The British Association of Gynaecological Pathologists

Lecturer – Prof James Brenton

James D. Brenton is a medical oncologist specializing in gynaecological cancer, a senior group leader at the Cancer Research UK (CR-UK) Cambridge Institute and Professor of Ovarian Cancer Medicine in the University of Cambridge. He leads the Functional Genomics of Ovarian Cancer Laboratory and is joint lead for the CRUK Cambridge Centre Women^{+}s Cancer programme and the Mark Foundation Institute for Integrated Cancer Medicine. He was elected as a Fellow of the European Academy of Cancer Sciences in 2015.

His research focuses on understanding the extreme genomic complexity of ovarian cancer and identifying blood and tissue genomic biomarkers to predict therapy. His group was the first to show that mutations in the *TP53* gene are ubiquitous in high grade serous ovarian carcinoma and to discover copy number aberration signatures of mutational processes. He has used these discoveries to develop personalized circulating tumour DNA assays and genomic biomarkers in clinical trials.

The British Association of Gynaecological Pathologists

Syndromic Tumours in Gynaepath
Diagnoses not to be missed by Pathologists

- Molecular testing beyond HRD for high grade advanced ovarian cancer
- Prof James Brenton
- CRUK Cambridge Institute, University of Cambridge
- 14 Nov 2025

The British Association of Gynaecological Pathologists

Speaker disclosures

Shareholder and co-founder of Tailor Bio (commercializing WGS biomarkers)

Received honoraria from GSK and AstraZeneca, personal fees from Clovis Oncology, GE Healthcare

Funding to University of Cambridge from Varsity Pharma, GE Healthcare and AstraZeneca

Molecular testing beyond HRD for high grade advanced ovarian cancer

James D. Brenton

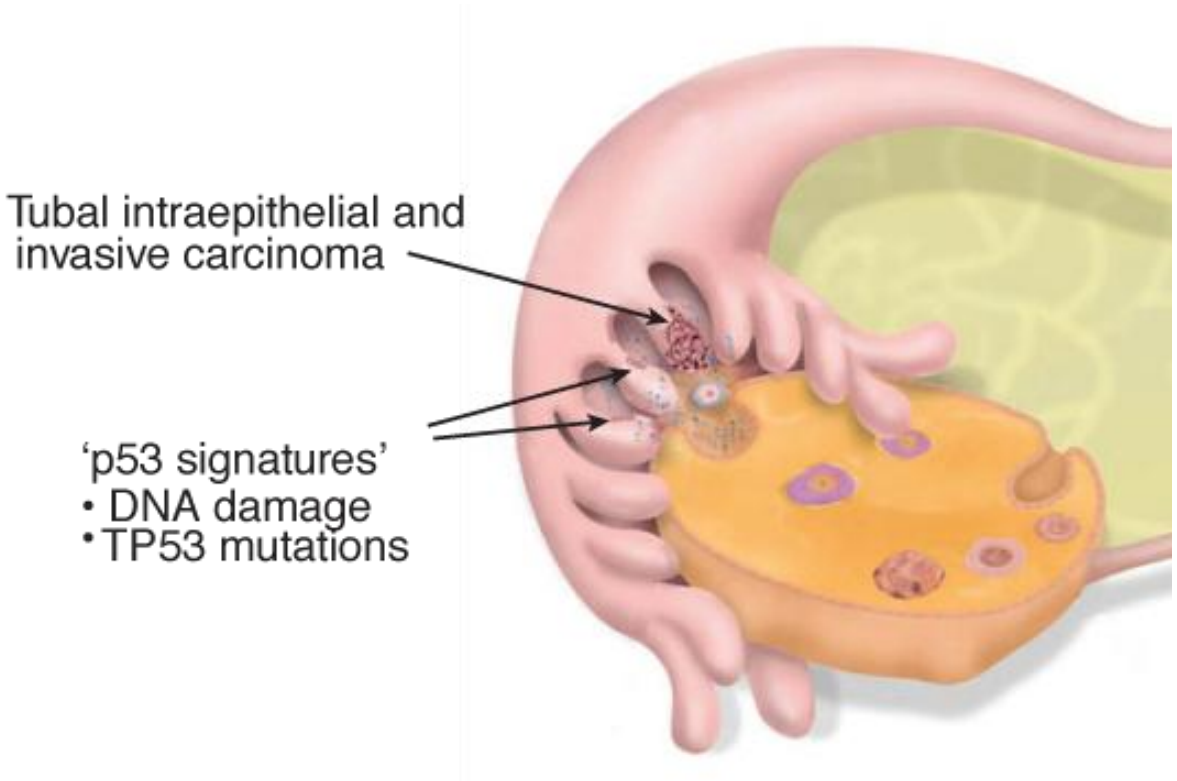
UNIVERSITY OF CAMBRIDGE

CANCER RESEARCH UK | CAMBRIDGE INSTITUTE

Objectives

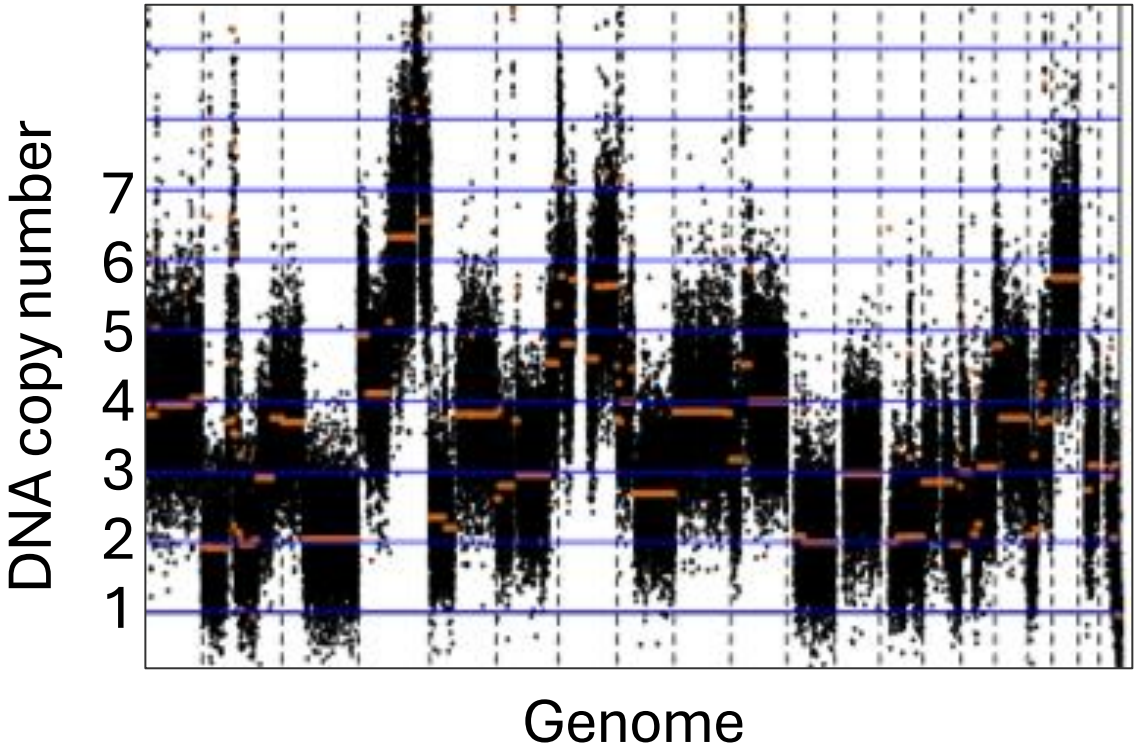
1. What is current personalized medicine for HGSC?
2. What are the limitations of current HRD testing?
3. Where should we be going for WGS?

