CANCER DIAGNOSIS & PROGNOSIS *6*: 737-744 (2026)
doi: 10.21873/cdp.10574

The Impact of Comprehensive Panel NGS Testing and Cascade Family Screening on Early Diagnosis of Prostate Cancer and MINAS (*ATM+MITF*) Management

İREM BİLGETEKİN[1,2], TAHA BAHSİ[3], YUSUF BAHAP[4], MEHMET ALİ ERGÜN[4] and İBRAHİM GÜLLÜ[5]

[1]Department of Internal Medicine, Uskudar University Faculty of Medicine, Istanbul, Turkey;
[2]Department of Medical Oncology, Memorial Ankara Hospital, Ankara, Turkey;
[3]Department of Medical Genetics, Memorial Ankara Hospital, Ankara, Turkey;
[4]Department of Medical Genetics, Gazi University Faculty of Medicine, Ankara, Turkey;
[5]Department of Medical Oncology, Hacettepe University Faculty of Medicine, Ankara, Turkey

Abstract

Background/Aim: With the expansion of next-generation sequencing (NGS)-based hereditary cancer panels, this study aimed to: (i) identify non-*BRCA* predisposition genes in an index case with three different primary cancers; (ii) demonstrate the clinical utility of cascade testing *via* comprehensive panel NGS testing for early cancer detection in asymptomatic relatives; (iii) discuss the potential association between a co-segregating *MITF* variant and a family history of recurrent meningioma; and (iv) provide a practical management framework for Multilocus Inherited Neoplasia Allele Syndrome (MINAS) in the context of dual *ATM+MITF* carriership.

Materials and Methods: Index patient and family members who have a history of cancer with a familial cancer pedigree were evaluated using a multigene NGS approach. Targeted sequencing was performed on the MGI DNBSEQ-G400 platform using the Twist Bioscience Hereditary Cancer Panel.

Results: A germline *ATM* variant was identified in the index case, and *ATM* carrier status was confirmed in his two sons. During cascade screening, early-stage colon cancer was detected on colonoscopy in one son, while prostate cancer was diagnosed in the other. *MITF* carrier status was identified in three family members; among them, the index patient's sister and one nephew had a history of meningioma, and the nephew was also shown to be an *ATM* carrier. A history of meningioma was also present in another family member with an *MITF* variant.

Conclusion: Large-panel NGS testing in cancer patients is transforming family-based risk management by enabling the identification of homologous recombination repair (HRR) genes (including *ATM*) beyond *BRCA1/2*. Cascade testing *via* comprehensive NGS provides tangible clinical benefits by detecting malignancies early in clinically silent carriers.

Keywords: Hereditary cancers, prostate cancer, meningioma, *ATM*, *MITF.*

İrem Bilgetekin, Memorial Ankara Hospital, Balgat Dist. Mevlana Blv., Balgat, 1422. Str. No. 4, 06520 Çankaya/Ankara, Turkey. E-mail: irembilgetekin@gmail.com

Received February 23, 2026 | Revised April 2, 2026 | Accepted April 9, 2026

Introduction

Germline genetic testing for cancer susceptibility genes is a clinically proven method for detecting, preventing, and managing cancer (1, 2). The indications for these tests typically are early age of onset, specific tumor pathologies, and extensive family history. A critical clinical indicator highlighted by the National Comprehensive Cancer Network (NCCN) is the presence of multiple primary malignancies within a single individual (3).

The clinical significance of hereditary genetic predisposition tests extends beyond risk prediction alone; it directly influences the entire diagnostic, screening, treatment, and family counselling processes. The detection of germline *BRCA1/2* and other homologous recombination gene mutations enables the identification of patient groups suitable for targeted therapies such as PARP inhibitors, while also facilitating the implementation of predictive testing and early screening strategies for family members. Therefore, current guidelines recommend germline genetic testing to be routinely included in the assessment of individuals with metastatic, high-risk, or familial prostate cancer (3-6).

