Review Article

The genetic susceptibility in the development of malignant pleural mesothelioma: somatic and germline variants, clinicopathological features and implication in practical medical/surgical care: a narrative review

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Background and Objective: Malignant pleural mesothelioma (MPM) is a very aggressive primary tumor of the pleura whose main risk factor is exposure to asbestos. However, only a minority of exposed people develops MPM and the incidence of MPM cases without an apparent association with asbestos exposure has been increasing in recent years, suggesting that genetic predisposing factors may play a crucial role. In addition, several studies reported familial cases of MPM, suggesting that heredity may be an important and underestimated feature in MPM development. Several candidate genes have been associated with a predisposition to MPM and most of them play a role in DNA repair mechanisms: overall, approximately 20% of MPM cases may be related to genetic predisposition. A particular category of patients with high susceptibility to MPM is represented by carriers of pathogenic variants in the *BAP1* gene. Germline variants in BAP1 predispose to the development of MPM following an autosomal dominant pattern of inheritance in the familial cases. MPMs in these patients are significantly less aggressive, and patients require a multidisciplinary approach that involves genetic counseling, medical genetics, pathology, surgical, medical, and radiation oncology expertise. In the present narrative review, we presented a comprehensive overview of genetic susceptibility in the development of MPM.

Methods: The narrative review is based on a selective literature carried out in PubMed in 2023. Inclusion criteria were original articles in English language, and clinical trials (randomized, prospective, or retrospective).

Key Content and Findings: We summarized the somatic and germline variants and the differences in terms of clinicopathological features and prognosis between gene-related MPM (GR-MPM) and asbestos-related MPM (AR-MPM). We also discussed the indications for screening, genetic testing, and surveillance of patients with BAP1 germline variants.

Conclusions: In this narrative review, we have emphasized that the *BAP1* gene's harmful germline variations are inherited in an autosomal dominant manner in familial cases. MPMs in individuals with these variations are less severe, and their medical care necessitates a collaborative effort. Additionally, we have outlined the current therapeutic prospects for MPM, including the possibility of gene-specific therapy, which is currently promising but still requires clinical validation.

Keywords: Malignant pleural mesothelioma (MPM); genetic susceptibility; BRCA1 associated protein 1 (*BAP1*); pleural tumors; genetic counseling

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Introduction

Malignant pleural mesothelioma (MPM) identifies a primary neoplastic lesion arising from the pleural layer, a very rare tumor with an incidence of about 3,500 cases in the United States and still increasing in most countries (1-4). MPM usually affects patients from the fifth to seventh decades, and it develops in males in 70–80% of cases (5). No efficacious treatment has been yet developed for MPM with the standard therapy consisting of the combination of chemotherapy and surgery in clinically fit patients (6). However, individuals with MPM have a very poor prognosis resulting in a 5-year survival rate of about 10% with a median overall survival (OS) of 8.3 months (7,8). Despite it being considered an asbestos-linked disease, other risk factors have been identified for its development, such as mantle radiation therapy in previous Hodgkin lymphomas (9). Moreover, a genetic susceptibility has been clearly reported in a minority of cases, especially related to the presence of germline pathogenic variants of the BRCA1-associated protein 1 (*BAP1*) gene, which is one of the most frequently altered genes in MPM, along with *NF2*, *TP53*, *CDKN2A*, *SETDB1*, and *SETD2* (10,11). In particular, germline *BAP1* pathogenic variants are associated with the possibility to develop *in situ* mesothelioma and consequently better survival rates, as compared to other forms of MPMs (1,6). It is difficult to distinguish somatic versus germline variants of *BAP1* due to tumor sample heterozygosity. Somatic variants may result in worse OS due to their late detection: they are usually not identified until a patient is diagnosed with MPM and the concurrence of other oncogenic variants within the tumor. Moreover, while the detection of a germline *BAP1* variant elicits genetic counseling and eventually tests involving family members who may carry the same genetic alteration and the related carcinogenic risk, a somatic *BAP1* variant does not require genetic counseling because it is not shared by relatives. *BAP1* is a tumor suppressor gene located on chromosome 3p21 whose product is involved in protein deubiquitination, cell cycle control, and apoptosis (12). The loss of function of *BAP1* is linked to a tumor predisposition syndrome-1 (*BAP1*-TPDS1) with an autosomal dominant pattern of inheritance, presenting susceptibility to MPM, uveal melanoma, cutaneous melanoma, benign melanocytic tumors, and other solid cancers such as breast adenocarcinoma, paraganglioma, cholangiocarcinoma, and renal cell carcinoma (13-15). Moreover, patients may develop peculiar skin tumors, called atypical Spitz tumors, that may be indicative of *BAP1*-TPDS1 and lead to genetic investigation (15-17). The MPM prevalence in *BAP1*-TPDS1 ranges between 6 and 8%, significantly higher than the 1% observed with sporadic MPM (14-18). Moreover, a significant survival improvement has been reported in MPMs in *BAP1*-TPDS1 with a median survival of 5–7 years with 26% of patients surviving 10 or more years (18). The different prognosis of MPM in *BAP1*-TPDS1 as compared to MPM with somatic *BAP1* variants suggests a tailored diagnostic as well as therapeutic management for this group of patients, also in consideration of the variant transmission and the penetrance in the family cluster.