High-grade serous ovarian carcinoma (HGSC)



- Not **"ovarian"**
- **Survival unchanged** over past 20 years
- **Limited molecular classification**

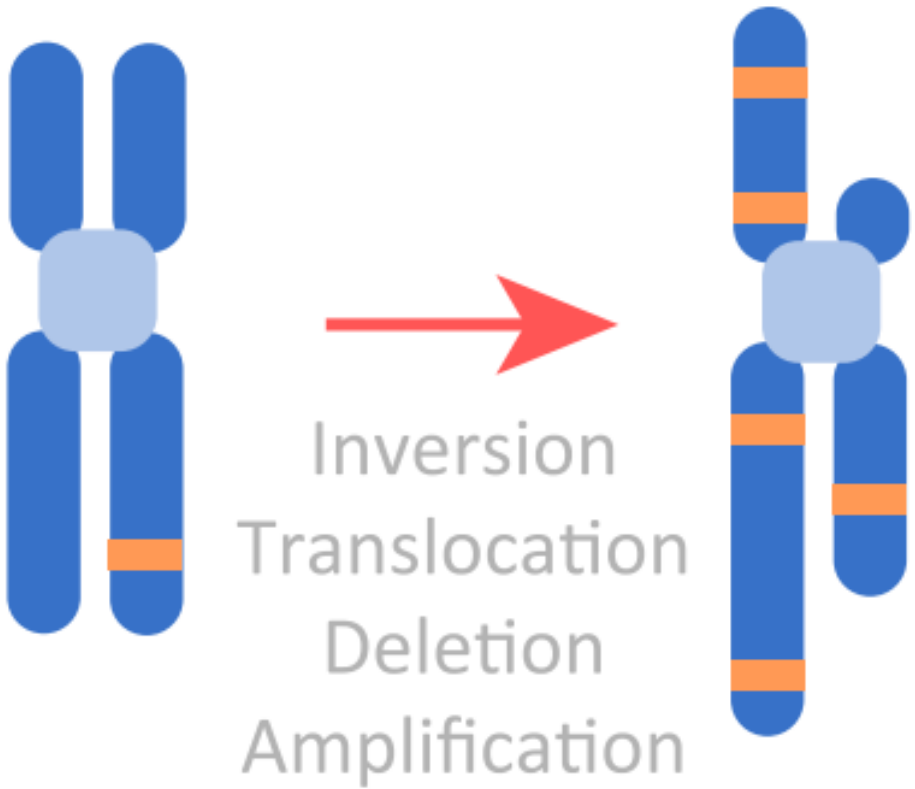
High-grade serous ovarian carcinoma (HGSC)

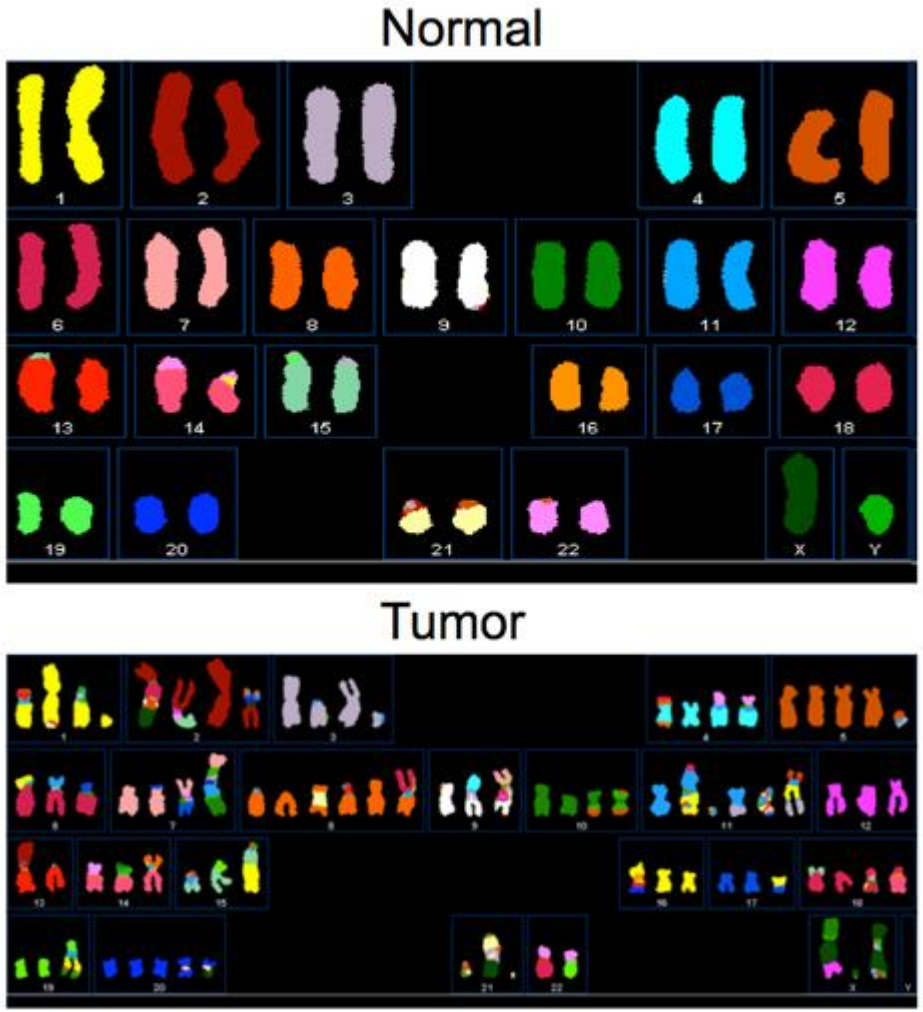


- Not “**ovarian**”
- **Survival unchanged** over past 20 years
- **Limited molecular classification**

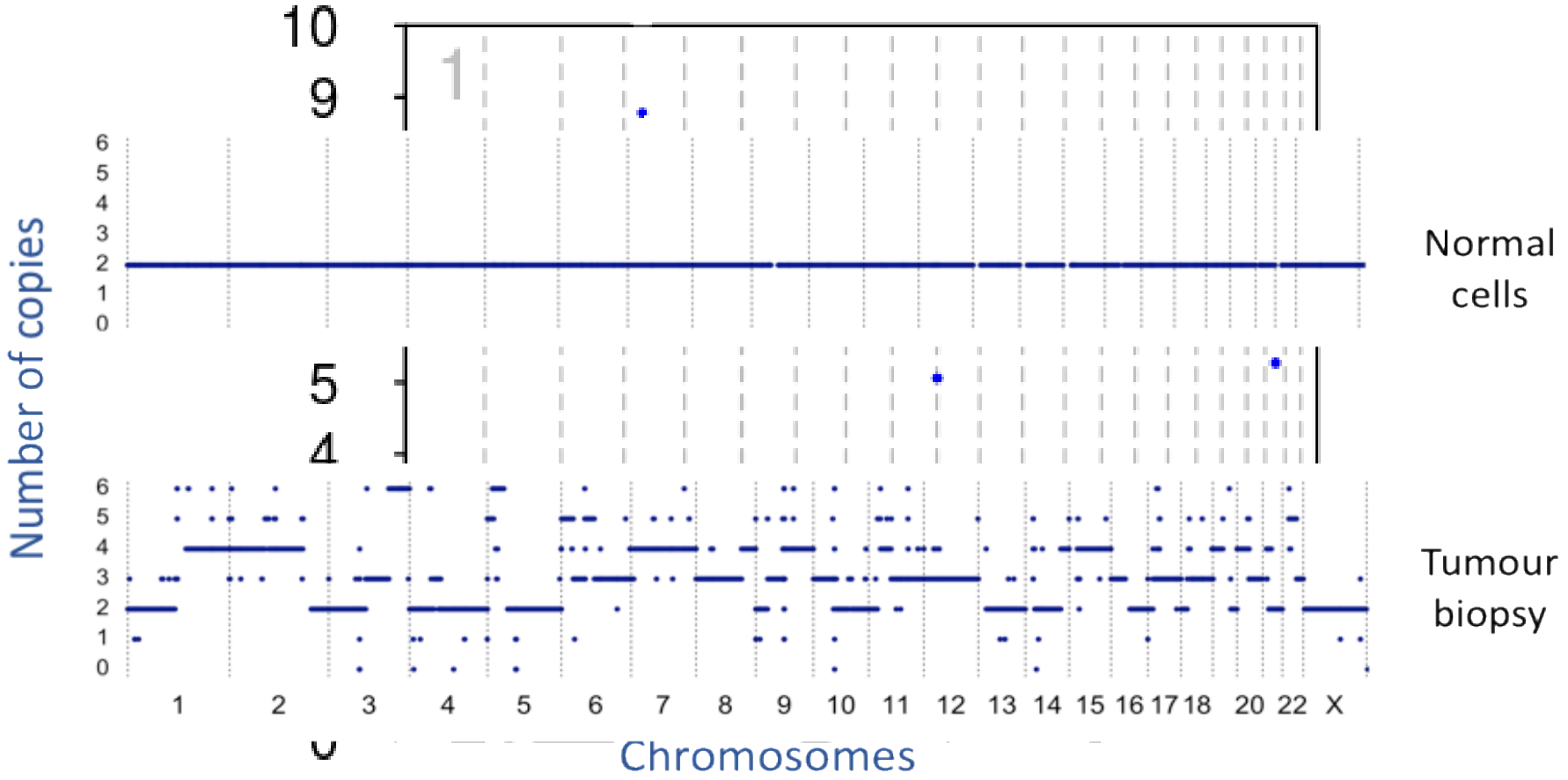
- Defined by ***TP53*** mutation and **chromosomal instability**
- **Mutational processes** may predict therapy
- “**HRD**” vs “homologous recombination proficient”

