of Oncology 10:S0923-7534(23)00797-4.

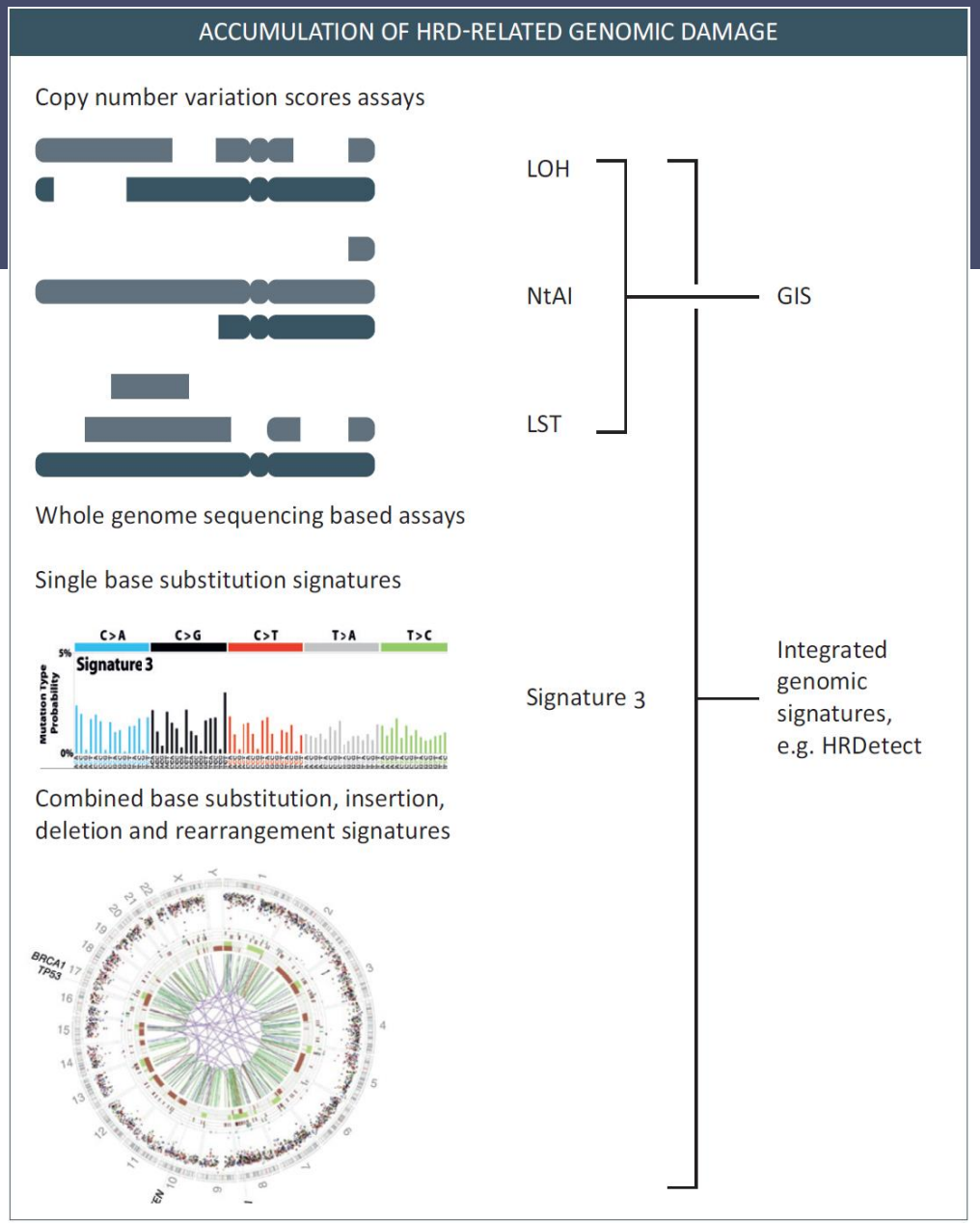
Common testing methods

ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer.

Recommendations:

- All patients with high-grade ovarian cancer should be tested for germline and/or somatic BRCA1/2-mut at diagnosis [I, A].