The aims of this narrative review are:

(I) To present a deep overview of genetic susceptibility in the development of MPM;
(II) To report the differences in terms of epidemiology, clinicopathological features, prognosis, and therapeutic strategies between patients with gene-related MPM (GR-MPM) and patients with asbestos-related MPM (AR-MPM);
(III) To describe the therapeutic frontiers in MPM, including the potentiality of a target gene therapy.

We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-611/rc).

Methods

The narrative review is based on a selective literature carried out in PubMed in 2023. We searched titles and abstracts in PubMed research papers using the search terms "Malignant Pleural Mesothelioma [MeSH]" AND "Genomic Analysis or Germline Variants [MeSH]" AND "BAP1 mutations

Table 1 The search strategy summary

Items	Specification
Date of search	January 2nd, 2023
Databases and other sources searched	PubMed
Search terms used	"Malignant Pleural Mesothelioma [MeSH]" AND "Genomic Analysis or Germline Variants [MeSH]" AND "BAP1 mutations [MeSH]"
Timeframe	January 1st, 2001–January 1st, 2023
Inclusion criteria	Original article, English language, and clinical trial (randomized, prospective, or retrospective)
Selection process	Two authors (F.L. and L.B.) independently reviewed abstracts identified with this search, while a third author (M.T.C.) was consulted in case of discrepancies

[MeSH]" AND (2001/1/1: 2023/1/1) [pdat]AND (english) [filter].

Inclusion criteria were original article, English language, and clinical trial (randomized, prospective, or retrospective); in case of duplication of data of the same author, we chose the most recent study.

Two authors (F.L. and L.B.) independently reviewed abstracts identified with this search, while a third author (M.T.C.) was consulted in case of discrepancies. Selected articles were examined in full, processed, summarized and used in the different paragraphs, according to their relevance and adherence to the topic. The search strategy is summarized in *Table 1*.

