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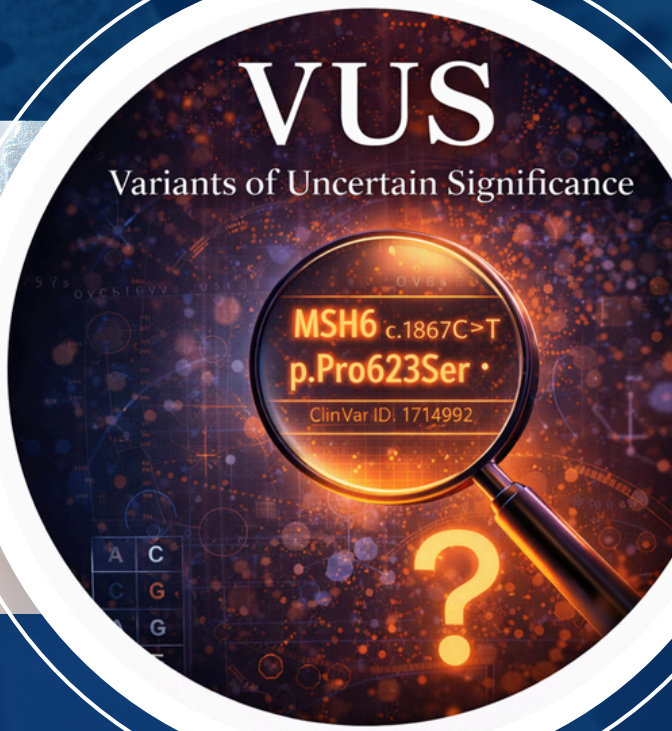
CASE – 5

MSH6 Variant of Uncertain Significance in Two Sisters with Breast Cancer: Is This Lynch Syndrome?



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CHAPTER 5

MSH6 Variant of Uncertain Significance in Two Sisters with Breast Cancer: Is This Lynch Syndrome?