- Testing for HRD is recommended in advanced high-grade cancers [I, A].



Miller, R. E. et al. 2020, Annals of Oncology 31:1606-1622
González-Martín A. et al. 2023, Annals of Oncology 10:S0923-7534(23)00797-4.

Technologies for HRD testing in clinical research

- Array based
- Targeted NGS based
- WGS based

Algorithms:

- Combination of LOH, LST, TAI
- Only LOH
- Proprietary algorithms
- Unbalanced copy number alterations

Research Study

Analytical validation of Genomic Instability Metric (GIM) in a series of tumor samples with known market reference (GIS)

Samples from Tuebingen:

55 cases of tubo-ovarian high-grade serous carcinoma from Gynecologic Oncology Center at Tuebingen University

DNA isolated from same specimens as were used for market reference, min 90 ng DNA.

Analytical validation of Genomic Instability Metric (GIM) against

- *BRCA1/2* – status
- Non-BRCA mutational status (HRR Genes)
- Market Reference (GIS)

Limitation: in 6 cases only one score was available (quality of material or sample withdrawal)

OCA Plus - HRD assessment

Oncomine Comprehensive Assay Plus

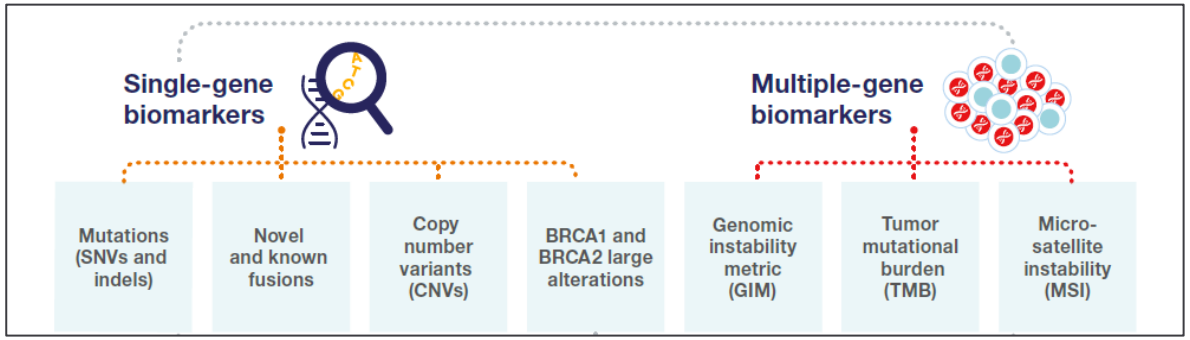
500+ genes comprehensive genomic profiling:

- mutations (hotspot regions and full-coding sequences)
- CNV gains or loss
- fusions
- *BRCA1/2* and 46 HRR genes

Complex biomarker assessment:

- TMB (>1 mb exonic footprint)
- MSI
- LOH
- GIM

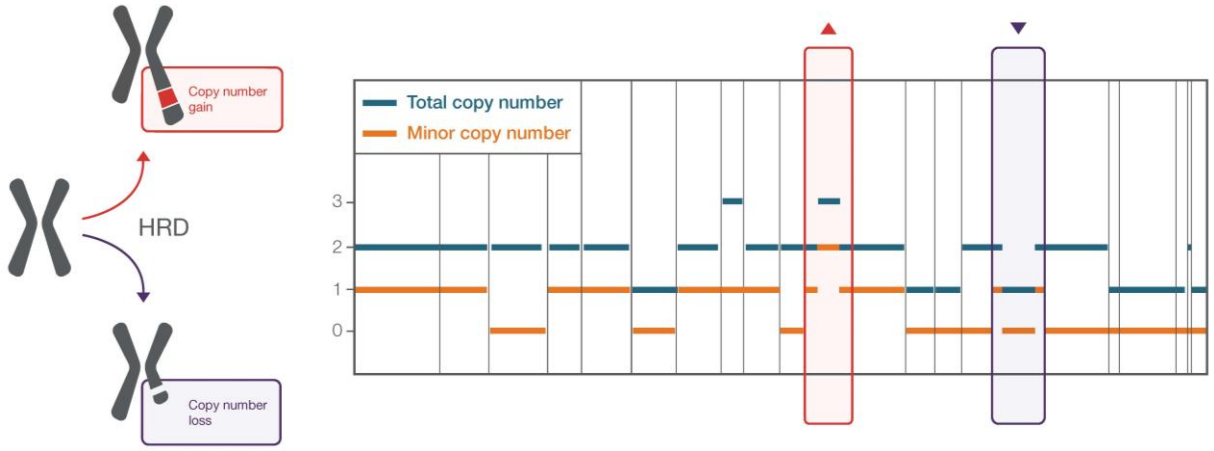
NGS performed on the Ion GeneStudio S5 prime on 550 chips