Genetics of MPM: somatic and germline variants

The current genetic landscape of MPM is difficult to establish due to the rarity of the condition that limits the overall sample size for available genome and transcriptome information in databases. While most MPMs arise from exposure to environmental carcinogenic factors, about 20% of cases occur spontaneously from somatic or germline variants. Somatic variants are cell-specific and can be heterogeneous within tumors, whereas germline variants are present in all the cells of an individual and are more likely to be present in family members. In order to better understand the pathogenesis of MPM and potential gene-driven therapeutics, genetic variants are of great interest to both researchers and physicians. While germline variants can be more easily identified because of their potential segregation in a family, the presence of accompanying clinical signs and symptoms, and the tendency to increase the risk of developing various types of malignancies, sporadic variants, albeit theoretically less rare, are not associated with any inheritance pattern, lack the signs of a syndromic presentation, and are usually detected after the onset of MPM. *Table 2* summarizes the most relevant research conducted in the past 10 years, and illustrates the genetic variants, clinical information, and common histological classifications. Oncogenic pathways, such as mTOR, Hippo, and p53, have been associated with MPM, and about half of the genes identified in *Table 2* are a part of those pathways (19). Hippo and mTOR pathways mediate the increase in transcription of genes involved with cellular division and migration (31,32). The p53 pathway is common in about half of all cancers and is responsible for regulating cell cycle arrest after DNA damage has occurred in the cell (33). The disruption of these oncogenic pathways is usually the result of loss-of-function variants affecting *NF2*, *SETD2*, and *TP53*. The University of California, Santa Cruz (UCSC) Genome Browser was used to find the top 50 important gene interactions for each gene listed in *Table 2*. *Figure 1* below displays these interactions categorized by pathways common to other cancer types and MPM colored in yellow/orange and pathways with lesser-known associations colored in blue. The thickness of the arrows corresponds to the strength of association based on the number of selected articles that identified at least one gene in the pathway. The genes with unknown interaction with the other pathways were then run through the top gene to identify potentially significant biological and disease pathways for future research. The most significant biological processes identified were regulation of nucleotide-excision repair, leukocyte differentiation, and hemopoiesis which involved variants in *SMARCA4*, *SMARCC1*, *SMARCD1*, *SMARCD3*, *ARID1B*, *PBRM1*, *ARID2*, *HOXA7*, *GNAS*, *CTNNB1*, *MMP14*, *DICER1*, and *FANCA*; while medulloblastoma and tubulovillous adenoma were the most significant diseases

Table 2 Major genetics findings associated with malignant pleural mesothelioma

Study	Number of patients	Genes identified	Germline or somatic variance	Clinical information	Histological classification
Bueno *et al.*, 2016, (19)	216	*BAP1, NF2, TP53, SETD2, DDX3X, ULK2, RYR2, SETDB1, DDX51*	Not stated explicitly	Primary	Sarcomatoid, epithelioid, biphasic-epithelioid (biphasic-E), and biphasic-sarcomatoid (biphasic-S)
Kiyotani *et al.*, 2017, (20)	6	*TP53, BAP1*	Somatic	TNM, primary	Epithelioid (n=3), biphasic (n=3)
Creaney *et al.*, 2022, (21)	229	*SETDB1, BAP1, CDKN2A, NF2, RBFOX1, SBS40, SBS5*	Germline, somatic		Epithelioid, biphasic, sarcomatoid
Taghizadeh *et al.*, 2020, (22)	14	*BAP1, FANCA, NF1, NF2, PD-L1, SETD2, SRC, TP53*	Not stated explicitly	Metastatic	Not stated specifically
Meiller *et al.*, 2021, (23)	16	*TERT, BAP1, CTNNB1, NF2, TP53, SETD2, ARID2, CDKN2A*	Not stated explicitly	Not stated explicitly	Epithelioid, biphasic
Pagano *et al.*, 2020, (24)	164	*MXRA5, BAP1, NF2, NOD2, RAPGEF6, PIK3CB, RDX, ACTG1*	Somatic	Not stated explicitly	Epithelioid, biphasic, sarcomatoid, stage IV, stage III
Yoshikawa *et al.*, 2020, (25)	101	*BAP1, CDKN2A, NF2, MLH1, SETD2, SETBP1, ARID1B, ARID2, PBRM1, SMARCA4, SMARCC1, SMARCD1, SMARCD2, SMARCD3*	Germline	Not stated explicitly	Epithelioid, biphasic, sarcomatoid
Zauderer *et al.*, 2021, (26)	194	*BAP1, NF2, TP53, SETD2, LATS2, CDKN2A, CDKN2B, TP53, TERT, GNAS, DICER1, PBRM1*	Somatic	Primary	Epithelioid, biphasic, sarcomatoid, stage I–IIIA, stage IIIB–IV
Nastase *et al.*, 2022, (27)	121	*CDKN2A, SUFU, RB1, RASSF7, NF2, LATS1, LATS2, BAP1, PTCH2, GJB2, NHS, HOXA7, ARL3, TRIM8*	Somatic	Not stated explicitly	Epithelioid, biphasic, sarcomatoid
Matullo *et al.*, 2015, (28)	835	*SLC7A14, THRB, CEBP350, ADAMTS2, ETV1, PVT1, MMP14*	Not stated explicitly	Not stated explicitly	Not stated explicitly
Campanella *et al.*, 2020, (29)	43	*TP53, ERBB2, BRAF, PDGFRA, NRAS, EGFR, KIT, AKT1, PIK3CA, FOXL2*	Not stated explicitly	Not stated explicitly	Epithelioid, sarcomatoid
Guo *et al.*, 2021, (30)	47	*AURKA, GAPDH, TOP2A, PPARG, SCD, FABP4, CEBPA*	Not stated explicitly	Primary	Epithelioid (n=42), biphasic (n=3), sarcomatoid (n=2)