The molecular landscape of hereditary cancers is characterized by significant genetic heterogeneity, where mutations in diverse signaling pathways can manifest as overlapping clinical phenotypes. For instance, the DNA damage response pathway – encompassing high-penetrance genes such as *BRCA1/2* as well as moderate-penetrance genes such as *PALB2*, *ATM*, and *CHEK2* – illustrates how distinct molecular defects can confer a shared predisposition to breast and pancreatic malignancies. Similarly, the mismatch repair (MMR) pathway and the base excision repair mechanism (*e.g.*, *MUTYH*) represent distinct biochemical pathways that converge to increase colorectal cancer risk. Because these pathways are often interconnected, a mutation in a gene not traditionally associated with a specific syndrome may still contribute to the patient's oncogenic profile, underscoring the limitations of single-syndrome testing (5, 7-9).

Consequently, the shift from single-gene analysis to comprehensive multigene panels has become a clinical necessity. These panels offer a high-throughput, cost-effective approach to identify pathogenic variants that might be missed by phenotype-driven testing alone. This is particularly vital for patients with "atypical" presentations or those with multiple primary tumors that do not strictly adhere to the classical criteria of a single syndrome (1). It is also beneficial for cases that are clinically non-recognizable for Multilocus Inherited Neoplasia Allele Syndrome (MINAS) (10-12). By capturing a broader spectrum of the genetic architecture, multigene panels facilitate the detection of rare or moderate-penetrance alleles, thereby providing a more granular risk assessment. This holistic view of the patient's genetic predisposition is essential for implementing precision surveillance and management protocols.

The ataxia-telangiectasia mutated (*ATM*) gene is a key tumour suppressor that encodes a serine-threonine kinase, which plays a central role in the detection and repair of double-strand DNA breaks. The *ATM* gene, which plays a critical role in initiating the cellular DNA damage response (DDR), is a key regulator of cell cycle control, homologous recombination repair, apoptosis, and genomic stability. Germline biallelic *ATM* mutations cause ataxia-telangiectasia, while heterozygous carrier status is associated with an increased cancer risk and is relatively common in the population. Therefore, *ATM* is considered a medium-to-high penetrance cancer susceptibility gene.

Germline *ATM* pathogenic variants are associated with an increased risk for many solid tumours, particularly breast, prostate, pancreatic, and gastric cancers (3, 13). Clinically, *ATM* mutations are not limited to risk determination; they also influence treatment decisions. In tumours with *ATM* loss, DNA repair deficiencies, sensitivity to platinum-based chemotherapy may increase, whereas response to PARP inhibitors is more heterogeneous than in *BRCA1/2* mutations. Therefore, *ATM* is recognised as a critical biomarker in both hereditary risk assessment and the determination of targeted treatment strategies (5, 8, 9).

MITF and cancer susceptibility. Microphthalmia-associated transcription factor (*MITF*) is a key transcription factor

that regulates melanocyte development, differentiation, and cellular survival. This gene, which plays a central role in melanocyte biology, controls the expression of numerous target genes associated with pigmentation, cell cycle regulation, and apoptosis (14). Germline *MITF* variants have been associated with increased cancer susceptibility, particularly in relation to melanocytic tumours (15). In this context, *MITF* stands out as a unique susceptibility gene that exerts its effects through a biological mechanism distinct from that of classical DNA repair genes.

In particular, the *MITF* p.E318K variant has been strongly associated with a moderately increased risk of melanoma and has been repeatedly reported in familial melanoma cases. In addition, some studies have reported its association with renal cell carcinoma, pancreatic and prostate cancer; thus, *MITF* has been considered a gene with an expanding cancer susceptibility spectrum. The risk posed by *MITF* variants mostly arises from interactions with environmental factors (particularly UV exposure) and other genetic variables. Therefore, personalised screening approaches, dermatological follow-up, and family-based genetic counselling are important for *MITF* carriers. Current data indicate that *MITF*, unlike classical tumour suppressor genes, possesses the characteristics of a 'contextual susceptibility gene' and acts as a lineage-specific oncogene that dictates distinct oncogenic or suppressive outcomes, which occupies a unique position in cancer biology (15-18).