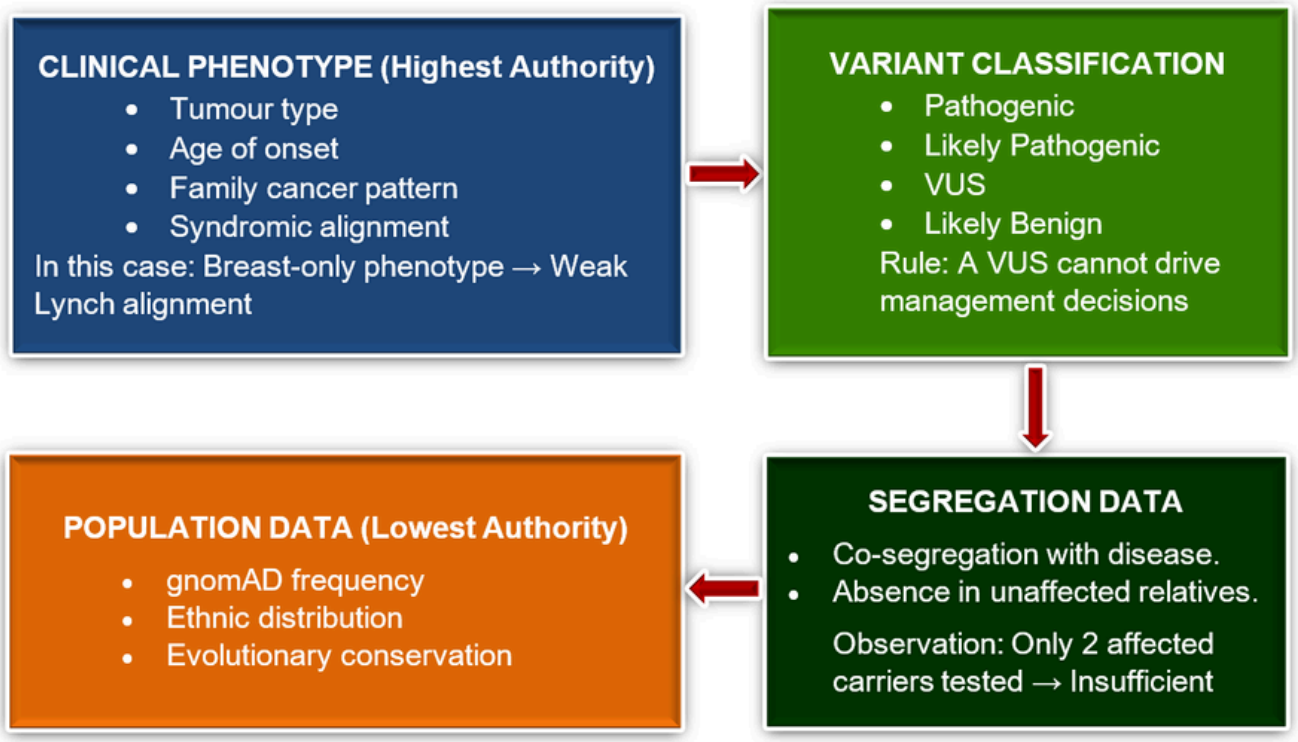
Case Overview

Table 1: At-a-Glance Case Summary

Domain	Key Information
Patient Profile	42-year-old female
Performance Status	ECOG 1
Cancer Type	Invasive ductal carcinoma, right breast
Subtype	ER+/PR+/HER2+
Stage	pT1cN1M0 (AJCC Stage IIA)
Prior Therapies	Neoadjuvant TCHP ×6 → Near-PCR → Planned modified radical mastectomy
Germline Finding	MSH6 c.1867C>T (p. Pro623Ser), heterozygous
Variant Classification	Variant Uncertain Significance (ClinVar ID 1714992)
Population Data	Extremely rare (gnomAD 0.0001239%); absent in 1000 Genomes
Functional Evidence	No published functional assays: in silico predictors suggest benign
Family History	Sister (51 yrs) with breast IDC — same MSH6 VUS; second-degree male relative with breast cancer; no Lynch-spectrum cancers
Dominant Clinical Question	Does shared MSH6 VUS establish Lynch syndrome?
Phenotype–Genotype Concordance	Breast-only phenotype; no colorectal or endometrial malignancies
vMTB Focus	ACMG evidence weighting; phenotype alignment; role of MSI/IHC; avoidance of VUS-driven overtreatment
Primary Recommendation	Treat MSH6 VUS as clinically negative for Lynch syndrome
Surveillance Plan	No Lynch-directed surveillance; age-appropriate screening only
Next Strategic Step	Cascade segregation testing; re-evaluate VUS in 2–3 years

A 42-year-old female (ECOG PS 1, no comorbidities) was diagnosed in February 2025 with invasive ductal carcinoma of the right breast, ER+/PR+/HER2+, pathological stage pT1cN1M0 (AJCC Stage IIA). She received six cycles of neoadjuvant TCHP chemotherapy and achieved near-complete metabolic response on PET-CT, corresponding to partial response by RECIST 1.1 criteria, with modified radical mastectomy planned. Germline hereditary cancer panel testing (Med Genome, 158-gene panel; peripheral blood lymphocytes) identified as heterozygous MSH6 c.1867C>T (p. Pro623Ser) variant classified as Variant of Uncertain Significance (VUS). Notably, the patient's older sister (aged 51, left breast IDC, residing in the USA) was independently found to harbour the identical MSH6 VUS on a separate HBOC extended panel (Agilus Diagnostics). The sister had undergone bilateral nipple-sparing mastectomy and bilateral salpingo-oophorectomy in the USA. A second-degree male relative also has a history of breast cancer. The case was presented to the Molecular Tumour Board (MTB) to address whether this familial MSH6 VUS constitutes Lynch syndrome and whether Lynch-directed clinical protocols should be initiated.

