



# Comprehensive molecular analysis of synchronous liver metastases identifies independent drivers of metastasis and endocrine resistance in hormone receptor–positive breast cancer

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## ABSTRACT

**Background:** Endocrine resistance in hormone receptor positive (HR+)/HER2 – metastatic breast cancer is commonly inferred from plasma-based biomarkers or single-site tissue biopsy. These approaches implicitly assume genomic homogeneity across metastatic disease which is an assumption that may not hold in the presence of spatially restricted resistant clones.

**Methods:** We report a patient with HR+ /HER2 – metastatic breast cancer who achieved a complete metabolic response to first line ovarian suppression, aromatase inhibition, and CDK4/6 inhibition, followed by isolated hepatic progression. Comprehensive genomic profiling was performed on the diagnostic liver biopsy and on multiple surgically resected liver metastases, enabling lesion-level comparison of responding and resistant disease.

**Results:** Baseline profiling demonstrated activating *AKT1* mutation, biallelic *ARID1A* alterations, and *FGFR1* amplification. Following prolonged endocrine control, pathological analysis of six resected liver specimens revealed marked inter-lesional genomic heterogeneity. Despite preserved oestrogen receptor expression across all metastases, canonical mechanisms of endocrine resistance, including an *ESR1* Y537N mutation, high-level *FGFR1* amplification, and an *ERCC2* alteration, were confined to a single non-responding lesion, while other metastases retained genomic features consistent with ongoing endocrine sensitivity. Despite uniform oestrogen receptor expression, divergent genomic evolution defined therapeutic resistance.

**Conclusions:** This case demonstrates that endocrine resistance in HR+ /HER2 – metastatic breast cancer may arise from spatially restricted genomic evolution rather than uniform tumour-wide escape and may not be captured by single-site biopsy or plasma analysis, with direct implications for disease sampling and precision therapy selection.

## 1. Introduction

Endocrine therapy combined with CDK4/6 inhibition represents the standard first-line treatment for hormone receptor positive (HR+), HER2-negative metastatic breast cancer, achieving durable disease control in many patients [1]. Nonetheless, acquired resistance inevitably develops, driven by diverse genomic mechanisms including *ESR1* mutations, fibroblast growth factor receptor amplification, and alterations

in PI3K–AKT signalling and chromatin remodelling pathways [2–4].

Molecular characterisation of resistance is increasingly guided by plasma circulating tumour DNA (ctDNA), which offers a minimally invasive means of detecting emergent resistance-associated variants [5]. However, ctDNA represents a spatially averaged signal derived from all shedding lesions and may fail to capture biologically dominant but anatomically restricted resistant clones [6]. Similarly, reliance on single-site tissue biopsy assumes genomic homogeneity across

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metastatic deposits, an assumption increasingly challenged by multi-region sequencing studies [7,8].

Opportunities to directly compare responding and resistant metastatic clones within the same organ are rare. Surgical resection of metastatic disease, although uncommon, provides a unique window into spatial genomic heterogeneity under active systemic therapy.

Here, we describe a patient with HR+ /HER2 – metastatic breast cancer who achieved an initial complete metabolic response to endocrine therapy and CDK4/6 inhibition, followed by isolated progression within the liver. Multi-lesion genomic profiling of resected liver metastases revealed striking lesion-specific genomic divergence, identifying molecular alterations confined to endocrine-resistant disease. This case illustrates how spatial genomic heterogeneity can underpin therapeutic resistance and highlights critical implications for precision oncology strategies, including the potential value of metastasis-directed therapy in the setting of limited disease progression.

## 2. Methods

This retrospective case study describes a patient with HR+ /HER2 – metastatic breast cancer managed at a tertiary-referral oncology centre. Written informed consent was obtained for the use of anonymised clinical and molecular data.

Radiological assessment included serial fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET–CT) and magnetic resonance imaging (MRI). Histopathological evaluation of tissue specimens included immunohistochemistry for oestrogen receptor (ER), progesterone receptor (PgR), HER2, Ki-67, and GATA3.