Materials and Methods

Index case. The index case in the family is an 82-year-old male patient initially diagnosed with gastric adenocarcinoma. During his clinical follow-up, an investigation initiated due to elevated prostate-specific antigen (PSA) levels led to the subsequent diagnoses of early-stage prostate carcinoma and incidental non-invasive bladder carcinoma within the same calendar year. The patient's medical history is significant for a heavy smoking history. His brother was diagnosed with rectal carcinoma at the age of 71, and his mother had a history of pancreatic carcinoma (Figure 1). These familial occurrences, when combined with the patient's own history of multiple primary tumors (gastric, prostate, and bladder), necesitated further genetic evaluation to investigate a potential hereditary predisposition, despite the patient's advanced age and environmental risk factors. A comprehensive hereditary cancer panel was performed in line with the clinical course.

The patient's family history was further characterized by a cluster of central nervous system tumors, specifically meningiomas in his first cousin and the cousin's two daughters. Given the high prevalence of consanguinity within the family and the diverse spectrum of malignancies observed across multiple generations multigene panel testing strategy was employed to screen family members.

DNA isolation and library preparation. Peripheral blood samples were collected in EDTA tubes, and genomic DNA was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) and the Promega Maxwell RSC Blood DNA Kit (Promega, Madison, WI, USA) according to the manufacturers' protocols. DNA quantity and purity were assessed using NanoDrop spectrophotometry and Qubit fluorometric quantification (Thermo Fisher Scientific, Waltham, MA, USA).

Next-generation sequencing and bioinformatics. Sequencing data were processed using vendor-specific pipelines. Raw reads underwent demultiplexing and adapter trimming. Sequences were aligned to the human reference genome (GRCh37/hg19) using BWA-MEM (Burrows-Wheeler Aligner-Maximal Exact Matches). Targeted sequencing was performed using the Twist Bioscience Hereditary Cancer Panel (Twist Bioscience, South San Francisco, CA, USA), covering a comprehensive set of cancer predisposition genes which includes *MITF, ATM, and BRCA1/2*.

Library preparation was carried out according to the manufacturer's protocol, followed by circularization and generation of DNA nanoballs (DNBs). Sequencing was