HGSC has extreme chromosomal instability

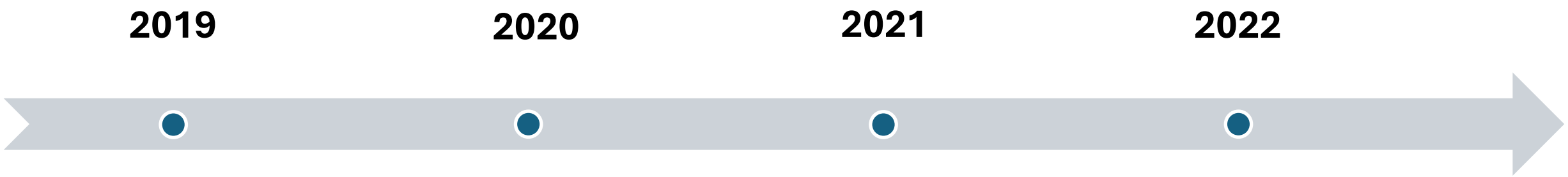




Whole genome representation of copy number aberrations



BRCA1/2 and HRD testing: current and evolving guidelines



NHS

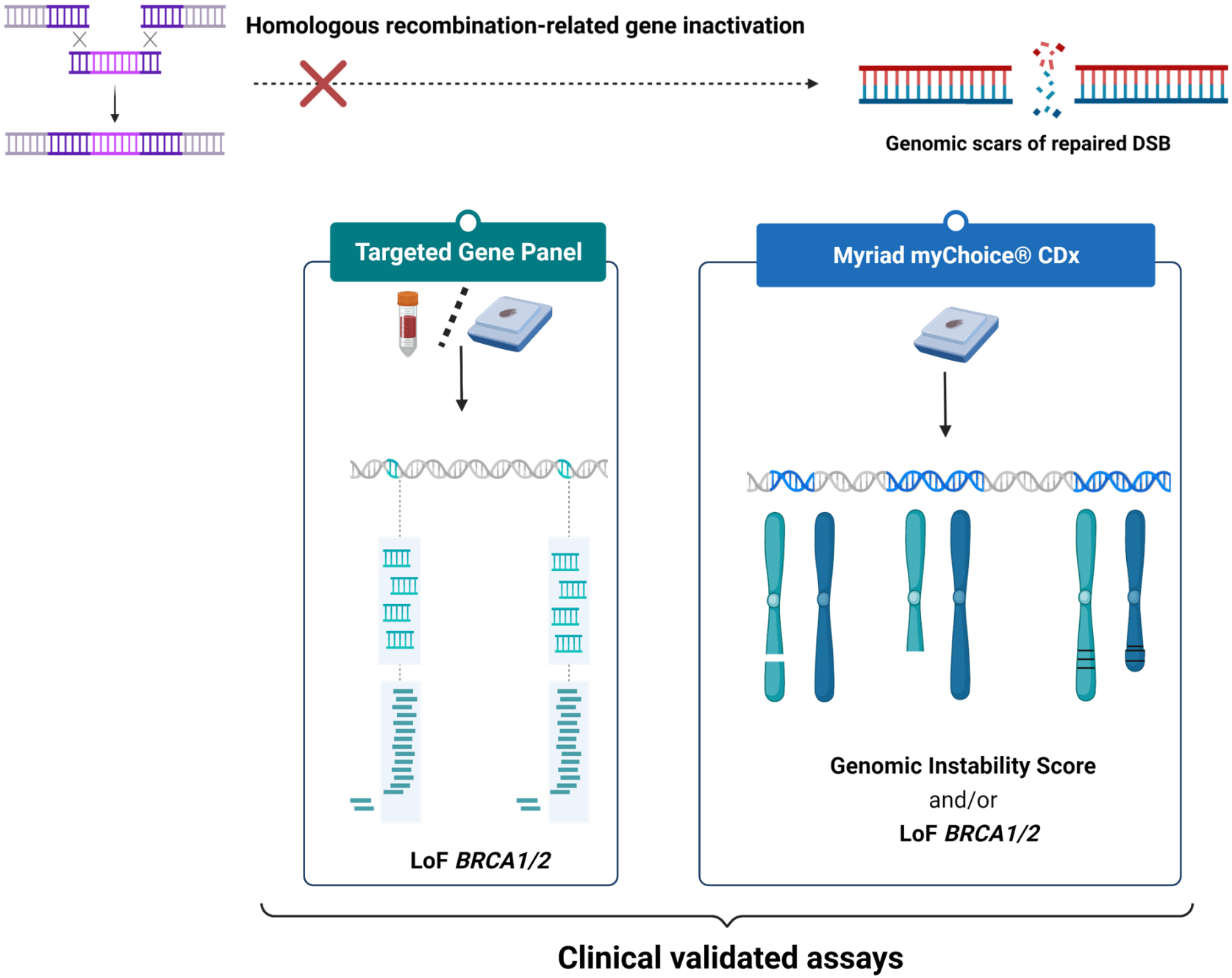
- **Mainstreaming testing for germline *BRCA1/2* mutations**
- **Early access programme HRD biomarker**
- **WGS testing**

ASCO

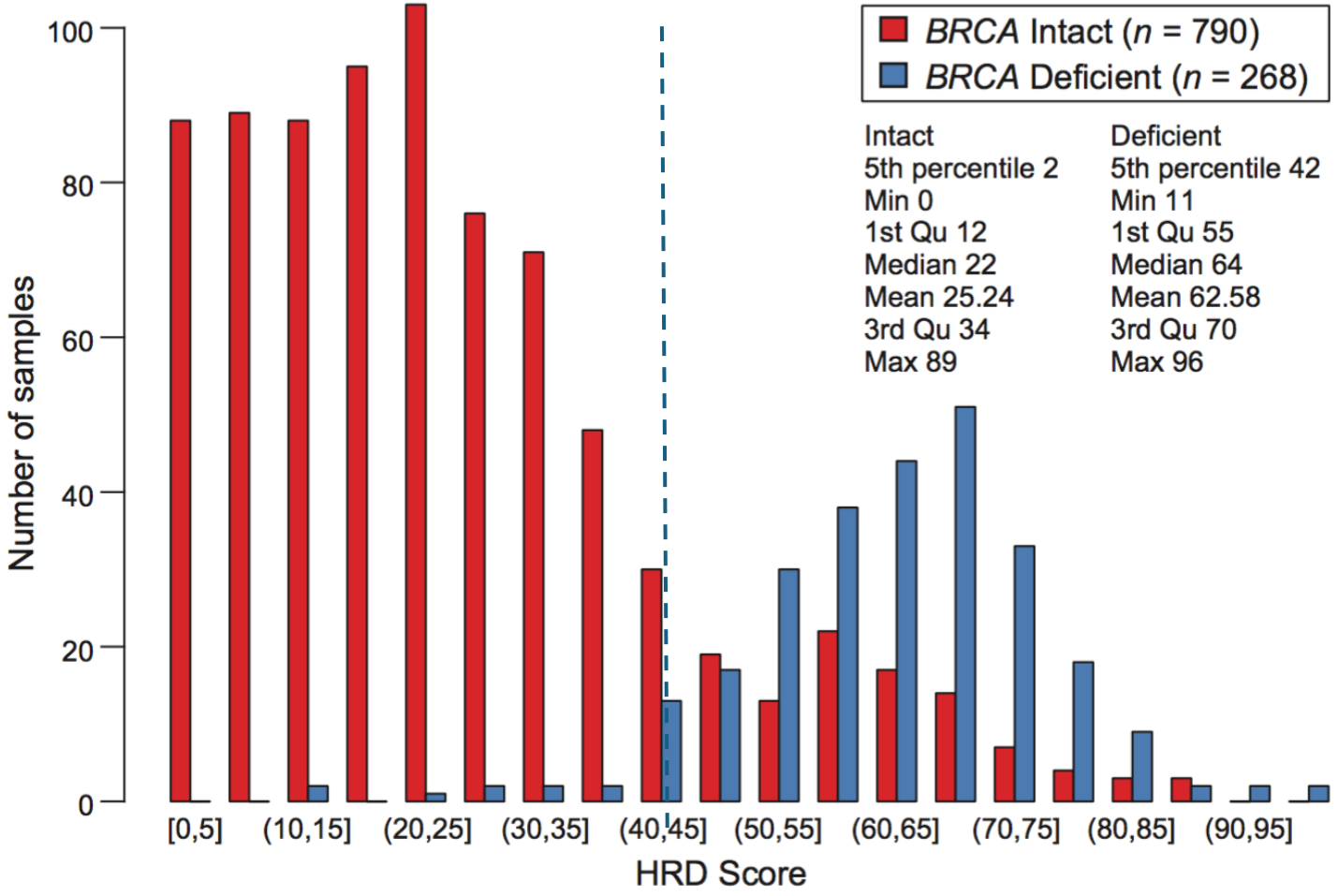
- **Germline genetic testing for *BRCA1/2*, and other ovarian cancer susceptibility genes**.
- If germline negative, pursue **somatic *BRCA*** testing

ESMO

- **Germline/somatic *BRCA1/2* mutations** at diagnosis
- **Testing for genomic instability (HRD)** is recommended.