FIGURE 1: Molecular Hierarchy Framework (Conceptual Diagram)



NGS SUMMARY

Gene	Variant	Zygosity	Classification
MSH6	c.1867C>T (p. Pro623Ser); Exon 4	Heterozygous	Variant of Uncertain Significance (VUS) ClinVar ID 1714992

Additional findings: No pathogenic single-nucleotide variants, insertions/deletions, or copy-number variants (CNVs) detected across 158 hereditary cancer genes. Digital MLPA confirmed no exonic deletions or duplications in MSH6 or other MMR genes. In silico predictors (SIFT, LRT, MutationTaster2) classify the variant as benign. Population frequency is extremely rare (gnomAD: 0.0001239%; absent from 1000 Genomes). No tumour MSI testing was performed; IHC for MMR proteins was not reported. There are no actionable therapeutic targets derived from this germline finding at the present time.

CLINICAL QUESTIONS TO THE MTB

- Does the shared MSH6 c.1867C>T VUS between two affected sisters fulfil criteria for Lynch syndrome diagnosis?
- Should Lynch syndrome-directed surveillance (colonoscopy, endometrial assessment) be initiated in the index patient?
- Can MSI testing by PCR/NGS or MMR IHC serve as an indirect functional surrogate to clarify the pathogenicity of this VUS?
- Was the prophylactic bilateral salpingo-oophorectomy and nipple-sparing mastectomy performed in the sister justified based on a VUS alone?
- What is the appropriate surveillance and re-evaluation strategy for this VUS in the family?

MTB DISCUSSION: CLINICAL CONTEXT (From Transcript)

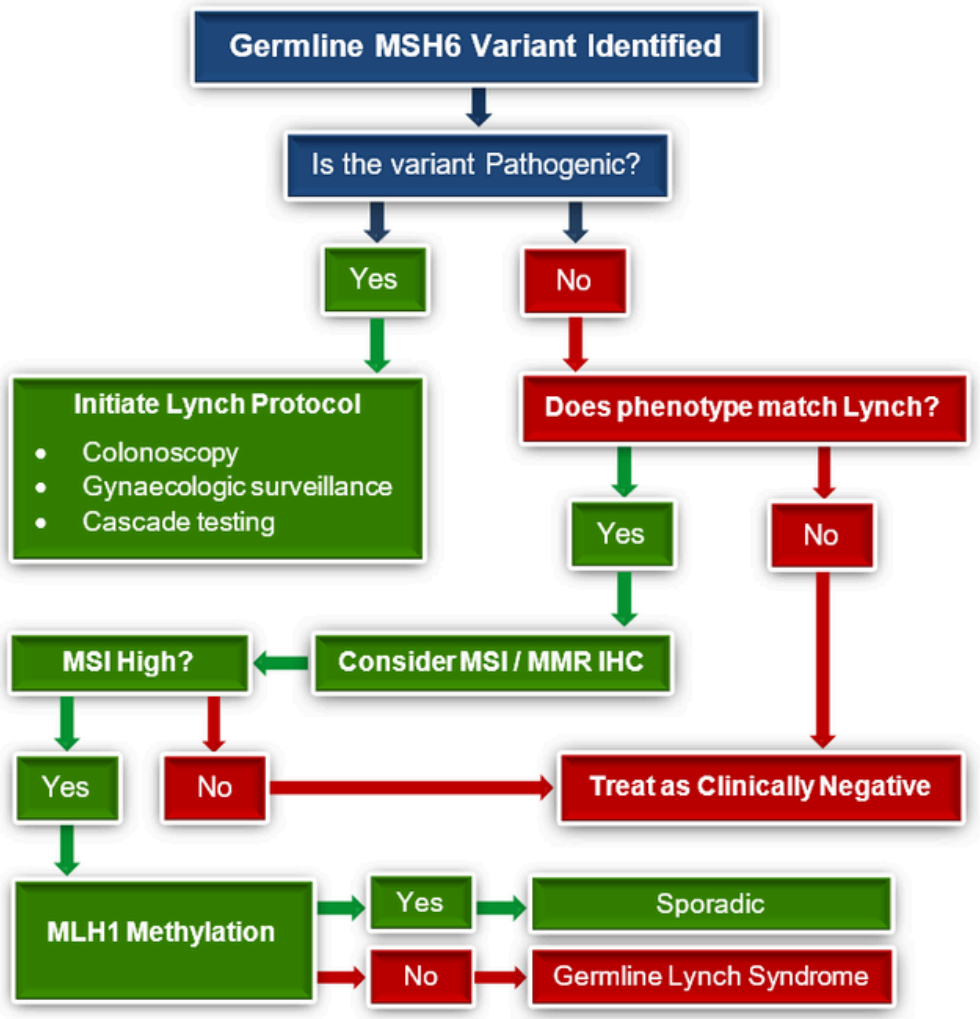
The MTB panel opened by noting that the patient's index cancer — HER2-positive stage II breast cancer — is being managed appropriately with standard-of-care neoadjuvant TCHP, yielding an excellent near-pCR response. The molecular question, therefore, was not about acute therapeutic decision-making but about long-term hereditary risk stratification. The expert panel presented the case, flagging that the same germline MSH6 VUS was independently detected in both the 42-year-old proband and her 51-year-old sister with left breast IDC. The treating team was concerned that the sister's decision to undergo bilateral prophylactic surgery in the USA was made based on this VUS, prompting the question of whether equivalent aggressive management was warranted for the proband.