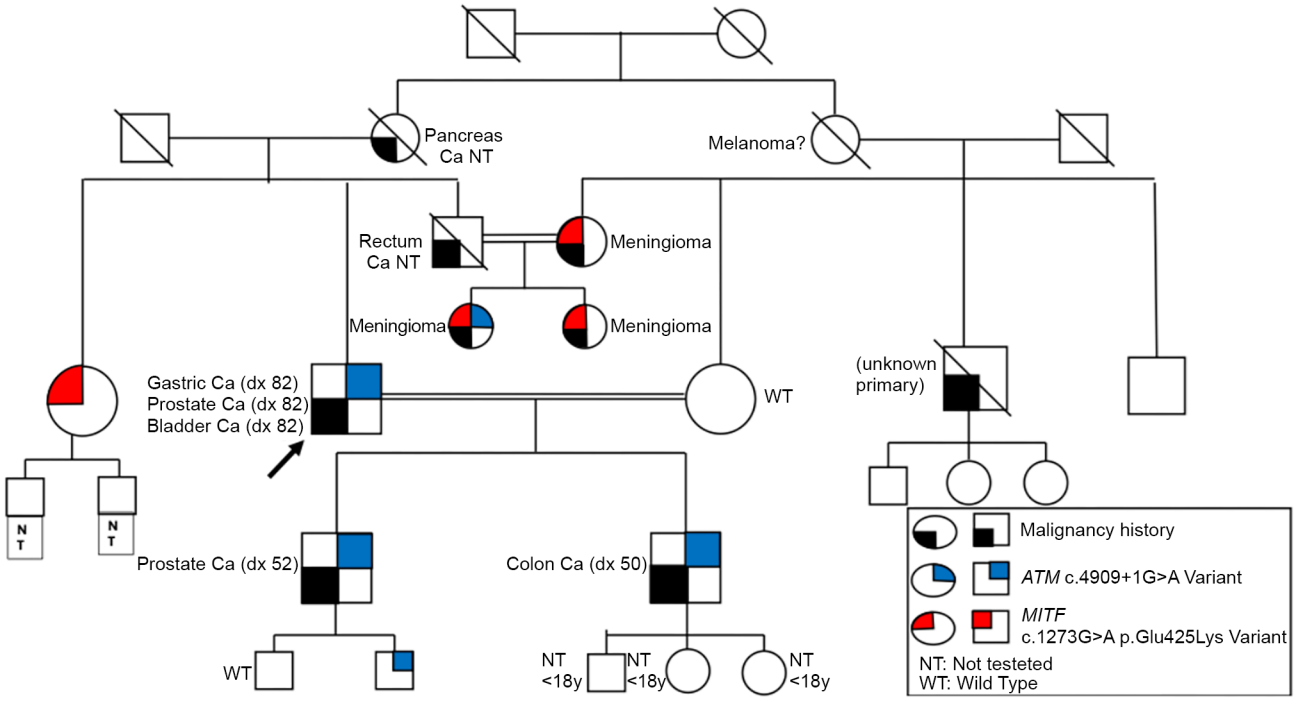

Figure 1. *Pedigree of the family. Ca: Cancer.*

conducted on the MGI DNBSEQ-G400 platform (MGI Tech Co., Ltd., Shenzhen, P.R. China) using pairedend reads (2 Å~ 150 bp) with combinatorial Probe-Anchor Synthesis (cPAS) chemistry. Raw data were processed through MGI's standard pipeline for base calling, demultiplexing, and adapter trimming. Reads were aligned to the human reference genome (GRCh37/hg19) using BWA-MEM. Variant calling and downstream analysis were performed using the GenomizeSeq clinical bioinformatics pipeline. Single nucleotide variants (SNVs) and small insertions/deletions (indels) were annotated and classified according to the 2015 ACMGAMP guidelines. Copy number variants (CNVs) were evaluated using depth-of-coverage–based algorithms embedded within the GenomizeSeq platform. All pathogenic (P) and likely pathogenic (LP) variants, along with variants of uncertain significance (VUS), were reviewed and manually curated in a clinical context. The final report included detailed variant annotation, zygosity, American College of Medical Genetics and Genomics (ACMG) classification, associated phenotypes, and clinical actionability, if applicable. Quality control thresholds included minimum coverage of ≥100Å~ and variant allele frequency (VAF) ≥0.2 for heterozygous variants.

Variant annotation and classification. Variants were annotated using the Genomize Seq Platform and classified following the ACMG/AMP 2015 guidelines (19). Classifications were cross-referenced with ClinVar, gnomAD, HGMD Professional, and LOVD databases. Only pathogenic or likely pathogenic (LP/P) variants were included in the final analysis. VUS were excluded. Zygosity was determined by examining VAF and sequencing reads.

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval for the study was granted by the Gazi University Faculty of Medicine Clinical Research Ethics Committee on 25.11.2025, with the reference number' '202-1956'. Informed consent was obtained from the participants for the inclusion of their clinical and genetic data in this study.

Results

The test results in the index case revealed a clinically significant germline heterozygote variant in the *ATM* gene (*ATM* c.4909+1G>A). This variant was considered pathogenic according to ACMG criteria and is also reported as pathogenic in the ClinVar database (19, 20).