Homologous recombination-related gene inactivation
Genomic scars of repaired DSB
Targeted Gene Panel
LoF BRCA1/2
Myriad myChoice® CDx
Genomic Instability Score
and/or
LoF BRCA1/2
Clinical validated assays

Myriad testing is a simple similarity score

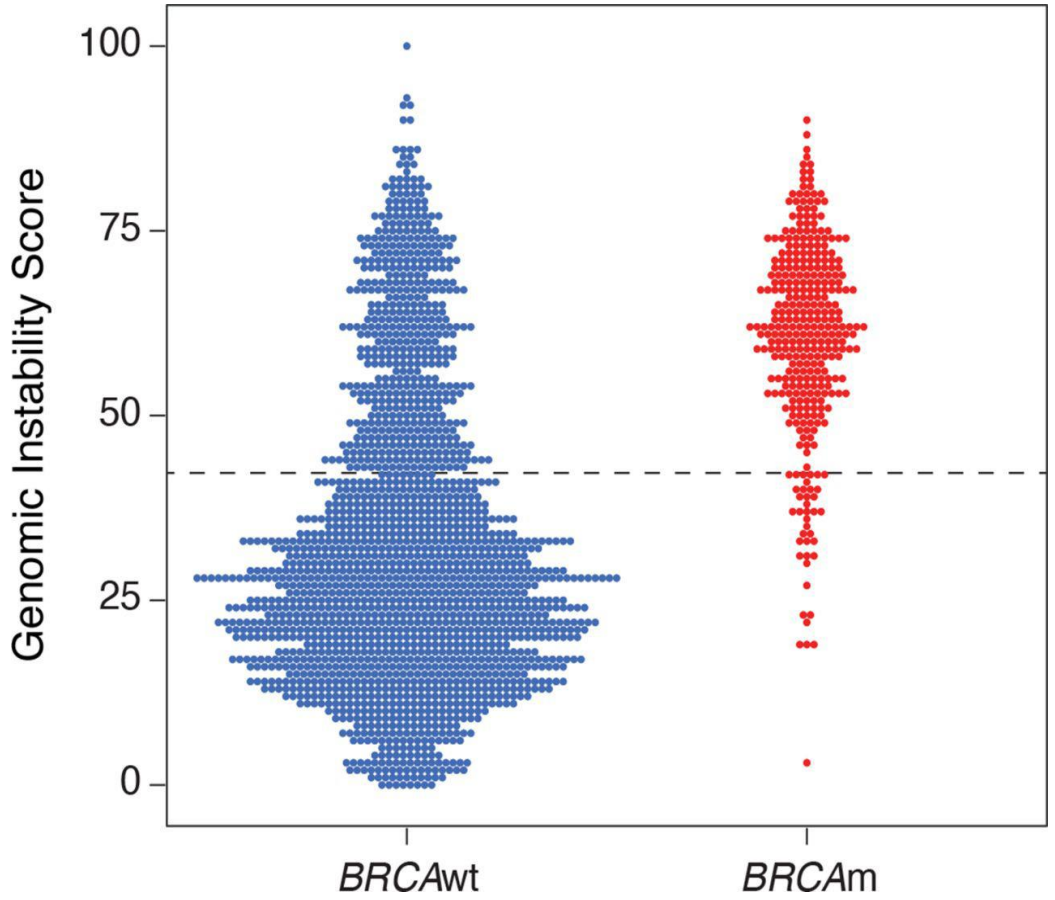


See also Abkevich V. et al. 2012. Patterns of genomic loss of heterozygosity predict homologous recombination repair defects in epithelial ovarian cancer. Br J Cancer 107:1776–1782. doi:10.1038/bjc.2012.451

Real-world HRD testing

- 2829 tumours
- Sample failures dropped from 22% to 5% after 2021
- Somatic mutation testing

Gene	%	*N*	
BRCA1	9	220	
BRCA2	7	165	
	16	**385**	**2474**



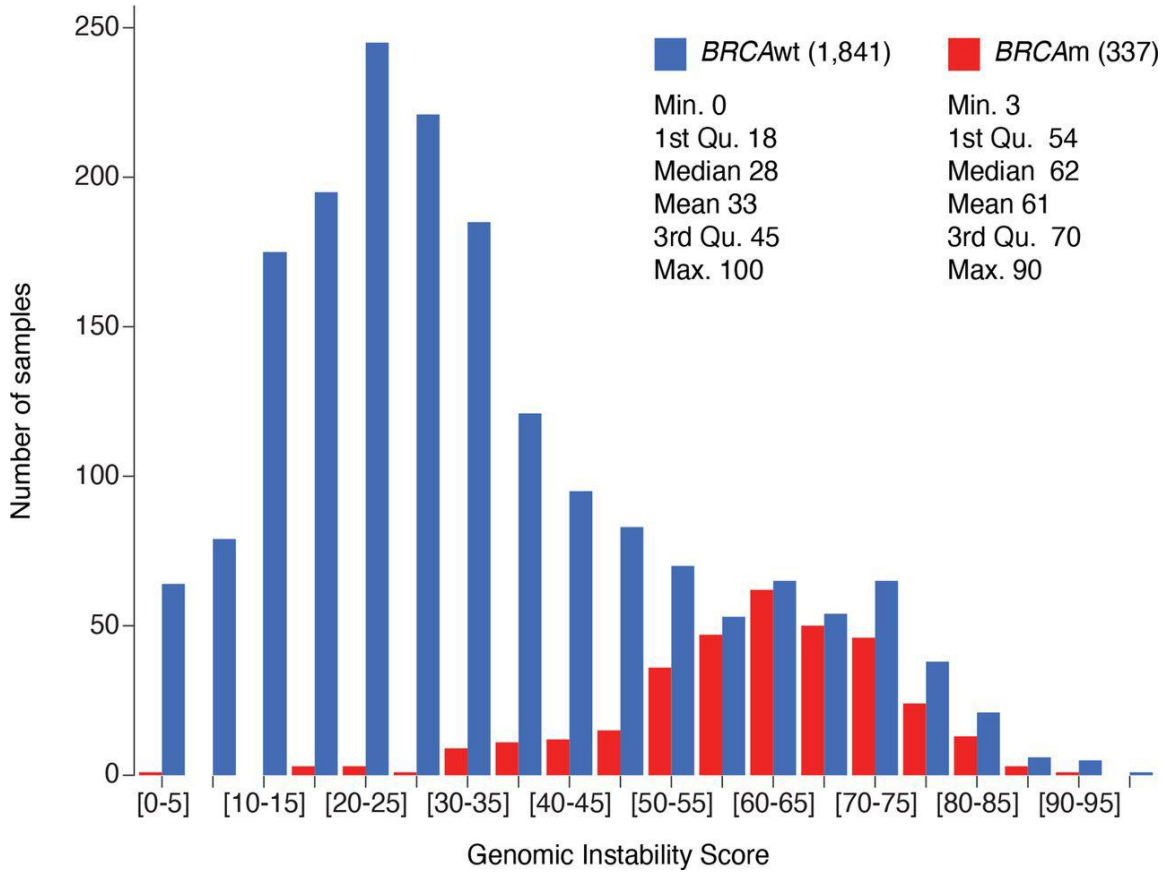
Morgan RD et al. 2023. Homologous recombination deficiency in newly diagnosed FIGO stage III/IV high-grade epithelial ovarian cancer: a multi-national observational study. *Int J Gynecol Cancer* ijgc–2022–004211. doi:10.1136/ijgc-2022-004211

Real-world HRD testing

- 37% tumours had GIS ≥42

(*N* = 814/2178)

Somatic mutation	%	*N*
BRCA1/2	37	304
WT	63	510
		814



Morgan RD et al. 2023. Homologous recombination deficiency in newly diagnosed FIGO stage III/IV high-grade epithelial ovarian cancer: a multi-national observational study. *Int J Gynecol Cancer* ijgc–2022–004211. doi:10.1136/ijgc-2022-004211

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

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

R. E. Miller[1,2], A. Leary[3], C. L. Scott[4,5], V. Serra[6], C. J. Lord[7,8], D. Bowtell[4,5], D. K. Chang[9,10], D. W. Garsed[4,5], J. Jonkers[11], J. A. Ledermann[12], S. Nik-Zainal[13,14], I. Ray-Coquard[15,16], S. P. Shah[17], X. Matias-Guiu[18], E. M. Swisher[19] & L. R. Yates[20,21*]

Miller RE et al. 2020. ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. *Ann Oncol* **31**:1606–1622. doi:10.1016/j.annonc.2020.08.2102

Consensus statement

British Gynaecological Cancer Society/British Association of Gynaecological Pathology consensus for genetic testing in epithelial ovarian cancer in the United Kingdom