Comprehensive genomic profiling was performed on DNA and RNA extracted from formalin-fixed paraffin-embedded (FFPE) tumour tissue derived from the diagnostic liver biopsy and individually resected metastatic lesions using a semiconductor-based targeted next-generation sequencing assay (OncoPrint™ Comprehensive Assay Plus; Thermo Fisher Scientific), interrogating 511 oncogenes and tumour suppressor genes. All analysed samples were reviewed for tumour content, with a target threshold of  $\geq 20\%$  viable tumour content. Per-lesion tumour content estimates and sequencing metrics are provided in [Supplementary Table 1](#). The analytical sensitivity for detection of single-nucleotide variants and small insertions/deletions was 98.7%, with a lower limit of detection of approximately 5% variant allele fraction, and analytical specificity of 99.9%. Detection of copy number variants, including gene amplification and homozygous deletion, was supported across targeted regions, with sensitivity dependent on tumour purity and sequencing depth. Germline sequencing was not performed, and the assay does not distinguish between somatic and germline variants. Known population single-nucleotide polymorphisms were filtered using the proprietary bioinformatic pipeline of the sequencing provider. Tumour mutational burden (TMB), single-nucleotide variants, insertions/deletions, and copy number alterations were assessed. Genomic findings were interpreted in the context of treatment response.

DNA and RNA were extracted from formalin-fixed paraffin-embedded (FFPE) tissue using the QIAamp DNA FFPE Advanced Kit and RecoverAll™ Total Nucleic Acid Isolation Kit for FFPE, respectively, according to the manufacturers' protocols. Library preparation was performed using the OncoPrint™ Comprehensive Assay Plus workflow with 20 ng input nucleic acid. Sequencing was performed on an Ion GeneStudio™ S5 System (Thermo Fisher Scientific). Raw sequencing data were processed using Torrent Suite™ Software v5.18.1 (Thermo Fisher Scientific). Variant calling and annotation were performed using Ion Reporter™ Software v5.20 (Thermo Fisher Scientific), applying predefined thresholds for single-nucleotide variants, insertions/deletions, and copy number alterations. Quality control metrics included mean sequencing depth  $\geq 1000\times$ , coverage uniformity  $> 80\%$ , MAPD  $< 0.5$ , and amplicon coverage defined as  $\geq 95\%$  of amplicons covered at  $\geq 100$  reads. Copy number variation analysis was normalised against a baseline reference and interpreted in the context of tumour purity and

ploidy.

## 3. Results

### 3.1. Baseline Diagnosis and Molecular Profile

A 42-year-old woman was initially diagnosed in 2019 with a pT2N0 grade II/III invasive ductal carcinoma of the left breast, with receptor expression ER 8, PgR 8, and HER2 negative. Oncotype DX recurrence score was 8. She underwent breast-conserving surgery, adjuvant radiotherapy, and adjuvant endocrine therapy with tamoxifen.

Metastatic relapse involving the liver and lungs was identified in November 2023. Liver biopsy performed in December 2023 demonstrated metastatic carcinoma with retained hormone receptor expression (ER 8, PgR 8) and HER2 low (1 +/2 +; FISH non-amplified). PD-L1 expression was negative by both 22C3 and 28–8 assays, and tumour mutational burden was low (5 mutations/Mb).

Baseline genomic profiling identified an activating *AKT1* p.D323Y mutation, biallelic *ARID1A* alterations, and variants in *VHL* and *SETD2*. High-level copy number amplifications were detected in *FGFR1*, *CCND1*, and multiple *FGF* ligands, along with additional amplifications involving *EMSY*, *BCL2L12*, and *ZNF217* ([Table 1](#)).

### 3.2. Treatment Course and Emergence of Oligoprogression

First-line systemic therapy with ovarian suppression, letrozole, and ribociclib was initiated in March 2024, resulting in a rapid and complete metabolic response on FDG PET–CT. After sustained disease control, the patient elected to discontinue ribociclib in December 2024 while continuing endocrine therapy.

Subsequent surveillance imaging in September 2025 demonstrated progressive enlargement and increasing FDG avidity of a solitary liver lesion, with MRI and FDG PET–CT confirming isolated hepatic progression and no evidence of systemic escape.

Given the prolonged disease control elsewhere and isolated progression within the liver, multidisciplinary discussion supported surgical resection of metastatic disease to achieve local control and to enable detailed pathological and molecular assessment of resistant versus responding lesions.