The expert panel unanimously emphasized three clinical observations: first, the family phenotype consists exclusively of breast cancer — a tumour type only weakly and inconsistently associated with germline MSH6 pathogenic variants. Second, there is no history of the classical Lynch syndrome-associated malignancies (colorectal cancer, endometrial cancer, ovarian cancer, gastric cancer, urinary tract cancer) in either the patient or her family. Third, the absence of MSI-high or dMMR pathology in either tumour further weakens the case for Lynch syndrome. The expert panel concurred unanimously that, in the absence of these classical phenotypic features, the VUS should be clinically treated as negative for Lynch syndrome at this time.

TEACHING POINT – VUS AND CLINICAL PHENOTYPE

A VUS should never independently drive management decisions. The clinical phenotype — including tumour type, age of onset, and family history pattern — must be integrated before initiating surveillance or prophylactic procedures. In Lynch syndrome, the canonical cancers are colorectal and endometrial; breast cancer is a rare and debated association, predominantly seen with MSH6 and PMS2 pathogenic variants.

FIGURE 2: Molecular Pathway Integration (Flow Diagram)



MSH6 AND THE MISMATCH REPAIR SYSTEM — MECHANISTIC OVERVIEW

To appreciate the significance of this variant, it is essential to understand the normal function of MSH6 within the mismatch repair (MMR) pathway. DNA replication is an extraordinarily high-fidelity process, but errors are inevitable. During cell division, when the entire genome is copied, occasional mismatches occur — a wrong base is inserted, or a small stretch of DNA is slipped and misread. Left uncorrected, these errors become permanent mutations in daughter cells, accumulating over time and potentially driving cancer.

The MMR system functions as the cell's molecular proofreader. It operates in two sequential steps. First, the detection step: MSH6 heterodimerizes with MSH2 to form the MutSα complex, which actively patrols newly synthesized DNA strands and physically recognizes single base–base mismatches and small insertion-deletion loops.

The equivalent of a spell-checker scanning a document for typos. Second, the repair step: once a mismatch is detected, the MutSα complex recruits a second protein pair — MLH1 and PMS2 — forming the MutLα complex. This repair crew then exercises the erroneous segment of the newly synthesized strand and directs accurate re-synthesis using the original template strand as a guide.

MSH6 encodes a 1,360-amino-acid protein belonging to the MutS family. Germline pathogenic loss-of-function mutations in MSH6 disrupt this proofreading process. When MSH6 is non-functional, replication errors accumulate preferentially in short repetitive DNA sequences called microsatellites, producing a molecular phenotype known as microsatellite instability (MSI). Over years of accumulated replication errors in rapidly dividing tissues, this drives Lynch syndrome — an autosomal dominant hereditary cancer predisposition syndrome (OMIM #614350) characterized predominantly by endometrial and colorectal cancers, with incomplete penetrance. Incomplete penetrance means that not all individuals who inherit a pathogenic MMR variant will develop cancer; other genetic and environmental modifiers influence individual risk.