Elaine YL Leung [1], Shibani Nicum,[2] Jo Morrison,[3,4] James D Brenton,[5] Ionut-Gabriel Funingana,[5] Robert D Morgan [6,7], Sadaf Ghaem-Maghami,[8] Tracie Miles,[9] Ranjit Manchanda [10,11], Rebecca Bowen,[12] Adrian Andreou,[12] Will Loughborough,[12] Susan Freeman,[13] Ketan Gajjar,[14] Sarah Coleridge,[14,15] Mercedes Jimenez-Linan,[16] Janos Balega,[17] Jonathan Frost,[12] Amy Keightley,[18] Yvonne Wallis,[19] Sudha Sundar,[1,17] Raji Ganesan[19]

Leung EY et al. 2024. British Gynaecological Cancer Society/British Association of Gynaecological Pathology consensus for genetic testing in epithelial ovarian cancer in the United Kingdom. *Int J Gynecol Cancer* **34**:1334–1343. doi:10.1136/ijgc-2024-005756

BGCS/BAGP consensus for genetic testing

Table 1 A summary of recommended genetic testing in ovarian cancer

	Germline testing	Tumor testing
Indications – histologic type	Offer to all patients with EOC	Offer to all patients with high-grade EOC
Indications- stage	All stages	Stages III and IV*
Timing of test	Offer from as early in a patient's journey as possible. If the patient wants time to consider further, offer storage for DNA banking.	At the time of histological diagnosis
Sequence of testing	Parallel testing	Parallel testing
Information provided to patient	**Mandatory** written information on the implications for patients and their family.	**Good practice** to have written information regarding test including implications for treatment and germline testing if test results relevant.
Consent	Written consent to be obtained, if mandated by the testing laboratory. If a patient declines testing, this should be documented.	Reflex theranostic tumor testing with an established pathway set up locally to manage test results.† Opt-out option may be provided according to local protocol.

*Tumor testing for *BRCA* mutations could be performed in Stage I-II disease, although this does not currently influence standard-of-care treatment choices in first-line settings.
†Some devolved nations in the United Kingdom already have an established national reflex theranostic tumor testing strategy.
EOC, epithelial ovarian cancer.

Leung EY et al. 2024. British Gynaecological Cancer Society/British Association of Gynaecological Pathology consensus for genetic testing in epithelial ovarian cancer in the United Kingdom. *Int J Gynecol Cancer* **34**:1334–1343. doi:10.1136/ijgc-2024-005756

Cancer National Test Directory v13.1

Code	Test	Target genes	Further eligibilty
M2.1	Multi-target NGS panel - small variant (BRCA1, BRCA2, SMARCA4)	BRCA1, BRCA2, SMARCA4	Known high grade serous ovarian carcinoma or In cases of diagnostic uncertainty of small cell carcinoma of the ovary
M2.5	HRD status (either positive for BRCA 1 and/or 2, or HRD positive)	BRCA1/2 and/or genomic instability	Patient is eligible for first line treatment and has a diagnosis of high grade ovarian cancer
M233.1	WGS Germline and Tumour	All including burden / signature	Histologically proven high grade ovarian carcinoma including endometrioid carcinoma where the patient has exhausted standard of care testing and there is a clear clinical question, and results have expected utility/impact Routine standard of care testing should proceed in parallel. "

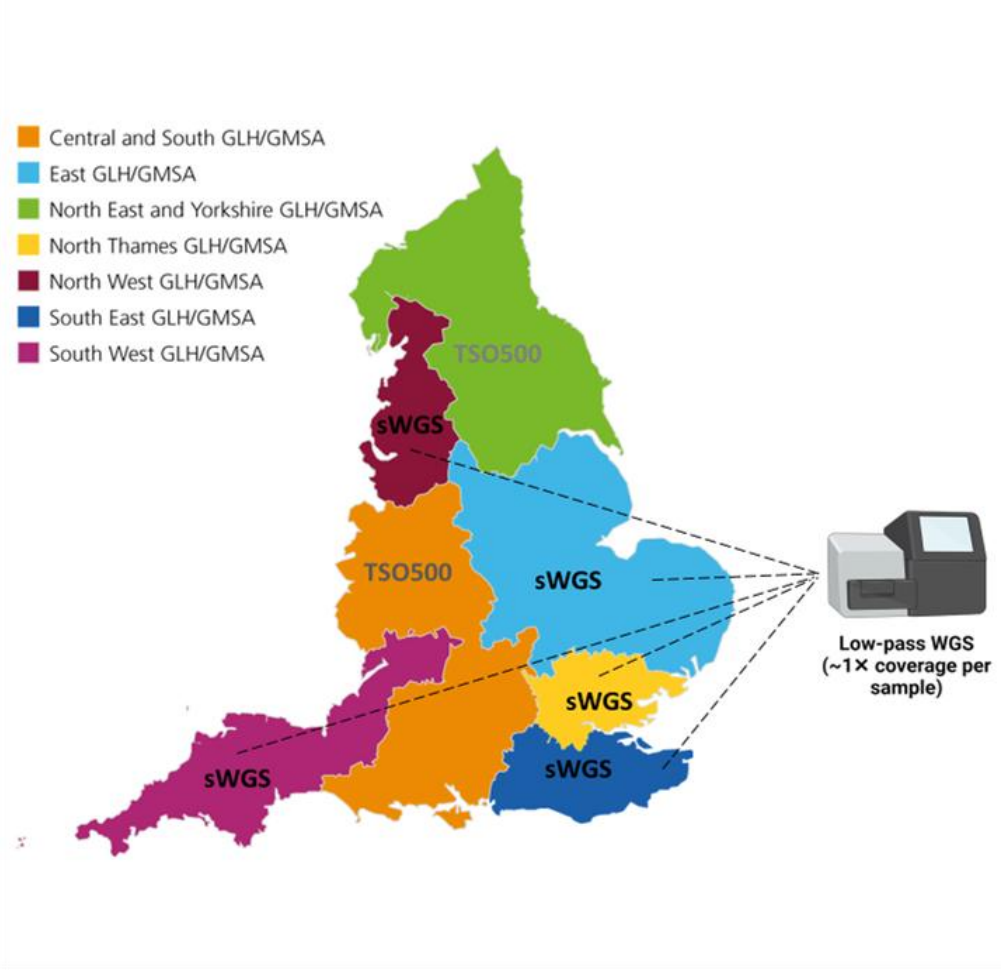
NHS England » National genomic test directory

Biopsy pathway for neoadjuvant patients

- Typical sites are peritoneal/omental disease, lymph nodes and pelvic masses
- Decision by an experienced radiologist supported by a multidisciplinary tumor board
- Balance between tissue accessibility and procedural risks (alternatively consider laparoscopic biopsy)
  - BriTROC study demonstrated safety (2.4% complications) with 14G or 16G needles
  - Co-axial needle technique is recommended for patient comfort and multiple sampling

Goranova T et al. 2017. Safety and utility of image-guided research biopsies in relapsed high-grade serous ovarian carcinoma-experience of the BriTROC consortium. *Br J Cancer* **116**:1294–1301. doi:10.1038/bjc.2017.86

NHS HRD testing will use sWGS and commercial providers



- Shallow whole genome testing is now commonest assay
- Performed together with cancer panel testing

New HRD tests

Test	Origin	Type	PAOLA-1 patients (n)	Presentation
myChoice	Myriad (USA)	BRCAm + GIS ≥42	806	PAOLA-1 NEJM
Leuven	Leuven (Belgium)	90,000 SNPs + HRR panel	468	Loverix et al (2023) EJC
Geneva	HUG (Swiss)	Normalised LST	469	Christinat et al (2023) JCO Precis Oncol
NOGGO-GIS	Hamburg (Germany)	20,000 SNPs	383	ESGO Berlin 2022
Köln – NKI	Köln (G) – NKI (Netherland)	LOH, scoring	469	
GIScar	Caen (France)	Instability score 127 genes	469	ESMO gyn Barcelona 2023
Curie	Curie (France)	sWGS	469	ESMO gyn Barcelona 2023
SOPHiA Genetics	CLB (France) Sophia (Swiss)	sWGS + gene panel	195	ESGO poster 2022
Illumina	Myriad/AZ-MSD-Illumina	Myriad assay	400	ESGO Prague 2021
SeqOne	SeqOne (France)	sWGS + gene panel	364	ESMO gyn Barcelona 2023

Abstract;201;Pujade-Laurain E;Int J Gynecol Cancer;2021;31;A208

Current HRD reports

Clinical Indication Ovarian Carcinoma M2

Sample Details

PS25-31987 A1: Peritoneal biopsy - serous carcinoma, likely high grade. For treatment decision

Tumour Nuclei % 30-50%

Result

HRD Assay Result

QA Status	GI Index	HR Status
High	-4.8 (Negative)	**HR Proficient**

HR Deficient = GI Index equal to or greater than zero
HR Proficient = GI Index less than zero

Result Summary

The negative GI index indicates this specimen is **homologous recombination proficient.**

BRCA testing will follow as a separate report.