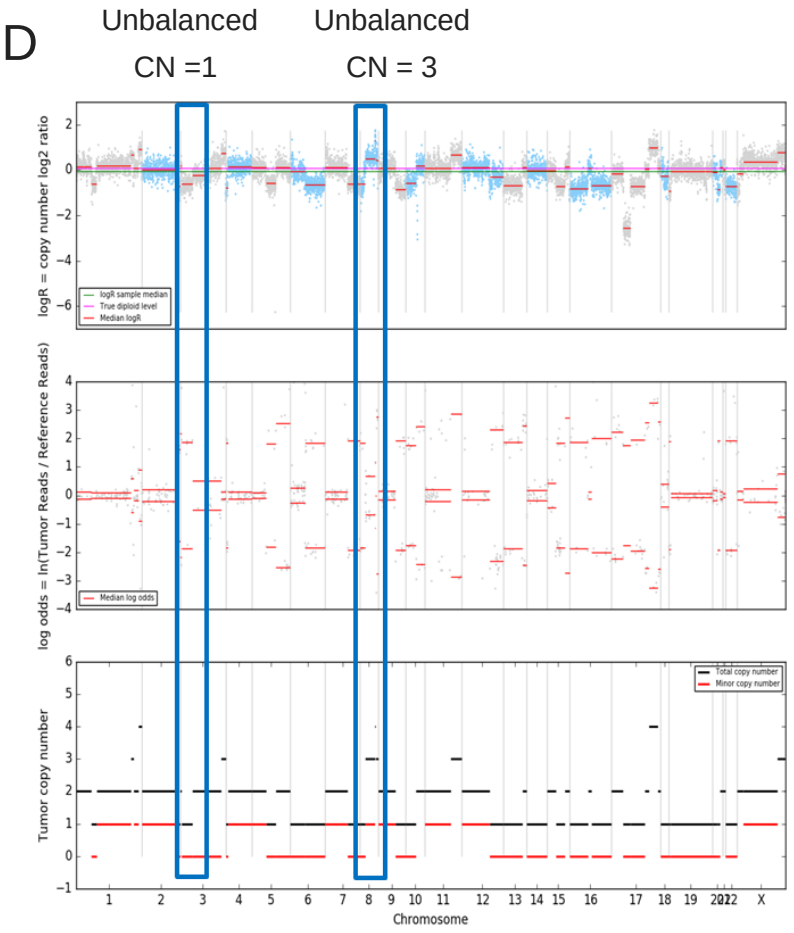


Genomic Instability Metric (GIM)