### 3.3. Pathological Findings from Liver Metastectomy

In December 2025, six liver specimens were resected. Four of six specimens contained metastatic adenocarcinoma, all completely excised

**Table 1**  
Baseline genomic alterations from diagnostic liver biopsy (December 2023).

Gene	Variant
<i>ARID1A</i>	p.M793Wfs*40 (MAF 30.12% at 1448X)
<i>AKT1</i>	p.D323Y (MAF 32.26% at 341X)
<i>ARID1A</i>	p.A2237V (MAF 48.25% at 1052X)
<i>VHL</i>	p.I147V (MAF 51.25% at 780X)
<i>SETD2</i>	p.K629E (MAF 48.71% at 1099X)
<i>FGFR1</i>	Amplification (13 copies)
<i>CCND1</i>	Amplification (15 copies)
<i>FGF19</i>	Amplification (9 copies)
<i>FGF4</i>	Amplification (10 copies)
<i>FGF3</i>	Amplification (8 copies)
<i>EMSY</i>	Amplification (6 copies)
<i>BCL2L12</i>	Amplification (26 copies)
<i>ZNF217</i>	Amplification (8 copies)
<i>GNAS</i>	Amplification (6 copies)

Note: *VHL* p.I147V and *SETD2* p.K629E are classified as variants of uncertain significance (VUS) in the somatic setting and may represent germline variants in the absence of matched normal sequencing in the current analysis.

without capsular breach. Histopathological examination revealed variable degrees of fibrosis across lesions, consistent with heterogeneous treatment response (Fig. 1).

Notably, the largest lesion (27 mm) demonstrated minimal fibrosis, whereas smaller lesions within the same hepatic segment exhibited more prominent fibrotic change, suggesting differential sensitivity to endocrine therapy. Immunohistochemistry across all tumour-containing specimens showed preserved lineage and receptor expression, with CK7 and GATA3 positivity, ER 8, PgR 6, HER2 1 + (low), and Ki-67 approximately 30%.

Despite uniform hormone receptor positivity, the absence of fibrosis in the dominant lesion indicated biological resistance rather than phenotypic escape via receptor loss.

Blue indicates treated disease; red indicates active, treatment-resistant disease. Liver segments are shown.

### 3.4. Lesion-Specific Genomic Heterogeneity

Comprehensive genomic profiling of individual resected metastases revealed marked inter-lesional heterogeneity despite shared histopathological features. All tumour-containing specimens harboured truncal alterations, including biallelic *ARID1A* variants and shared *VHL* and *SETD2* mutations, consistent with early driver events retained throughout disease evolution.

In contrast, genomic alterations associated with endocrine resistance were confined to a single lesion corresponding to the radiologically and pathologically resistant focus. This lesion uniquely harboured an *ESR1* Y537N mutation, high-level *FGFR1* amplification (11 copies), and an *ERCC2* R112C variant. The activating *AKT1* p.D323Y mutation identified at baseline was retained in this resistant clone (Table 2). Notably, *FGFR1* amplification detected at baseline was absent in multiple responding lesions while retained at high level in the resistant lesion. This pattern is consistent with clonal selection under therapeutic pressure, with persistence of an *FGFR1*-driven resistant subclone.

By comparison, responding lesions demonstrated divergent evolution of the *AKT* pathway. One lesion showed complete loss of the *AKT1* p.D323Y mutation with restoration of wild-type sequence, while another exhibited *AKT1* gene amplification in the absence of the activating point mutation. Importantly, *ESR1* mutation and *FGFR1* amplification were absent from all responding lesions.

These findings demonstrate that endocrine resistance arose from a spatially restricted clone rather than global tumour evolution. Despite anatomical proximity within the liver and preserved oestrogen receptor expression, only the resistant lesion acquired canonical mechanisms of

endocrine escape (Fig. 2).