TNM, tumor-node-metastasis.

that have previously been linked to variants in *PTCH2*, *SMARCA4*, *AURKA*, *GJB2*, *GNAS*, *CTNNB1*, *MMP14*, *SUFU*, *TOP2A*, *FABP4*, and *MLH1*. Germline variants in *BAP1* predispose to the development of MPM following an autosomal dominant pattern of inheritance in the familial cases (19-25,34). Inactivation of two specific additional genes, *NF2* and *SETD2*, due to splicing alterations has been reported in several studies (19,21,24-27). Creaney *et al.* 2022 (21), have found that MPM is an unusual type of cancer, predominantly driven by the loss of tumor suppressor genes (*BAP1*, *NF2*, and *CDKN2A*) with a lack of oncogenic gain-of-function activities. Several studies have investigated genes and genetic mechanisms associated with MPM, employing Sanger sequencing, genome-wide association study (GWAS), whole-genome sequencing, and various other technologies (*Table 2*). A concise definition of the genes and genetic mechanisms is still problematic due to the need for further primary research findings. The field is continuing to develop, AR-MPM is a much more significant portion of the causality for MPM (around 80%) and thus the germline and somatic mutants—often combined with the exposure to asbestos—are less investigated. Only adult cases were considered for this table, however, there is an additional study discussing 5 cases from a pediatric cohort