New approach to quantifying genomic scars/instability associated with HRD

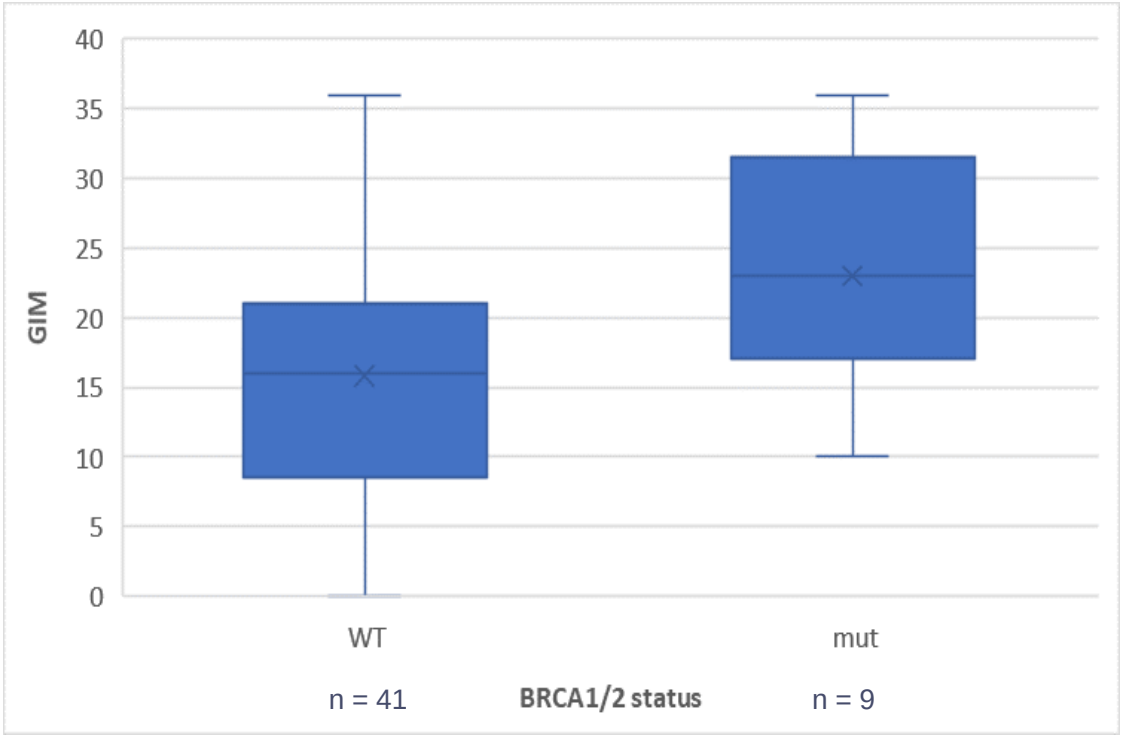
- Genome segmentation to determine copy number changes
- Includes different types of unbalanced copy number events
- Metric ranges from 0-100. The higher the value, the more genomic instability
- GIM above threshold for ovarian cancer (≥ 16) will result in a sample being called GI-High. Threshold is set in software.





Provided by Thermo Fisher Scientific

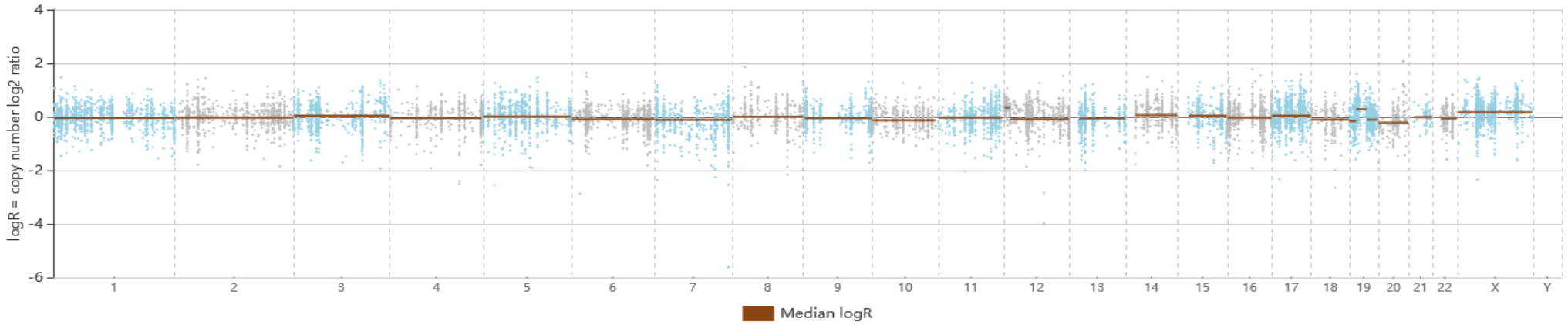
Analytical validation of Genomic Instability Metric (GIM) in a series of tumor samples with known BRCA status