The collective GI Index and BRCA1/2 result is required to finalise overall HRD status.

Current HRD reports

Test Methodology

HRD Assay Methodology

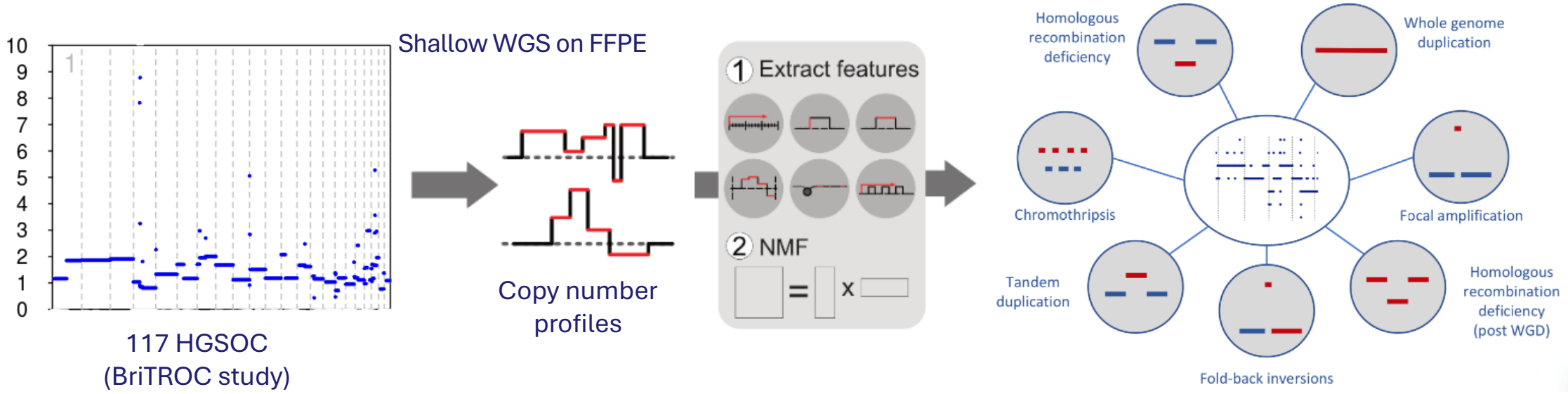
Low-pass (shallow depth) whole genome sequencing was performed using a commercial protocol and reagents (Illumina DNA PCR-Free Library Prep Tagmentation). DNA libraries were sequenced on the NovaSeq 6000 platform using an SP Flow cell running 300 cycles.

The low-pass WGS (lpWGS) data is analysed by a commercial supplier (Giinger-Sophia Genetics) which uses a deep learning algorithm that has been specifically trained to recognise patterns of Homologous Repair Deficiency in the genome of Ovarian cancer samples. The algorithm analyses low-pass WGS
(lpWGS) data and produces a "Genomic Integrity" (GI) index that is a quantitative measurement of the level of genomic aberrations present in the sample being tested.

– **HR deficient** = GI positive: samples with a **GI index larger or equal to 0.**
– **HR proficient** = GI negative: samples with a **GI index smaller than 0**.

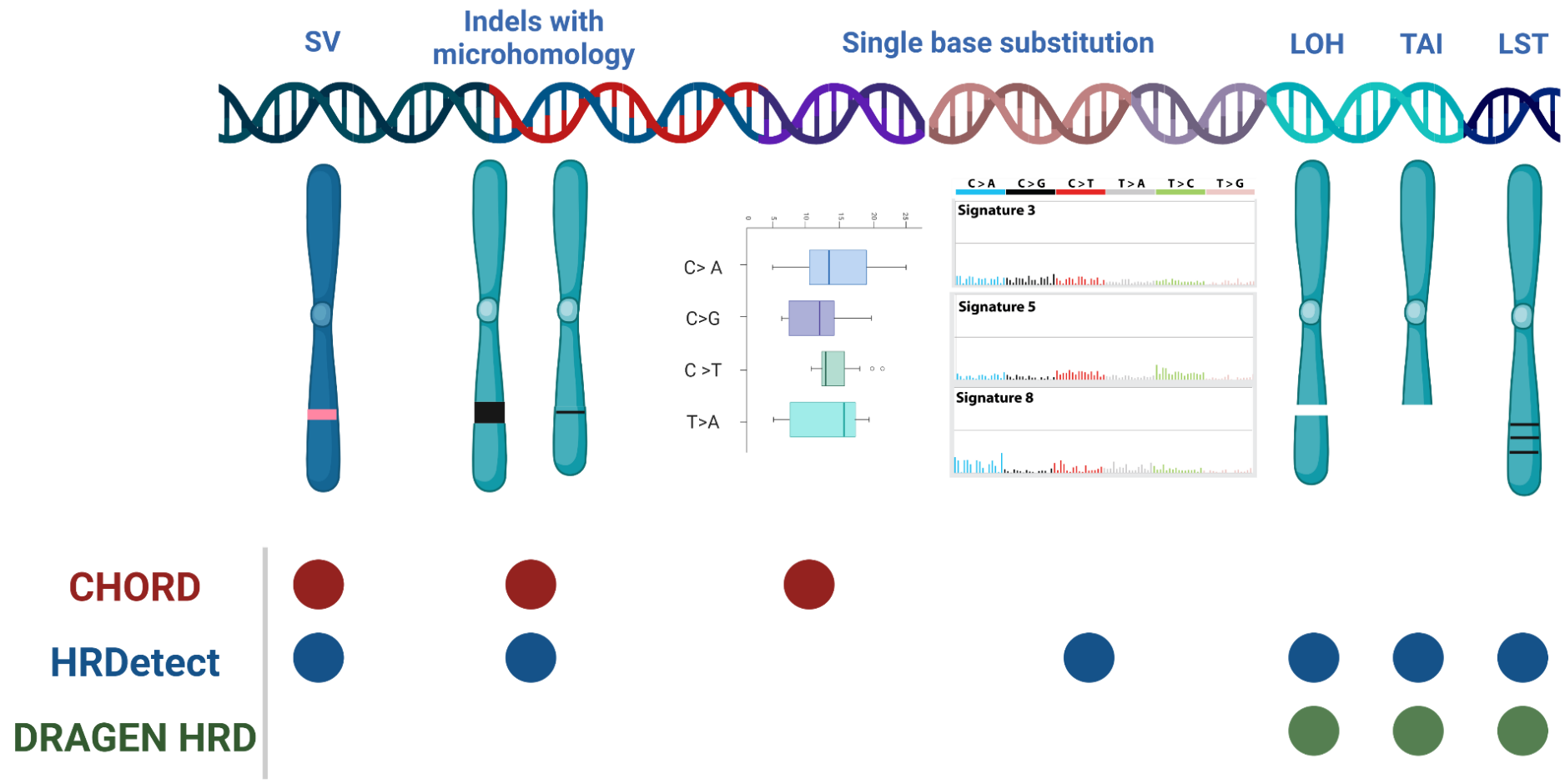
Data quality
A quality score of the available lpWGS data is calculated as follows:
– High quality: the quality of the data is sufficient to confidently compute a GI index and a GI status.
– Medium quality: the quality of the data is lower (compared to high quality) and, as a consequence,
the deep learning algorithm may not succeed in computing a GI index.
– Low quality: the quality of the data does not meet the criteria required to compute a GI index.