A comprehensive genetic cancer panel was again performed on the two sons of the index case, and both were found to be heterozygous carriers of the c.4909+1G>A variant in the *ATM* gene. Subsequently, a screening programme was initiated with genetic counselling. During screening, early-stage colon cancer was detected in one son *via* colonoscopy, and early-stage prostate cancer was detected in the other son *via* biopsy following a suspicion of elevated PSA. These findings demonstrate that cascade screening can enable early diagnosis in clinically silent carriers.

The same multi-gene panel was also applied to other relatives (a total of 10 individuals) of the index case who were called for screening, and the c.1273G>A p.Glu425Lys variant in the *MITF* gene was detected in three additional family members. One of the *MITF* carriers also carried the *ATM* c.4909+1G>A variant. A notable feature in the clinical history of these individuals carrying pathogenic *MITF* mutations is that all three have a history of meningioma. The index case's sister (*MITF* mutant, meningioma), a niece (*MITF* and *ATM* mutant, meningioma), and another family member (*MITF* mutant, meningioma) are shown in Figure 1. To explain this pattern, tissue-based transcriptome analysis and functional studies are planned to evaluate the possibility of a second hit in meningioma tissue (somatic second hit, Loss-of-Heterozygosity, copy number alteration, *etc*.) and/or the effects of the *MITF* variant on expression/splicing. Additionally, the family's genetic testing and cancer history pedigree are shown in Figure 1.

Discussion

Multigene panels enhance risk management for both index cases and family members by detecting not only *BRCA1/2* but also non-*BRCA* HRR/DDR genes, such as *ATM*, in complex pedigrees. Narrow-panel approaches may miss clinically meaningful variants in non-*BRCA* genes and limit cascade screening opportunities, especially in families with consanguinity and and a clustering of atypical cancers.

The significance of non-BRCA genes in prostate cancer, particularly ATM. Germline *ATM* variants may be associated with a moderately increased risk for different cancers. Risk management for *ATM* carrier status in prostate cancer should be personalised based on family history, individual risk profile, and current guideline recommendations. In this family, the detection of prostate cancer in both the index case diagnosed with prostate cancer and one of the two sons who are *ATM* carriers reinforces the high pathogenicity of the mutation in the *ATM* gene in this family and the importance of carrier status in terms of clinical follow-up and early detection.

The early diagnosis outcome of cascade screening. The greatest clinical benefit in hereditary cancer genetics is the transmission of the germline variant detected in the index case to eligible family members through cascade screening, and the prevention of cancer or its detection at an earlier, more treatable stage through early diagnosis. In this family, the detection of early-stage colon cancer in one son and prostate cancer in another through cascade screening demonstrates the direct contribution of the germline genetic testing to family health. Furthermore, by including other *ATM* carrier individuals in the family in early screening programmes, it will enable the very early detection of potential cancers and reduce cancer-related morbidity/mortality.

Performing cascade screening with a multigene panel revealed another pathogenic variant in *MITF* present in the family but not in the proband. This approach, according to targeted testing, is particularly beneficial in families where consanguineous marriages are common and/or atypical cancer types are observed.

MITF–meningioma association: a hypothesis-generating observation. MITF variants have been classically

associated with melanoma and, in some studies, renal cell carcinoma (15-17). There is no evidence in the literature supporting an association with familial meningioma. The occurrence of meningioma in three MITF carriers in this family is hypothesis-generating and could strengthen the association if supported by additional molecular studies, such as second-hit analyses in tumour tissue. Planned tissue-based DNA and RNA analyses may be critical for elucidating the functional effect of the variant and its potential relationship with tumours.