## 4. Discussion

This case provides direct evidence that endocrine resistance in HR+ /HER2 – metastatic breast cancer can be driven by spatially discrete genomic clones within the same metastatic organ. By analysing multiple liver metastases resected at a single time point, we demonstrate that alterations in *ESR1* and *FGFR1*—well-established mediators of endocrine resistance [2,4,9]—together with acquisition of an *ERCC2* variant implicated in DNA damage repair and treatment tolerance [10], were confined to the non-responding lesion, while adjacent metastases remained genomically consistent with endocrine sensitivity. The differential distribution of *FGFR1* amplification across lesions provides insight into the evolutionary dynamics of metastatic disease. Loss of amplification in responding lesions may reflect effective suppression or elimination of *FGFR1*-driven clones, whereas its retention in the resistant lesion supports a role in therapeutic escape. This pattern is consistent with spatially distinct clonal evolution and highlights the potential for polyclonal metastatic seeding, with subclones exhibiting differential pathway dependencies across anatomical sites. Such findings reinforce the importance of spatially resolved genomic profiling in understanding resistance mechanisms.

Beyond individual driver events, the co-occurrence of genomic alterations may further refine clinical stratification. In this case, concurrent alterations in *ARID1A* and *AKT1* suggest interaction between chromatin remodelling and PI3K–AKT pathway activation, which may influence both tumour behaviour and therapeutic sensitivity. The persistence of truncal alterations alongside lesion-specific resistance mechanisms highlights the need to consider combinatorial genomic contexts rather than single biomarkers when guiding treatment decisions.

The persistence of uniform oestrogen receptor expression across all lesions underscores that endocrine resistance is not synonymous with receptor loss. In the absence of matched germline sequencing, variants such as *VHL* p.I147V and *SETD2* p.K629E cannot be definitively classified as somatic drivers and may represent germline variants. These alterations are therefore interpreted with caution. Instead, resistance emerged through lesion-specific genomic evolution, highlighting the limitations of both single-site biopsy and plasma-based approaches that average signals across heterogeneous disease [6,7].

The observed divergence in *AKT1* alterations further illustrates the complexity of therapeutic targeting. While activating *AKT1* mutation was retained in the resistant lesion, its loss or replacement by gene

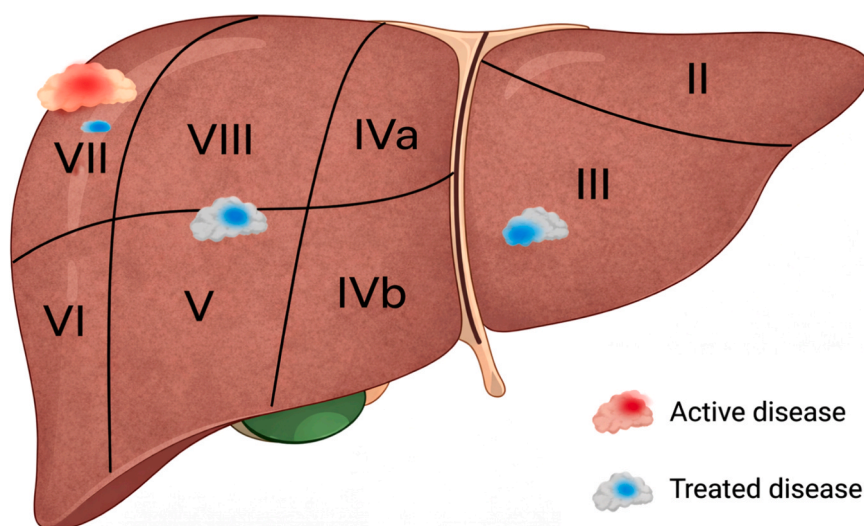


Fig. 1. Spatial distribution of responding and resistant liver metastases.

Table 2

Lesion-by-lesion genomic alterations in resected liver metastases compared with baseline. Blocks B, C, E, and F correspond to individually resected liver metastases as labelled in the surgical pathology report (segmental origin shown in the column header).