Copy number signatures identify mutational processes

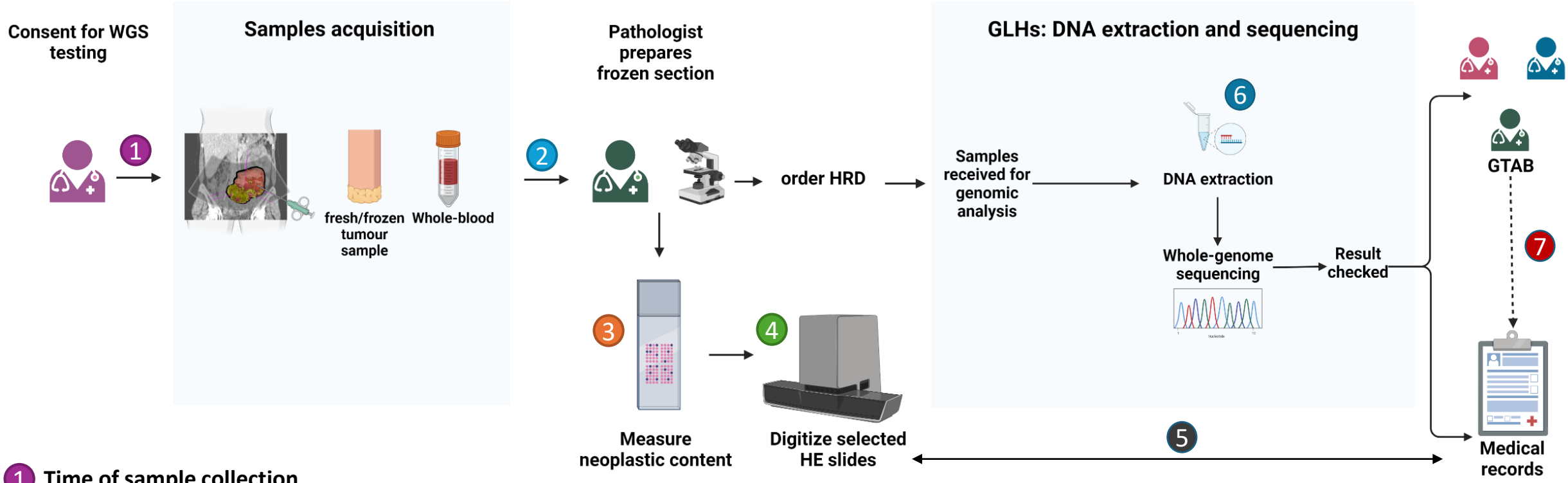


1. Thompson JS et al. 2025. Predicting resistance to chemotherapy using chromosomal instability signatures. *Nat Genet* **57**:1708–1717. doi:10.1038/s41588-025-02233-y
2. Drews RM et al. 2022. A pan-cancer compendium of chromosomal instability. *Nature* **606**:976–983. doi:10.1038/s41586-022-04789-9
3. Macintyre G et al. 2018. Copy number signatures and mutational processes in ovarian carcinoma. *Nat Genet* **50**:1262–1270. doi:10.1038/s41588-018-0179-8
4. Piskorz AM et al. 2016. Methanol-based fixation is superior to buffered formalin for next-generation sequencing of DNA from clinical cancer samples. *Ann Oncol* **27**:532–539. doi:10.1093/annonc/mdv613

Deep whole genome sequencing

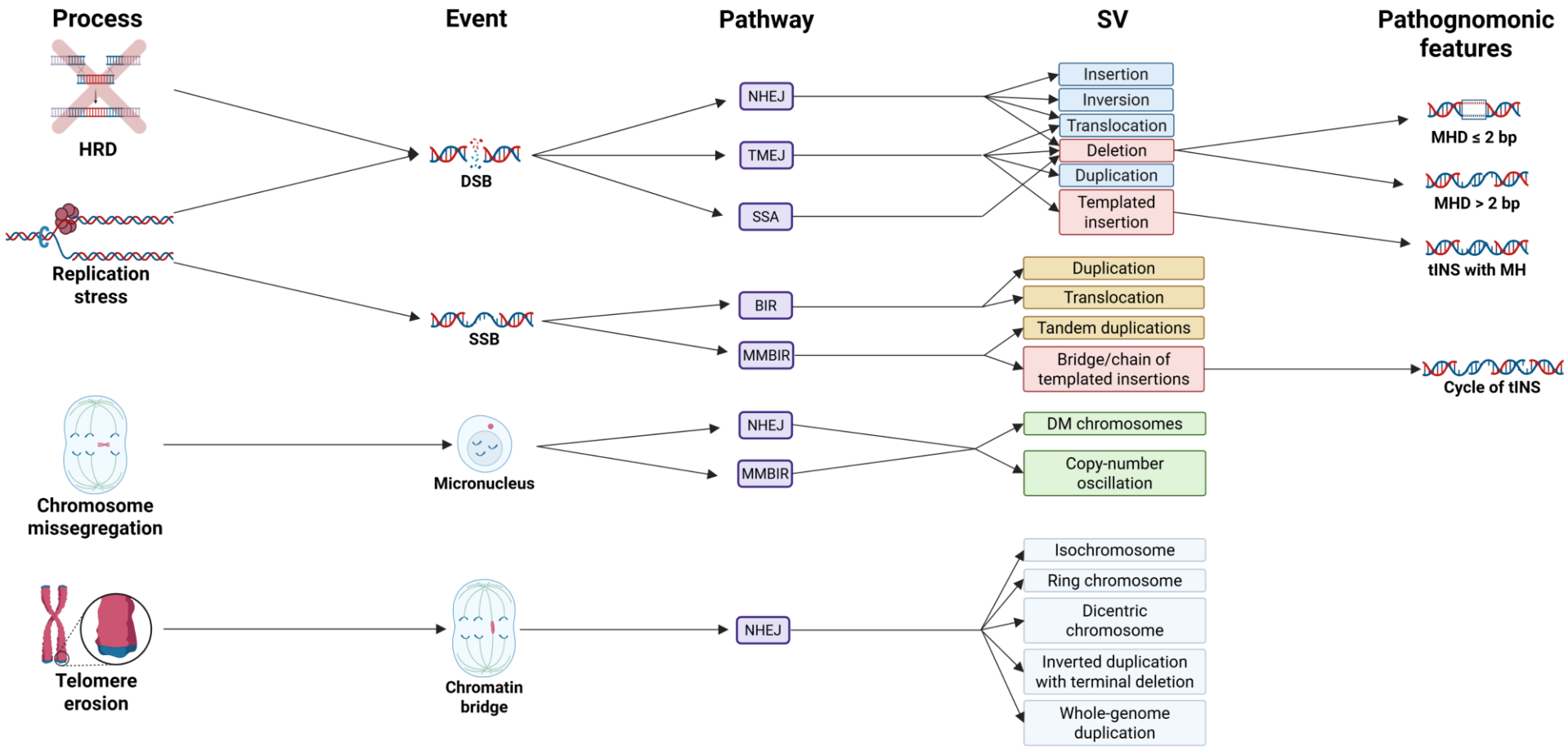


WGS pathway



1. Time of sample collection
2. Time of sample arrival in the Pathology department
3. Tumour cellularity: 1. Percentage of area occupied in the whole-slide and 2. Percentage of area occupied in the marked tumour area
4. Digitize selected HE slides to measure : 1. Reproducibility 2. Evaluate tumour versus normal DNA content and 3. Develop teaching set
5. Turnaround time of WGS report
6. Tumour mass received (mg)/ DNA extraction yield (µg)
7. Success rate of WGS testing

Mechanisms of CIN and the structural variants (SV) they leave behind



- Cosenza MR. Structural variation in cancer: role, prevalence, and mechanisms. Annu Rev Genomics Hum Genet 23:123–152. doi:10.1146/annurev-genom-120121-101149

Why aren’t we using WGS?

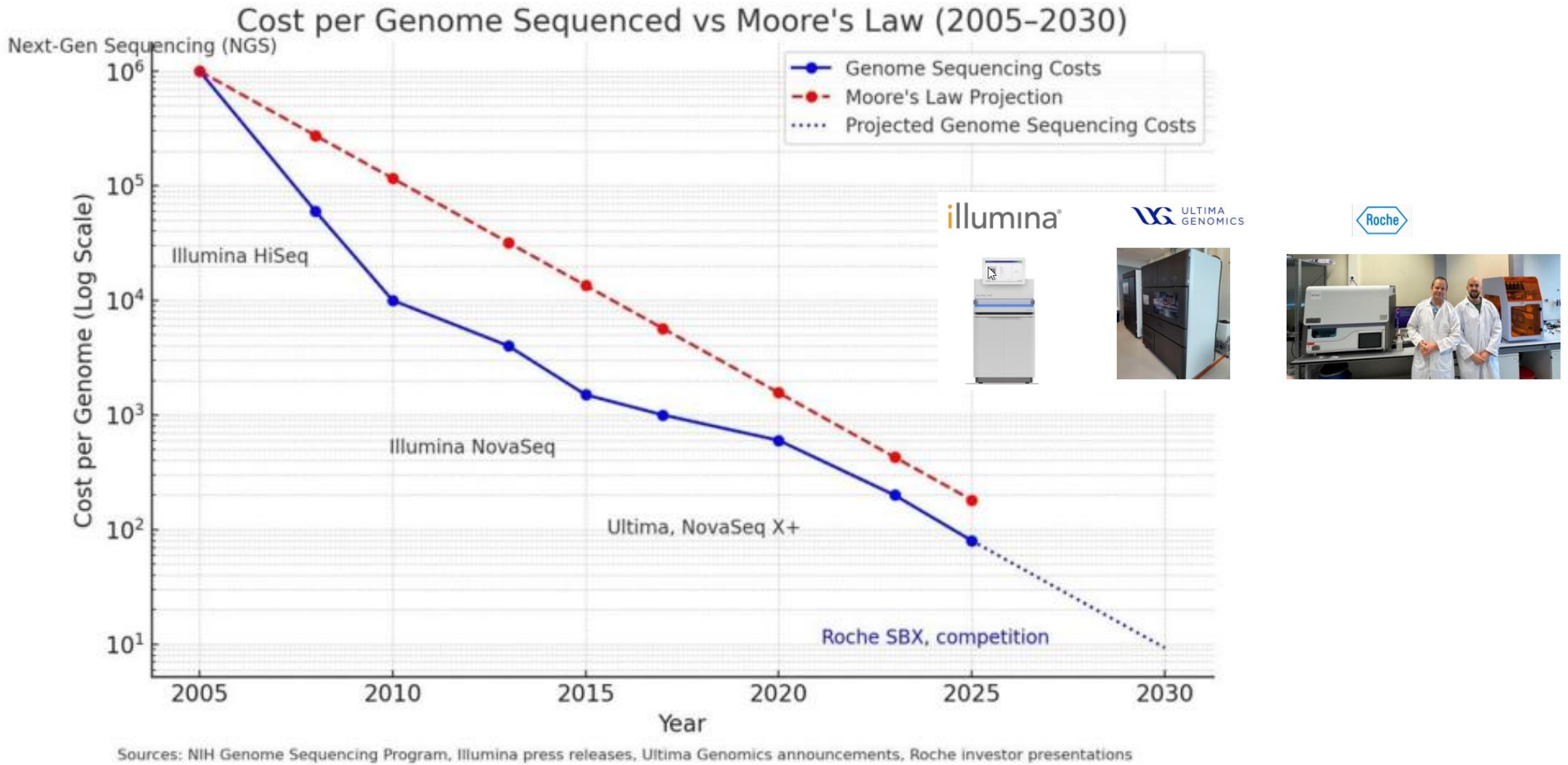
Only WGS can resolve complexity of HGSC genomes