THE SPECIFIC VARIANT — P. PRO623SER

The variant under discussion — p. Pro623Ser — is a missense substitution in exon 4 of MSH6, replacing a proline residue with a serine at codon 623. Proline is structurally unique among amino acids: its cyclic side chain forms a ring that bonds back to the peptide backbone, introducing a fixed, rigid kink in the protein chain. This rigidity is often functionally important, particularly in regions where precise protein geometry is required. Serine, by contrast, is a small, flexible, hydroxyl-bearing amino acid. Substituting proline with serine at position 623 could theoretically alter the local three-dimensional conformation of the MSH6 protein, potentially disrupting its interaction surface with MSH2 or its DNA-binding properties. However, multiple silico algorithms — SIFT, LRT, and MutationTaster2 — all predict a benign effect for this specific substitution, suggesting the region may tolerate this change. The reference proline at position 623 is conserved across mammals, adding mild evolutionary constraint evidence. Critically, no functional laboratory studies have been performed to directly test whether this substitution impairs MMR activity. Until such data exists, the functional consequence of this substitution remains genuinely uncertain.

MSI TESTING AS A FUNCTIONAL SURROGATE — POSSIBILITIES AND LIMITATIONS

The MTB panel deliberated on whether functional surrogate testing — specifically MSI by IHC or PCR — could help resolve the pathogenicity of this VUS. This is a conceptually appealing approach: if the MSH6 protein is non-functional due to this variant, one might expect to see downstream evidence of MMR failure in the form of MSI in the tumour tissue.

However, the expert panel provided a nuanced explanation of why MSI testing cannot serve as a definitive arbiter in this context, for two distinct reasons. A negative MSI result cannot exclude pathogenicity. MSH6 germline mutations produce a characteristically subtler MSI pattern compared to MLH1 or MSH2 mutations. Where MLH1 or MSH2 deficiency typically results in high-grade, multi-marker MSI readily detectable on standard panels, MSH6 deficiency tends to predominantly mononucleotide repeat instability — a milder, more focal pattern that standard MSI assays may miss entirely. The MMR system may remain partially functional, yielding a microsatellite-stable result even in the presence of a genuinely pathogenic MSH6 variant. A negative MSI result therefore does not exonerate the variant.

A positive MSI result does not confirm pathogenicity of the VUS. MSI-high tumours are not caused exclusively by germline MMR mutations. In fact, the most common cause of MSI-high in sporadic tumors — particularly colon cancer — is somatic, acquired silencing of the MLH1 gene through epigenetic methylation of its promoter region. This has nothing to do with inheritance or Lynch syndrome.

If MSI testing returned a positive result in this patient's tumour, the first mandatory investigative step would be to test for MLH1 promoter hypermethylation. Only if methylation is excluded can MSI positivity be attributed to a germline MMR defect — and even then, it cannot specifically implicate the MSH6 VUS without additional evidence.
The expert panel therefore concluded that MSI testing may offer an indirect clue and is worth performing for completeness, but it cannot definitively reclassify the VUS in either direction or should never be the sole basis for a Lynch syndrome diagnosis.

TEACHING POINT – BRCA VUS VS MMR VUS

Functional Surrogates for Somatic BRCA VUS, HRD (Homologous Recombination Deficiency) testing may support functional loss, as discussed in prior sessions. For germline MMR VUS, the analogous surrogate is MSI or MMR IHC. However, MSH6 mutations are associated with lower-grade MSI and variable dMMR expression, making the analogy imperfect. A negative MSI result is insufficient to exclude Lynch syndrome with confirmed pathogenic MMR variants.

EVIDENCE REVIEW

The MTB discussion was guided primarily by VUS classification principles from ACMG/AMP guidelines and guideline recommendations from NCCN and ESMO. The key evidence points reviewed are as follows.