Gene	Variant	Baseline	Block B (Segment 5–8, responding)	Block C (Segment 3, responding)	Block E (Segment 7, responding)	Block F (Segment 7, resistant)
<i>ESR1</i>	p.Y537N	-	-	-	-	+
<i>AKT1</i>	p.D323Y	+	+	+	+	+
<i>AKT1</i>	Amplification	-	+	-	-	-
<i>FGFR1</i>	Amplification	+	-	-	-	+
<i>ERCC2</i>	p.R112C	-	-	-	-	+
<i>CCND1</i>	Amplification	+	-	-	+	+
<i>FGF19</i>	Amplification	+	-	+	-	+
<i>FGF4</i>	Amplification	+	-	+	-	+
<i>EMSY</i>	Amplification	+	-	-	-	+
<i>BCL2L12</i>	Amplification	+	-	-	-	+
<i>ZNF217</i>	Amplification	+	-	-	-	-
<i>GNAS</i>	Amplification	+	-	-	-	+
<i>FGFR3</i>	Amplification	-	+	+	+	-
<i>ARID1A</i>	p.M793Wfs*40	+	+	+	+	+
<i>ARID1A</i>	p.A2237V	+	+	+	+	+
<i>FGF3</i>	Amplification	+	+	+	+	+
<i>VHL</i>	p.I147V	+	+	+	+	+
<i>SETD2</i>	p.K629E	+	+	+	+	+
Fibrosis (histology)			+	+	+	-
Treatment response			Responsive	Responsive	Responsive	Resistant

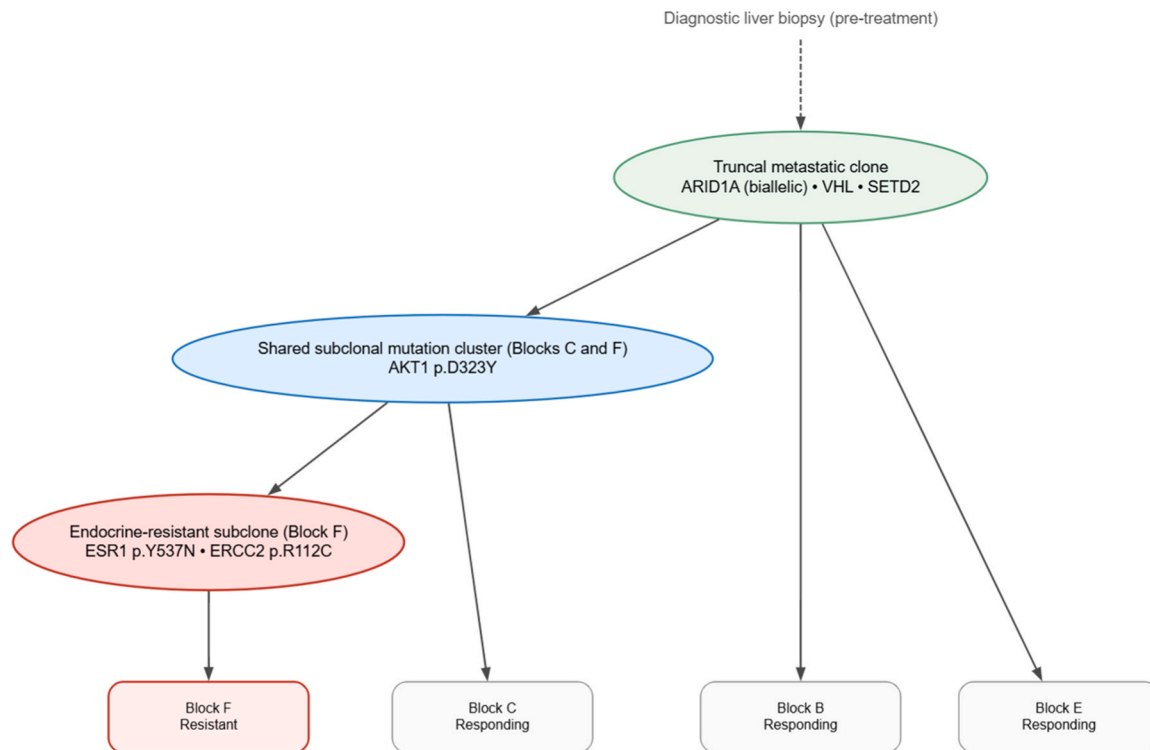


Fig. 2. Depiction of inferred clonal relationships among four resected liver metastases (Blocks B, C, E, and F). All lesions share a truncal mutation cluster characterised by *ARID1A* alterations, and shared *VHL* p.I147V and *SETD2* p.K629E variants. Lesion-level divergence is observed with a shared subclonal mutation cluster involving *AKT1* p.D323Y in Blocks C and F, and a spatially restricted endocrine-resistant subclone confined to Block F, defined by acquisition of *ESR1* p.Y537N and *ERCC2* p.R112C. The clonal tree was generated using LICHeE (Lineage Inference for Cancer Heterogeneity and Evolution) from a variant allele fraction matrix comprising 7 somatic variants identified by targeted next-generation sequencing. The tree was rendered in Graphviz format.