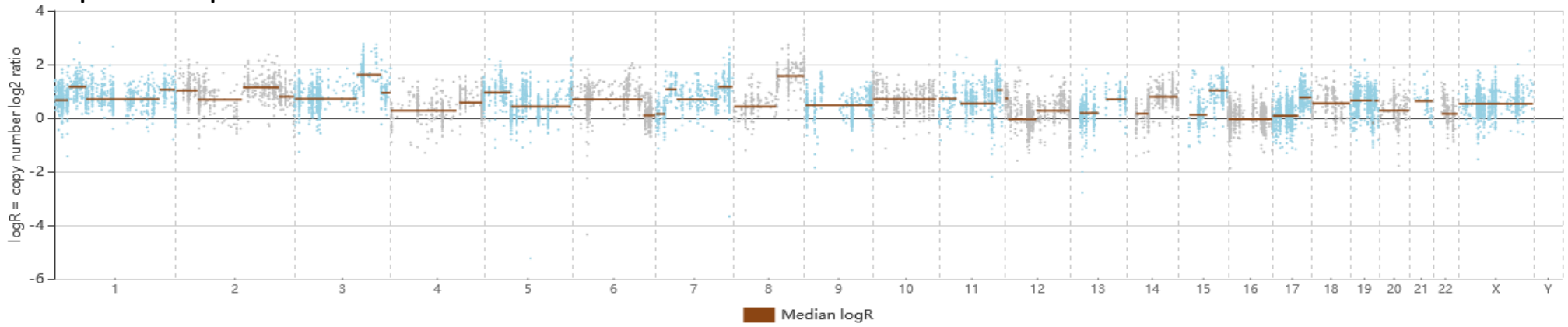
Gene	Variant (gene level)	Variant (protein level)	Interpretation	GIM score
BRCA1	c.4117G>T	p.E1373*	Pathogenic	28
BRCA2	Exon 25 del	-	Pathogenic	23
BRCA1	c.4675+3_4675+4 del	intronic	Likely Pathogenic	36
BRCA2	c.8755-1G>A	intronic	Pathogenic	18
BRCA1	c.181T>G	p.C61G	Pathogenic	16
BRCA2	Whole gene deletion	-	Pathogenic	35
BRCA1	c.3481_3491del	p.E1161fs*3	Pathogenic	QC fail
BRCA1	c.2477_2478del	p.T826Rfs*4	Pathogenic	10
BRCA1	c.2338C>T	p.Q780*	Pathogenic	23