- Is now feasible using NHSE pathways
- Provides value for today’s patient care
- Is getting cheaper with emerging technologies

Major barriers remain

- Pathology and clinical workflows
- Major variation in reporting times

Costs are falling



Summary

- Successful molecular profiling in HGSC requires expert and audited biopsy pathway for neoadjuvant patients
- Current “HRD” tests are measuring patterns of loss of heterozygosity — and have significant limitations for true personalized medicine
- Cost and availability of WGS are rapidly changing — and WGS has best potential for clinical prediction reading out biological features of DNA repair

Patient resources

What is an Ultrasound-guided Needle Biopsy?

https://youtu.be/tZKInrUV3v4

DEMO: GENETIC TESTING PATIENT INFORMATION

As part of IMPROVE UK and in collaboration with Sandwell and West Birmingham NHS Trust, and Cancer Research UK Cambridge Centre, we've created videos around genetic testing for ovarian cancer patients were created with patients from Birmingham and Cambridge.

The videos have been developed and translated to improve quality of care for those diagnosed with ovarian cancer across the UK.

Each video has been translated into Bengali, Polish, Punjabi, Romanian and Urdu. You'll find a playlist of translations for each video below, as well as some helpful materials.

GENETIC TESTING TRANSLATED VIDEOS | WHAT IS GENETIC TESTING?

This NHS video playlist offers patient information on genetic testing, associated with gynaecological cancers, translated in Bengali, Polish, Punjabi, Romanian and Urdu.

GENETIC TESTING TRANSLATED VIDEOS | WHAT ARE THE NEXT STEPS?

This video playlist offers patient information on the results of genetic tests, associated with gynaecological cancers, translated in Bengali, Polish, Punjabi, Romanian and Urdu.

GENETIC TESTING TRANSLATED VIDEOS | WHAT DO MY RESULTS MEAN?

This video shows patients recently diagnosed with cancer, what happens when they agree to genetic testing, and how it helps them – translated in Bengali, Polish, Punjabi and Urdu.

DEMO UK | Genetic Testing, Test Results and Next Steps Videos | Ovarian Cancer Action

Big thanks!

UNIVERSITY OF CAMBRIDGE

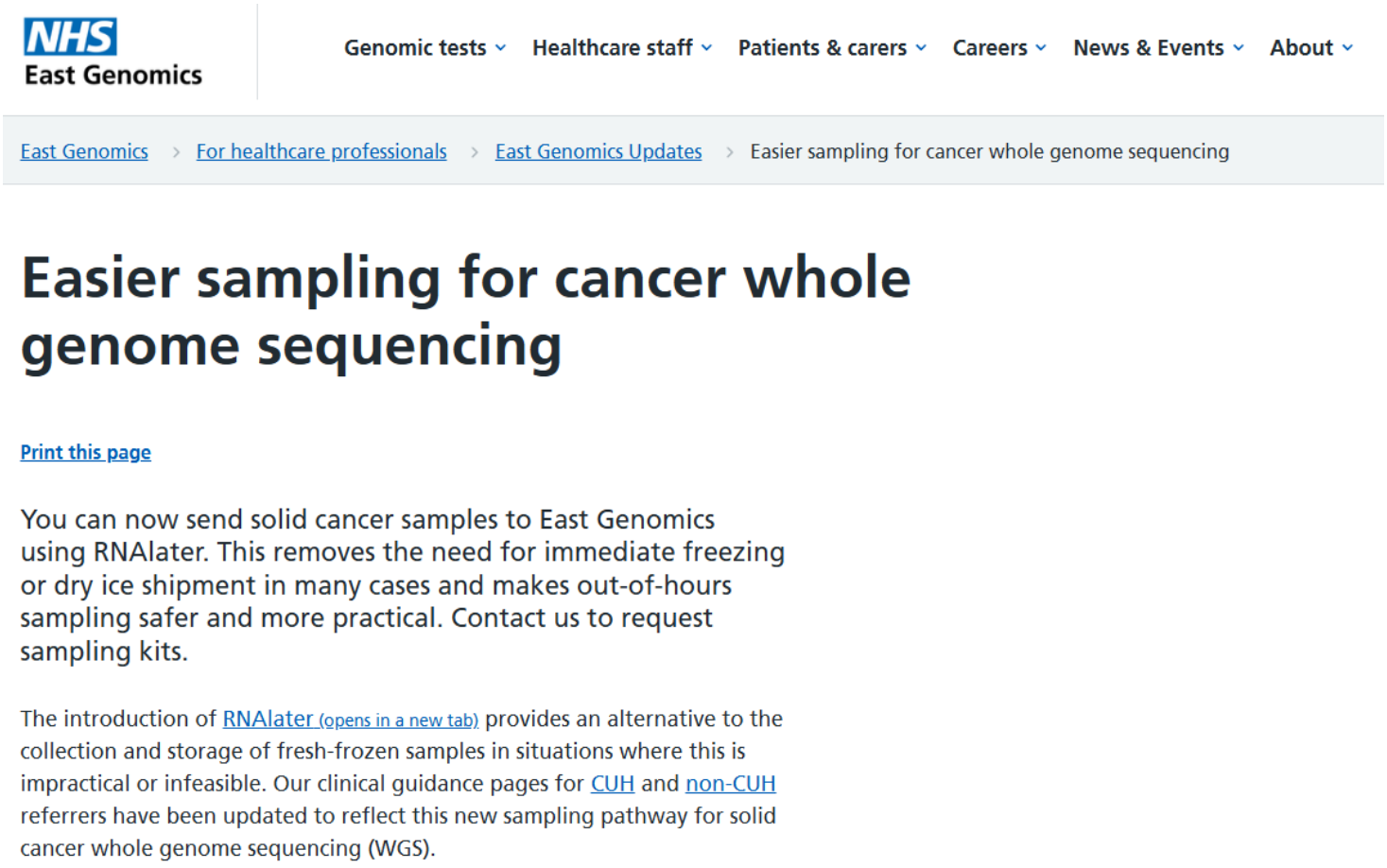
CANCER RESEARCH UK | CAMBRIDGE CENTRE

Cambridge University Hospitals NHS
NHS Foundation Trust

All participants in the studies
Dr Marie-Lyne Alcaraz
Dr Gabriel Funingan

Cambridge Women+s Cancer Programme
Addenbrookes Gynaecological Multidisciplinary Team and Molecular Pathology
Eastern GLH

New collection pathways



NHS East Genomics

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East Genomics › For healthcare professionals › East Genomics Updates › Easier sampling for cancer whole genome sequencing

Easier sampling for cancer whole genome sequencing

Print this page

You can now send solid cancer samples to East Genomics using RNAlater. This removes the need for immediate freezing or dry ice shipment in many cases and makes out-of-hours sampling safer and more practical. Contact us to request sampling kits.

The introduction of RNAlater (opens in a new tab) provides an alternative to the collection and storage of fresh-frozen samples in situations where this is impractical or infeasible. Our clinical guidance pages for CUH and non-CUH referrers have been updated to reflect this new sampling pathway for solid cancer whole genome sequencing (WGS).

RNAlater can be used to collect WGS samples without the need for freezing | East Genomics