VUS CLASSIFICATION AND MANAGEMENT PRINCIPLES

When a laboratory identifies a novel or rare genetic change, the central question is whether those variants cause disease or represent a harmless variation in the genome. To answer this systematically, the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) jointly developed a structured evidence-scoring framework, published in 2015 (Richards et al., Genetics in Medicine; PMID 25741868). This framework requires classifying germline variants into five categories — pathogenic, likely pathogenic, VUS, likely benign, and benign — based on the cumulative weight of evidence across multiple domains: population frequency, functional laboratory data, family segregation, and clinical phenotype.

A VUS sits in the middle of this spectrum: there is insufficient evidence to classify the variant as either harmful or harmless. Critically, the ACMG framework explicitly states that a VUS should NOT be used to guide clinical management decisions. Management changes — including surveillance protocols or prophylactic interventions — must be reserved for confirmed pathogenic or likely pathogenic variants.
The p. Pro623Ser variant was assessed across four key ACMG criteria, and the results reveal why it appropriately remains a VUS:

PM2 — Population rarity (Met): The variant was checked against two large global DNA databases — gnomAD, which contains sequencing data from over 140,000 individuals across diverse ethnic populations, and the 1000 Genomes Project, a reference database of global genetic variation. The p. Pro623Ser variant was found in gnomAD at a frequency of just 0.0001239% — approximately 1 in 800,000 individuals — and was completely absent from 1000 Genomes.

This extreme rarity satisfies the PM2 criterion, providing a mild point toward potential pathogenicity. However, rarity alone is not sufficient for disease causation. A variant may be rare simply because it arose recently in evolution, is restricted to a small ethnic subpopulation, or exists in a functionally tolerant region of the protein. Rarity raises a flag; it does not provide a verdict.

PS3/BS3 — Functional laboratory evidence (Not met): The most direct form of evidence — laboratory experiments testing whether the mutant MSH6 protein retains normal mismatch repair activity — is entirely absent for this variant. No cell-based assays, protein stability studies, or MMR activity assays have been published or submitted for p. Pro623Ser. Without this data, neither pathogenic functional evidence (PS3) nor benign functional evidence (BS3) can be applied. This represents the most significant evidentiary gap. Functional studies examining whether the proline-to-serine substitution at codon 623 disrupts MSH6-MSH2 heterodimerization or impairs DNA mismatch recognition would be highly informative and represent a research priority for this variant.

PP1/BS4 — Family segregation data (Not met): Co-segregation analysis examines whether the variant consistently appears in family members who develop cancer and is consistently absent in those who remain cancer-free. This is one of the most statistically powerful tools in variant classification. Currently, only two individuals have been tested — both sisters, both with breast cancer, both carrying the variant. While suggestive, two concordant affected carriers provide very limited statistical weight. By chance alone, two relatives could share a rare variant without it being the cause of their cancers. To meaningfully apply the PP1 criterion, systematic testing is required across multiple generations — including unaffected siblings, parents if living, and other at-risk relatives. Equally important, if unaffected relatives are found to carry the variant, this would provide evidence toward a benign classification (BS4). Neither conclusion is currently possible. The untested second-degree male relative with breast cancer represents an additional opportunity for segregation data. This gap is directly actionable through the cascade testing strategy recommended by the MTB.

PP4 — Clinical phenotype match (Not met): This criterion asks whether the patient's cancer type, age of onset, and family history pattern match the established clinical signature of pathogenic MSH6 mutations. The hallmark cancers of Lynch syndrome caused by MSH6 pathogenic variants are endometrial and colorectal malignancies. In this family, however, both affected sisters have breast cancer, and a second-degree male relative has breast cancer as well. There is no colorectal cancer, no endometrial cancer, and no other Lynch-associated malignancy anywhere in the reported family history. While emerging evidence suggests that confirmed pathogenic MSH6 variants confer a modest elevation in breast cancer risk (OR ~1.9, Roberts et al. 2018), breast cancer is not a canonical Lynch syndrome tumour type and is not incorporated into Lynch syndrome diagnostic criteria as a standalone indication. The family phenotype therefore does not match the expected clinical signature, and PP4 cannot be applied.