amplification in responding lesions suggests that sensitivity to AKT inhibition may vary spatially within the same patient [11]. Notably, divergent *AKT1* alterations were observed across responding and resistant lesions. These alterations ranged from retention of the activating mutation to gene amplification, and ultimately to complete loss. This finding suggests that alterations within the same signalling pathway may differ across metastatic lesions under the same therapeutic

pressure, with important implications for precision therapy selection. Together, these findings emphasise that precision oncology must account not only for which alterations are present, but where they reside. Image-guided tissue biopsy uniquely provides spatial and temporal separation of progressive and non-progressive disease, enabling rational targeting of the lesions that truly drive clinical outcomes [6,7]. These findings have potential implications for clinical algorithms in metastatic

breast cancer. Current approaches often rely on single-site biopsy or plasma-based assays to guide therapy selection. However, our data suggest that resistance mechanisms may be spatially restricted, raising the possibility that treatment decisions based on a single sample may not fully capture clinically dominant disease biology. Integrated profiling of fresh tissue biopsy specimens and circulating tumor DNA may provide a more comprehensive and precise approach to disease management. These observations raise clinically relevant questions regarding how resistance should be assessed and acted upon in practice, particularly when progression is driven by a spatially restricted clone rather than systemic escape. In this context, metastasis-directed therapies such as surgical resection, stereotactic ablative radiotherapy (SABR), or radio-frequency ablation may offer durable disease control in carefully selected patients with oligoprogressive disease, as supported by emerging phase II data including the AVATAR trial [12].

## 5. Conclusion

Multi-lesion genomic profiling of resected liver metastases revealed that endocrine resistance arose from a spatially restricted clone despite preserved hormone receptor expression across all lesions. This case illustrates the biological limitations of inferring resistance from single-site biopsy or plasma-based analyses alone and highlights the critical necessity of spatially informed disease sampling to guide optimal systemic therapy in HR+ /HER2 – metastatic breast cancer.

## Limitations

This report describes a single patient and cannot estimate the prevalence of spatial genomic heterogeneity or endocrine resistance mechanisms in HR+ /HER2 – metastatic breast cancer. Genomic analysis was limited to resected liver metastases, and resistant clones at other sites may not have been captured. Spatially resolved tissue sampling and metastasis-directed interventions are not universally feasible in routine clinical practice, and multi-region sequencing remains resource-intensive, potentially limiting the generalisability of this approach beyond selected patients treated at specialised centres. As an observational study, causal relationships between specific genomic alterations and treatment response cannot be inferred. The absence of matched germline sequencing limits definitive classification of certain variants as somatic versus germline.

## Ethics and consent to participate

This retrospective case study was conducted in accordance with institutional policies and ethical standards for case-based research. Written informed consent was obtained from the patient for use of anonymised clinical imaging and molecular data.

## Ethical committee

The hospital institutional review states that as a retrospective case study, formal ethical committee approval is not required.

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## CRedit authorship contribution statement

**Crispin Hiley:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Andrew Gaya:** Writing – review & editing, Writing – original draft, Investigation. **Vineet Datta:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Shahla Abu Naib:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation,

Conceptualization. **Eisa Velicaria:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Paul Ellis:** Conceptualization, Writing – review & editing. **Xi Wen Wang:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Joanna Lynch:** Writing – review & editing, Writing – original draft, Methodology. **Darshana Patil:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Tim Crook:** Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Formal analysis, Data curation, Conceptualization.

## Consent for publication

The patient gave written informed consent for publication of this case study.

## Declaration of Competing Interest

D.P. and V.D. are employees of Datar Cancer Genetics Ltd. The remaining authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.hmedic.2026.100462](https://doi.org/10.1016/j.hmedic.2026.100462).

## Data availability

Data will be made available on request.

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