ATM + MITF dual carrier status - (MINAS)- and management approach. Within the scope of MINAS, the co-inheritance of two germline susceptibility genes may result in a phenotype exhibiting the expected cancer spectrum of each gene separately or may lead to earlier onset and a tendency towards multiple malignancies. The practical management approach can be summarised as addressing each gene separately in terms of risk management, then combining the conditions requiring the earliest initiation and most frequent monitoring. Standard recommendations should be applied in areas with strong evidence (*e.g.,* prostate surveillance, dermatological monitoring); in areas with weak evidence (*e.g.,* meningioma), a measured and individualised strategy based on family phenotype and clinical context should be adopted. One of the most significant ongoing challenges in MINAS management concerns which gene should be prioritised in cancer prevention for individuals. The fact that the target tissues for cancer susceptibility differ between the *ATM* and *MITF* genes may make management slightly easier in this series. Furthermore, it is important to consider the epistatic effects of genes in MINAS management.

Conclusion

Comprehensive-panel NGS testing in prostate cancer facilitates identification of actionable DNA damage response genes beyond *BRCA1/2* (including *ATM*) and supports precision risk stratification at the family level (8, 21-23). Cascade screening can translate genetic findings into measurable clinical benefit by early detection of malignancies in asymptomatic carriers (8, 23). The presence of a history of recurrent meningioma along with the *MITF* variant in this pedigree is hypothetical; tumor-based second-hit assessment (e.g., LOH) and transcript-level analyses may help clarify the biological probability and variant effect (7, 15, 16, 24). For MINAS (*ATM+MITF*), a pragmatic approach is to integrate gene-specific surveillance recommendations, with a trend toward earlier ages of onset and/or shorter clinical surveillance intervals, when family history, penetrance, or tumor spectrum suggests additional risk (3, 4, 10-12).

Conflicts of Interest

The Authors declare that they have no conflict of interest in relation to this study.

Authors' Contributions

I.B.: Conceptualization, clinical evaluation, critical review, and surveillance management, manuscript drafting and editing; T.B.: Conceptualization, genetic testing planning and analysis, and manuscript drafting and editing; Y.B.: Manuscript editing, genetic test analysis; M.A.E.: Critical review, genetic analysis; I.G.: Clinical evaluation, critical review. All Authors read and approved the final manuscript.

Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (Gemini 3 Flash, Google, Mountain View, CA, USA) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

References

1 Hamilton JG, Symecko H, Spielman K, Breen K, Mueller R, Catchings A, Trottier M, Salo-Mullen EE, Shah I, Arutyunova A, Batson M, Gebert R, Pundock S, Schofield E, Offit K, Stadler ZK, Cadoo K, Carlo MI, Narayan V, Reiss KA, Robson ME, Domchek SM: Uptake and acceptability of a mainstreaming model of hereditary cancer multigene panel testing among patients with ovarian, pancreatic, and prostate cancer. Genet Med 23(11): 2105-2113, 2021. DOI: 10.1038/s41436-021-01262-2

2 Delacroix E, Austin S, Rice JD, Stoffel EM, Koeppe E, Griggs JJ, Resnicow K: Clinician recommendation for hereditary genetic testing in participants at increased risk for hereditary cancer. Cancers (Basel) 17(12): 1994, 2025. DOI: 10.3390/cancers17121994

3 National Comprehensive Cancer Network (NCCN): NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate. Version 3.2026, 2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf [Last accessed on February 20, 2026]

4 Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, Tombal B, Gillessen S, ESMO Guidelines Committee: Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 31(9): 1119-1134, 2020. DOI: 10.1016/j.annonc.2020.06.011

5 Yu EY, Rumble RB, Agarwal N, Cheng HH, Eggener SE, Bitting RL, Beltran H, Giri VN, Spratt D, Mahal B, Lu K, Crispino T, Trabulsi EJ: Germline and somatic genomic testing for metastatic prostate cancer: ASCO guideline. J Clin Oncol 43(6): 748-758, 2025. DOI: 10.1200/jco-24-02608