THE FINAL ACMG SCORECARD FOR THIS VARIANT IS SUMMARIZED BELOW:

ACMG Criterion	What It Assesses	Result
PM2	Population rarity	Met — mild point toward pathogenicity
PS3	Functional proof of protein dysfunction	Not available
BS3	Functional proof of normal protein function	Not available
PP1	Variant segregates with cancer across family	Insufficient — only 2 relatives tested
BS4	Variant present in unaffected relatives	Insufficient — unaffected relatives untested
PP4	Clinical phenotype matches MSH6/Lynch pattern	Not met — breast cancer phenotype only

With only one weak-to-moderate point in favor of pathogenicity and no supporting functional, segregation, or phenotypic evidence, the variant cannot cross the threshold into likely pathogenic or pathogenic classification. It correctly and appropriately remains a VUS — pending the accumulation of further evidence.

LYNCH SYNDROME — NCCN AND ESMO GUIDELINES

NCCN Genetic/Familial High-Risk Assessment: Colorectal (v2.2025) recommends Lynch syndrome surveillance (colonoscopy, endometrial assessment, urinary tract evaluation) only for individuals with confirmed pathogenic or likely pathogenic germline MMR variants. The guidelines explicitly state that a VUS should not be used to guide clinical management decisions. Similarly, ESMO Guidelines for Hereditary Gastrointestinal Cancers (Stepanovich et al., Ann Oncol 2019; PMID 31438098) affirm that Lynch surveillance is not warranted for MMR VUS.

MSH6 AND BREAST CANCER RISK

The association between germline MSH6 pathogenic variants and breast cancer remains a subject of ongoing research. Roberts ME et al. (J Clin Oncol. 2018;36:2961–2968; PMID 29345684) conducted a large case-control study demonstrating a statistically significant but modest elevation in breast cancer risk among MSH6 pathogenic variant carriers (OR ~1.9). Similarly, Win AK et al. (J Clin Oncol. 2012; 30:958–964; PMID 22291093) reported an increased standardized incidence ratio for breast cancer in Lynch syndrome families. Importantly, both studies focused exclusively on confirmed pathogenic or likely pathogenic MMR variants — not VUS. Extrapolating these risk estimates to a VUS is methodologically inappropriate, as the VUS has unconfirmed functional impact. The expert panel noted that both the proband and her sister have breast cancer — not endometrial or colorectal malignancy. While MSH6 and PMS2 pathogenic variants are the MMR genes most frequently linked to breast cancer, the breast cancer-MSH6 association remains inconsistently replicated and is not yet incorporated into NCCN breast cancer genetic testing indications as a standalone criterion. The expert panel emphasized that because this is a breast cancer phenotype rather than a classical Lynch phenotype, the clinical threshold for Lynch diagnosis must remain high.

MSI TESTING IN CONTEXT

MSI testing, first standardized by Boland CR et al. (Cancer Res. 1998;58:5248–5257; PMID 9823339), is the established functional readout of MMR pathway deficiency. However, MSH6 germline pathogenic variants produce a distinct and often subtler MSI pattern — predominantly mononucleotide repeat instability — compared to MLH1 or MSH2 mutations, and the MSI-high phenotype is not universally expressed.

Sehgal R et al. (J Clin Oncol. 2014) demonstrated that MSH6 mutation carriers have lower rates of MSI-high compared to MLH1/MSH2 carriers, complicating MSI interpretation in this context. As outlined in Section 4.2, a negative MSI result cannot exclude pathogenicity, and a positive result requires mandatory exclusion of MLH1 promoter hypermethylation before any germline attribution can be made.