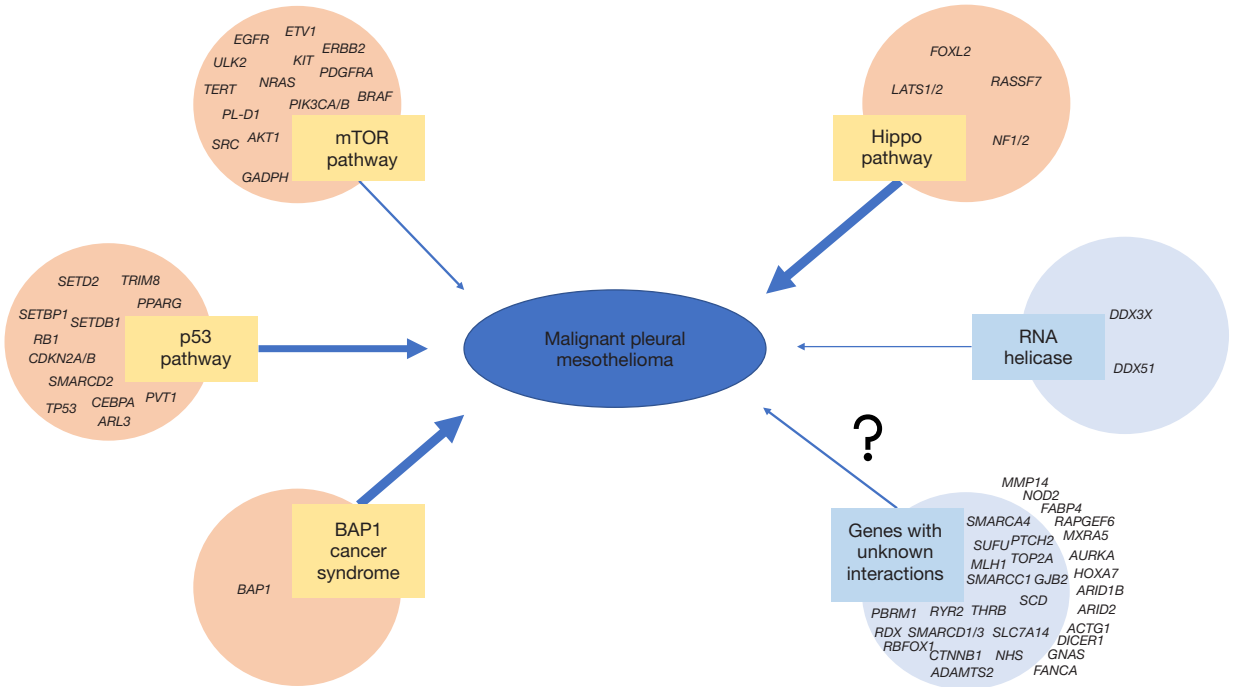

Figure 1 Relative contributions of different pathways to the onset of MPM. The different pathways whose disruption has been associated with MPM are represented as independent circles, which include the related genes. The thickness of the arrows is proportioned to the relative pathogenic contribution of each pathway (i.e., a larger arrow indicates a more substantive contribution). Promoting factors may lead to generic cancer syndromes (i.e., p53 and mTOR pathways) in addition to MPM or be specific to the latter (*BAP1*-TPDS1). MPM, malignant pleural mesothelioma.

characterized by *BAP1* variants, a congenital syndrome, and mesothelioma fusions (35). This study suggests the need for further investigation into the germline and somatic variants in the pediatric population affected with MPM.

MPM and BAP1-associated TPDS1

Pathogenic *BAP1* variants—either germline or somatic—were detected in 6 of the 12 large studies conducted (19,21,22,25,27,34) over the last decade while Kiyotani *et al.* (20) identified *BAP1* variants in 1 of 6 cases (17%) and *TP53* variants in 3 of 6 MPM cases (50%) (*Table 2*).

BAP1 encodes a tumor suppressor protein controlling gene transcription, cellular differentiation, DNA damage repair, apoptosis, and cell metabolism. Homozygous loss-of-function variants in this gene induce embryonic lethality, suggesting a pivotal role for the BAP1 protein in cellular development (36) *PARP1* and *2* have been shown to induce the accumulation of BAP1 at sites of DNA damage where it can then use multiple binding sites to control the accumulation of proteins (BRCA-1, RAD51, and RPA) to repair the DNA or induce cellular apoptosis (37). *BAP1*-associated TPDS1, also known as *BAP1* cancer syndrome, is the result of heterozygous germline variants in *BAP1* and is inherited in an autosomal dominant manner with incomplete penetrance within families (38).

The syndrome has been associated with an increased risk for MPM, uveal melanoma, cutaneous melanoma, renal cell carcinoma, and basal cell carcinoma and has possible associations with increased risk for hepatocellular carcinoma, cholangiocarcinoma, and meningioma (39). While isolated mesothelioma generally presents in the pleura (80–90% of cases), the peritoneum (10–15%), or sometimes the pericardium (less than 5%), the forms described in association with *BAP1*-TPDS1 have been shown to present equally between pleural and peritoneal (40). *BAP1*-TPDS1 has an earlier onset of tumors compared to the overall population and patients with MPM have a median age at diagnosis of 54.5 years compared to the overall population (72 years) (38). Mouse models of *BAP1*-TPDS1 have shown increased susceptibility after a lower threshold of environmental exposure and decreased OS