6 Liao CH, Bau DT, Wang BR, Chang SY, Hsia TC, Lee HT, Chen JC, Huang WC, Tsai CW, Wang YC, Shih HY, Chang WS: Impact of cyclin-dependent kinase inhibitor 1A genotypes on prostate cancer susceptibility prediction. In Vivo 39(6): 3184-3194, 2025. DOI: 10.21873/invivo.14118

7 Horton C, Hoang L, Zimmermann H, Young C, Grzybowski J, Durda K, Vuong H, Burks D, Cass A, LaDuca H, Richardson ME, Harrison S, Chao EC, Karam R: Diagnostic outcomes of concurrent DNA and RNA sequencing in individuals undergoing hereditary cancer testing. JAMA Oncol 10(2): 212-219, 2024. DOI: 10.1001/jamaoncol.2023.5586

8 Loeb S, Vadaparampil ST, Giri VN: Germline testing for prostate cancer: current state and opportunities for enhanced access. EBioMedicine 116: 105705, 2025. DOI: 10.1016/j.ebiom.2025.105705

9 Hall R, Bancroft E, Pashayan N, Kote-Jarai Z, Eeles RA: Genetics of prostate cancer: a review of latest evidence. J Med Genet 61(10): 915-926, 2024. DOI: 10.1136/jmg-2024-109845

10 Bahsi T, Seyhan S, Helvaci K, Demirci U, Bilgetekin I, Bayram S, Ozturk MA, Aydogan F, Keskin S, Pilanci K, Sener N, Tatlı M, Harputluoglu H, Namal E, Kargi A, Uysal M, Ilhan M, Erol C, Kose N, Okutur K, Karaca H, Dogan E, Berk V, Ekinci AS, Ozdogan M: Multilocus inherited neoplasia allele syndrome (MINAS) in a Turkish cohort: molecular insights and clinical relevance for precision oncology. Front Pharmacol 16: 1672774, 2025. DOI: 10.3389/fphar.2025.1672774

11 McGuigan A, Whitworth J, Andreou A, Hearn T, Genomics England Research Consortium, Tischkowitz M, Maher ER: Multilocus inherited neoplasia allele syndrome (MINAS): an update. Eur J Hum Genet 30(3): 265-270, 2022. DOI: 10.1038/s41431-021-01013-6

12 Yuen J, Zhou S, Caeser R, Venkatramani M, Bte Ishak DN, Li ST, Zhang Z, Chiang J, Chan SH, Ngeow J: Multi-locus inherited neoplasia alleles syndromes in cancer: implications for clinical practice. Eur J Hum Genet 33(3): 289-296, 2025. DOI: 10.1038/s41431-025-01785-1

13 Helgason H, Rafnar T, Olafsdottir HS, Jonasson JG, Sigurdsson A, Stacey SN, Jonasdottir A, Tryggvadottir L, Alexiusdottir K, Haraldsson A, Le Roux L, Gudmundsson J, Johannsdottir H, Oddsson A, Gylfason A, Magnusson OT, Masson G, Jonsson T, Skuladottir H, Gudbjartsson DF, Thorsteinsdottir U, Sulem P, Stefansson K: Loss-of-function variants in ATM confer risk of gastric cancer. Nat Genet 47(8): 906-910, 2015. DOI: 10.1038/ng.3342

14 Carreira S, Goodall J, Aksan I, La Rocca SA, Galibert M, Denat L, Larue L, Goding CR: Mitf cooperates with Rb1 and activates p21Cip1 expression to regulate cell cycle progression. Nature 433(7027): 764-769, 2005. DOI: 10.1038/nature03269

15 Guhan SM, Artomov M, McCormick S, Njauw CN, Stratigos AJ, Shannon K, Ellisen LW, Tsao H: Cancer risks associated with the germline MITF(E318K) variant. Sci Rep 10(1): 17051, 2020. DOI: 10.1038/s41598-020-74237-z