TEACHING POINT - SEGREGATION ANALYSIS FOR VUS RECLASSIFICATION

One of the most powerful tools to reclassify a VUS is co-segregation analysis. If additional affected family members carry the same VUS and unaffected members do not, this provides evidence towards pathogenicity (PP1 criterion in ACMG). Conversely, if unaffected relatives carry the VUS, it supports a benign classification (BS4). The MTB recommended systematic testing of first-degree relatives — both affected and unaffected — and submission of results to ClinVar to contribute to global evidence accumulation.

THERAPEUTIC CONSIDERATIONS

The MTB reached unanimous consensus that no change in the patient's current oncological management is warranted based on this VUS. The HER2-positive breast cancer treatment — completion of neoadjuvant TCHP, planned MRM, and subsequent adjuvant pertuzumab/trastuzumab with or without neratinib per NCCN — proceeds on its own merits, entirely independent of the germline MSH6 finding.

Regarding Lynch-directed protocols, the expert panel concluded: (a) no colonoscopy or endometrial surveillance beyond age-appropriate population screening is indicated; (b) no prophylactic gynecological surgery is recommended; and (c) the family should be counselled that the VUS is currently treated as clinically negative. The expert panel discussed the case of the sister's bilateral salpingo-oophorectomy with concern — this represents a clear example of over-management driven by VUS misclassification, with real and avoidable consequences for the patient.

For prospective reclassification, the expert panel recommended: first, cascade genetic testing of all first-degree relatives (including unaffected siblings and parents if alive) using targeted Sanger sequencing for the specific variant; second, submission of all segregation data and phenotypic information to ClinVar by both laboratories (Med Genome and Agilus) to upgrade the variant's evidence tier; and third, periodic re-evaluation of VUS classification at 2–3-year intervals via formal genetic counselling, as accumulating global data may lead to reclassification.

Pitfall Overinterpreting a VUS as pathogenic and initiating prophylactic surgery — as may have occurred in the patient's sister — represents a significant patient safety concern. Approximately 90% of VUS are ultimately reclassified as benign. Radical prophylactic interventions based on VUS alone expose patients to surgical risk, menopausal morbidity, and psychological harm without proven benefit. This case underscores the critical importance of involving a trained genetic counsellor and adhering to ACMG evidence standards before communicating any management implications of a VUS.

FINAL RECOMMENDATION (MTB CONSENSUS)

- Treat the MSH6 c.1867C>T (p. Pro623Ser) VUS as clinically negative for Lynch syndrome currently.
- Continue standard HER2-positive breast cancer management (neoadjuvant TCHP → MRM → adjuvant anti-HER2 therapy) without modification.
- No Lynch-directed surveillance (colonoscopy, endometrial assessment, prophylactic surgery) is indicated based on current evidence.
- Initiate cascade segregation testing in all first-degree relatives (affected and unaffected).
- Submit familial segregation data to ClinVar. Re-evaluate VUS classification every 2–3 years via formal genetic counselling.

KEY LEARNING POINTS

1. A VUS in any MMR gene is NOT equivalent to Lynch syndrome. Management must not be altered solely based on a VUS, regardless of family history.
2. Approximately 90% of VUS are ultimately reclassified as benign over time; premature prophylactic interventions carry real and avoidable harm.
3. MSH6 germline pathogenic variants are associated with Lynch syndrome characterized predominantly by endometrial and colorectal cancers; the association with breast cancer is modest and not a standalone indication for Lynch diagnosis.
4. MSI testing and MMR IHC can provide indirect functional information but cannot definitively reclassify a germline MSH6 VUS. A negative MSI result does not exclude a pathogenic variant; a positive result requires exclusion of MLH1 methylation before germline attribution is possible.
5. Segregation analysis — testing both affected and unaffected family members — is the most clinically actionable step for reclassifying a VUS, and results should be contributed to ClinVar.
6. Index tumour histology matters: the presence of two family members with breast cancer — and no colorectal or endometrial malignancy — makes a classical Lynch syndrome phenotype less likely.
7. In India, direct-to-clinician VUS reporting without genetic counselling oversight risks patient misinterpretation and over-treatment; institutional protocols for mandatory genetic counselling review should be established.

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