Table 3 Epidemiological and clinical differences between AR-MPM and GR-MPM

Epidemiological and clinical differences	AR-MPM	GR-MPM
Association with asbestos exposure	Strong	Not strong
Age of presentation (years), (mean)	72.3	56.3
Gender ratio (M:F)	5:1	1:1
Symptoms frequency	+++	+/–
Presence of pleural effusion	+++	+/–
Stage at presentation	Usually advanced	Usually initial

+++, common; +/–, rare. AR, asbestos-related; MPM, malignant pleural mesothelioma; GR, gene-related; M, male; F, female.

compared to wild-type mice (41). These mouse models contrast observational studies in human patients about OS, which was 60 months in patients carrying *BAP1* variants, as compared to 17 months in patients without the variant where both groups had previous asbestos exposure (42). This difference in OS of *BAP1* carriers can be attributed to the mouse model presenting almost completely with sarcomatoid malignant mesothelioma (MM) features, which are more aggressive, while the human carriers present with predominantly, around 70%, epithelioid MM features. The different presentations of MM are possibly due to interspecies differences since other independent mouse models for MM present with sarcomatoid features (41).

Differences between AR-MPM and non-AR-MPM

Differences in epidemiology and clinical presentation

The overall incidence of MPM is still increasing all over the world. The World Health Organization (WHO) estimates a peak in the incidence in several European countries in the years 2020–2030; however, the incidence rates reported in parts of Asia and Central or Eastern European countries may be lower than expected due to poorer quality of certification and diagnostic recording data (6).

On the contrary, in developed countries peak incidence is expected to occur before 2030 (43) and to drop gradually thereafter. The main reason is that health politics and governmental action, based on the understanding of the relationship between mesothelioma and asbestosis, have reduced exposure to asbestos in the workplace and the general environment. Some evidence suggests that epidemiology and clinical presentations differ between AR-MPM and non-AR-MPM (18): the main differences are summarized in *Table 3*.

A few more causes have been discovered in addition to GR-MPM, including exposure to the simian virus (SV40) or several mineral fibers such as erionite, silica, silver, and nickel, which are all examples of non-AR-MPM. Additionally, numerous case reports and large retrospective cohort studies have found an association between therapeutic radiation for different malignancies and the development of MPM (6,44). Concerning the epidemiology of AR-MPM, the development of neoplasm is typically delayed from the exposure with a latency period estimated in a range between 20 and 45 years (5). Estimates of latency continue to be revised as exposed populations age; the Western Australia Mesothelioma Registry initially reported a time since first exposure to the diagnosis of those diagnosed between 1960–1979 of 26 years (45), with the most recent estimate of latency in those diagnosed between 2010–2019 being 52 years (46). Exposure to asbestos is 5 times more frequent in males compared to females due to the higher number of male workers in industries with exposure risk. However, there is a certain body of evidence (47) suggesting exposure of family members to asbestos dust from the overalls of tradesmen is well-recognized. In this population, there is a higher proportion of women compared to other cohorts. In an Italian study based on a national register epidemiologic surveillance system, cases among females are due mainly to household contact with asbestos; occupational exposures among women mainly are related to work in the chemical and plastic industry and the non-asbestos textile sector (48). Among non-AR-MPMs, patients treated with chest and mediastinal ionizing radiotherapy for lymphoma, breast cancer, and testicular germ-cell tumors (although prophylactic mediastinal irradiation is no longer used since 2001) have a significantly increased risk of developing MPM (49,50). Individuals who develop non-AR-MPM after therapeutic irradiation for

Hodgkin disease or non-Hodgkin lymphoma are likely to have unusual histologic features, are significantly younger, and seem to have a longer OS compared with patients with AR-MPM (50). The observation of family aggregations could indicate a different genetically determined individual susceptibility. The demonstration that susceptibility to mesothelioma can be transmitted following a Mendelian pattern (51) and the subsequent discovery of a very high risk of mesothelioma in members of the same family with heterozygous inherited *BAP1* variants (52) underline a determining role of genetics in the development of mesothelioma (17,53).