16 Oliveira LJC, Gongora ABL, Lima FAS, Canedo FSNA, Quirino CV, Pisani JP, Achatz MI, Rossi BM: Expanding the phenotype of E318K (c.952G > A) MITF germline mutation carriers: case series and review of the literature. Hered Cancer Clin Pract 19(1): 32, 2021. DOI: 10.1186/s13053-021-00189-8

17 Harraka P, Bruinsma F, Nguyen-Dumont T, Jordan S, Giles GG, Winship IM, Tucker K, Southey MC: Is renal cell carcinoma associated with *MITF* c.952G>A (p.E318K)? J Med Genet 61(10): 937-938, 2024. DOI: 10.1136/jmg-2024-109984

18 National Center for Biotechnology Information, ClinVar; [VCV000029792.114], National Library of Medicine (US), Bethesda (MD). Available at: https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000029792.114 [Last accessed on February 10, 2026]

19 Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for

Molecular Pathology. Genet Med 17(5): 405-424, 2015. DOI: 10.1038/gim.2015.30

20 National Center for Biotechnology Information, ClinVar; [VCV000128031.91], National Library of Medicine (US), Bethesda (MD). Available at: https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000128031.92 [Last accessed on Feruary 10, 2026]

21 Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Brunckhorst O, Darraugh J, Eberli D, De Meerleer G, De Santis M, Farolfi A, Gandaglia G, Gillessen S, Grivas N, Henry AM, Lardas M, van Leenders GJLH, Liew M, Linares Espinos E, Oldenburg J, van Oort IM, Oprea-Lager DE, Ploussard G, Roberts MJ, Rouvière O, Schoots IG, Schouten N, Smith EJ, Stranne J, Wiegel T, Willemse PM, Tilki D: EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer – 2024 update. Part I: Screening, diagnosis, and local treatment with curative intent. Eur Urol 86(2): 148-163, 2024. DOI: 10.1016/j.eururo.2024.03.027

22 Tilki D, van den Bergh RCN, Briers E, Van den Broeck T, Brunckhorst O, Darraugh J, Eberli D, De Meerleer G, De Santis M, Farolfi A, Gandaglia G, Gillessen S, Grivas N, Henry AM, Lardas M, J L H van Leenders G, Liew M, Linares Espinos E, Oldenburg J, van Oort IM, Oprea-Lager DE, Ploussard G, Roberts MJ, Rouvière O, Schoots IG, Schouten N, Smith EJ, Stranne J, Wiegel T, Willemse PM, Cornford P: EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer. Part II – 2024 update: Treatment of relapsing and metastatic prostate cancer. Eur Urol 86(2): 164-182, 2024. DOI: 10.1016/j.eururo.2024.04.010

23 Xu J, Lu J, Gielzak M, Lilly Zheng S, Lu L, Wei J, Cornell B, Shi Z, Wang Q, Tran H, Engelmann V, Ashworth A, Lin K, Ross AE, Walsh PC, Marshall C, Luo J, Isaacs WB, Helfand BT, Pavlovich CP: Germline testing for prostate cancer patients: evidence-based evaluation of genes recommended by NCCN guidelines. Prostate 85(12): 1087-1095, 2025. DOI: 10.1002/pros.24918

24 Yurgelun MB, Chittenden AB, Morales-Oyarvide V, Rubinson DA, Dunne RF, Kozak MM, Qian ZR, Welch MW, Brais LK, Da Silva A, Bui JL, Yuan C, Li T, Li W, Masuda A, Gu M, Bullock AJ, Chang DT, Clancy TE, Linehan DC, Findeis-Hosey JJ, Doyle LA, Thorner AR, Ducar MD, Wollison BM, Khalaf N, Perez K, Syngal S, Aguirre AJ, Hahn WC, Meyerson ML, Fuchs CS, Ogino S, Hornick JL, Hezel AF, Koong AC, Nowak JA, Wolpin BM: Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. Genet Med 21(1): 213-223, 2019. DOI: 10.1038/s41436-018-0009-5