Molecular characteristics of samples with and without HRD

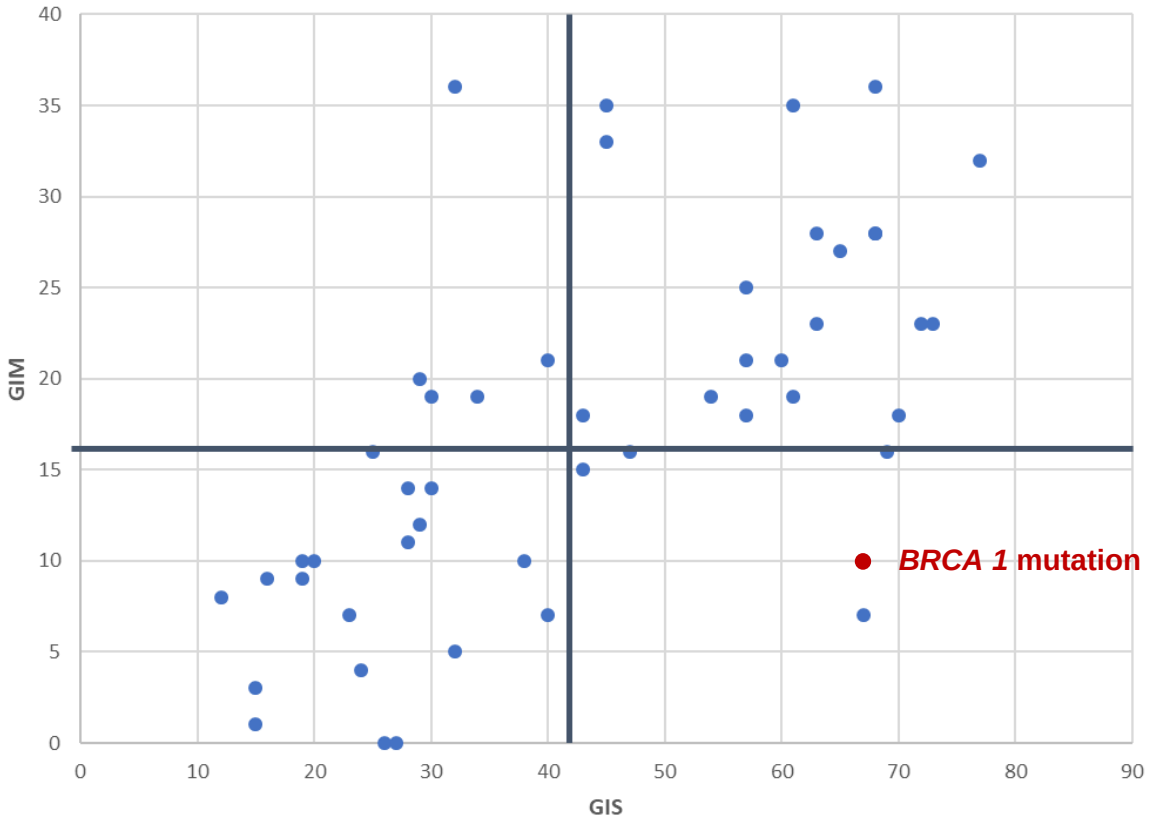
Sample HRD negative GIS: 15 GIM: 1



Sample HRD positive GIS: 65 GIM: 27



Analytical validation of Genomic Instability Metric (GIM) in a series of tumor samples with known reference standard (GIS)



- *BRCA1* p.T826Rfs*4, c.2477_2478del

Total (N=49)	GIM low (<16)	GIM high (≥16)
GIS low (<42)	18	6
GIS high (≥42)	3	22
Concordance	82%	

Total (N=54)	OCA Plus HRD-	OCA Plus HRD+
Ref. HRD -	18	6
Ref. HRD+	2	28
Concordance	85%	

OCA Plus HRD calling criteria: Any sample with BRCA mutation or GIM >= 16 is HRD+

Reference standard HRD calling criteria: Any sample with BRCA mutation or GIS >= 42 is HRD+

Clinical research characteristics of discrepant samples with HRD +

BRCA1/2 status	GIS	GIM	PARPi	response
WT	32	**36**	N/A	N/A
WT	40	**21**	Yes	PR
WT	29	**20**	No	CR
WT	30	**19**	No	PR
WT	34	**19**	Yes	PR
WT	25	**16**	Yes	PR
WT	43	**15**	No	PR
Mut.	67	**10**	N/A	N/A
WT	67	**7**	No	CR

GIS low GIM high

borderline

GIS high GIM low

Retrospective analysis of response data
Therapeutic decision based on GIS and other factors

Outlook

1. OCA Plus may introduce decentralized HRD Testing in any lab using Thermo Fisher NGS
2. Harmonization studies ongoing to ensure comparability of in-house assays assessing HRD status.
3. What about other cancer types? Will the instability cut-offs be different?
4. What are the sources of discrepancy? Questions for prospective studies
   >Tissue quality: preanalytic conditions: adequate fixation and DNA quality
   >Tissue amount, overall cellularity and relative tumor cell content (HRD+ are frequently immune hot)
   >Differences in spectrum of mutations?
   >Previous neoadjuvant treatment?

Study conclusions

1. OCA Plus may reliably detect HRD status in the high and low range.
2. GIS and GIM are continous variables, borderline cases may need additonal workup.
3. Discrepant cases with at least one test result HRD+ are most likely HRD+ as defined by response to PARPi.

Thank you!

Division of Molecular Pathology:

Irina Bonzheim
Isabell Götting
Franziska Otto
Franziska Mihalik
Falko Fend

Division of Gynecologic Patholoy:

Annette Staebler
Robert Rottscholl
Tanja Kopp

Thermo Fisher:

Ute Kusch
Philipp Jermann
Jose Luis Costa

University Womens‘ Hospital Tübingen:

Stefan Kommoss
Marcel Grube
Sara Brucker

Universitätsklinikum Tübingen