The study by Rai *et al.* (39) of 174 patients with germline *BAP1* variants found that 75% developed at least one of the five major malignancies associated with BAP1-TPSD1, including uveal melanoma (31%), malignant mesothelioma (22%), atypical intradermal benign tumors, with melanocytic *BAP-1*-mutated atypical intradermal tumor (*MBAIT*) (18%), cutaneous melanoma (13%), and renal cell carcinoma (10%). In addition, 90% of patients had a family history of at least two of these tumors in first- or second-degree relatives (39). Among the tumors associated with the *BAP1* cancer syndrome, uveal melanoma is the most aggressive type, with the greatest risk of metastasis and reduced OS (54,55).

Malignant mesothelioma is the second most common cancer. In approximately 60% of mesothelioma cases, somatic variants of *BAP1* have been detected: these variants occur in mesothelial cells, promoting the development and growth of cancer cells, underlining the critical role that *BAP1* has in the development of mesothelioma cells (19,56,57). Like mesotheliomas caused by environmental exposure, those related to inherited germline variants (GR-MPM) occur at a young age and with an male: female (M:F) ratio close to 1:1 (53,58). The mean age of onset in GR-MPM cases is significantly lower than in the ones with AR-MPM: 55 versus 72 years (59). Accordingly, the overall pleural-to-peritoneal mesothelioma ratio is 5:1 in men and women with asbestos exposure (60), as compared to subjects with *BAP1* variants, in which the same ratio is 1:1, and mesotheliomas often occur in patients with no or minimal asbestos exposure (61). Concerning the clinical onset, usually AR-MPM patients present with insidious gradually worsening pulmonary symptoms which may be present for months or longer prior to diagnosis (6). Symptoms are often non-specific such as chest pain, dyspnea, cough, hoarseness, night sweats, or dysphagia, which occur in the setting of extensive intrathoracic disease; cachexia is observed in up to 25% of patients usually related to tumoral dissemination and poor prognosis (61). Distant metastatic spread is less common but rarely can involve the bone, liver, or central nervous system. As far as symptoms are concerned, patients with the GR-MPM form of mesothelioma usually have milder symptoms than the AR-MPM form and sometimes they can even be asymptomatic. Therefore, the diagnosis of genetic predisposition to mesothelioma is recommended in a multidisciplinary group approach (62,63).

Differences in pathological features and therapeutic approach

Sometimes the diagnosis of MPM could be challenging for the difficulty to distinguish between benign, malignant, and reactive mesothelial proliferations. For this reason, if clinical conditions permit, pleural biopsies are necessary to obtain adequate samples to evaluate tissue invasion and for appropriate immunohistochemistry. Diagnosis of MPM, and in particular its subtypes, requires an experienced pathologist: in addition to the more frequent histotypes (epithelioid, biphasic, and sarcomatoid), unusual variants such as deciduoid, clear cell, small cell, signet ring cell, pleomorphic could make the differential diagnosis between MPM and metastatic carcinoma very insidious (64).

Survival is directly dependent on histology: epithelioid mesotheliomas are the least aggressive, with a median survival of 14 months (7) on the contrary sarcomatoid mesothelioma represents the subtype with the worst outcome and median survival ranging from 3.5 to 8 months (65).

Non-AR-MPMs, and in particular mesotheliomas in carriers of *BAP1* or other germline variants, are almost exclusively of the epithelioid type, are well differentiated, and seem to have significantly better survival than patients with MPMs in the Surveillance, Epidemiology, and End Results (SEER) cohort (52). If compared with epithelioid-AR-MPMs, their morphology is less aggressive, with oval cells with bland nuclei, rare mitoses, and no necrosis. The better survival could be due to the fact that most of these patients carried either pathogenic germline variants of *BAP1* or additional genes linked to cancer, some of which may have targeted-therapy options. Moreover, data from the International Association for the Study of Lung Cancer (IASLC) database suggest that only a highly select group of younger patients with an epithelioid mesothelioma histological subtype and no lymph node metastases may experience improved long-term OS with the surgical procedure (66); GR-MPM patients, being usually younger

Table 4 State of the art in cytotoxic systemic therapies for "wt" AR-MPM

Treatment	Line	ORR (%)	PFS (m)	OS (m)	Reference
ASC *vs*. MVP *vs*. ASC + vinorelbine	I	NR	5.1 *vs*. 5.1 *vs*. 5.6	7.6 *vs*. 8.5 *vs*. 9.4	Cedres S, *et al*. 2021, (73)
Pemetrexed + Vit B12 + folic acid *vs*. pemetrexed alone	I	16.3 *vs*. 9.5	NR	13.8 *vs*. 8.0	Sculco M, *et al*. 2022, (74)
Cisplatin + pemetrexed *vs*. cisplatin	I	41 *vs*. 17	5.7 *vs*. 3.9	12.1 *vs*. 9.3	Baldo P, *et al*. 2017, (75)
Cisplatin + raltitrexed *vs*. cisplatin	I	24 *vs*. 14	5.3 *vs*. 4.0	11.4 *vs*. 8.8	Danson S, *et al*. 2017, (76)
Carboplatin and pemetrexed	I	19	6.5	12.7	Krug LM, *et al*. 2010, (77)
Cisplatin and gemcitabine	I	33	6.4	11.2	Powell A, *et al*. 2006, (78)
Pemetrexed + cisplatin *vs*. pemetrexed	II	32.5 *vs*. 5.5	NR	7.6 *vs*. 4.1	Krug LM, *et al*. 2014, (79)
Pemetrexed + platinum	II	19	3.8	10.5	Ou SH, *et al*. 2015, (80)
Vinorelbine	II	16	NR	9.6	Dolly SO, *et al*. 2013, (81)

wt, wild type; AR, asbestos-related; MPM, malignant pleural mesothelioma; ORR, overall response rate; PFS, progression-free survival; m, months; OS, overall survival; ASC, active symptoms control; MVP, mitomycin-vinblastine-cisplatin; NR, non-recorded.

and asymptomatic with good performance status, could be the ideal patients who can benefit from surgical resection in early-stage disease. Extra pleural pneumonectomy (EPP) is no longer performed by many thoracic surgeons for the high rate of mortality and complications (up to 11% and 45% respectively) (67) in particular if compared to extended pleurectomy (EP) or pleurectomy/decortication (P/D). In the unique randomized controlled trial (RCT) published until now, no advantage in terms of OS and quality of life (QoL) was achieved by EPP with adjuvant hemithorax irradiation (68); on the contrary, a recent meta-analysis indicates that P/D compared to EPP is associated with enhanced outcomes regarding 30-day mortality, median OS, and complications (69). We are waiting for the results in terms of effectiveness, OS, health-related QoL, progression-free survival (PFS), and measures of safety (adverse events of a UK multicentric RCT comparing (extended) pleurectomy decortication plus chemotherapy versus chemotherapy alone (70). Even if a multimodal approach is considered the best option, we can offer to patients with MPM, the optimal combination remains debated, in particular for the bias due to the high selection of patients fit for surgery and the difficulty to obtain large series for RCT. Intraoperative lavage with chemotherapy compounds (cisplatin is the best choice, but also doxorubicin, mitomycin C, and gemcitabine) after P/D seems to give promising mid-term oncological results (71,72), but the lack of control non-surgical groups and the absence of controlled trials and prospective studies do not allow identification of any predictive factor of OS and disease-free survival (DFS) (*Table 4*). If the issue in AR-MPM is the selection of patients who are suitable for surgery, considering the impact on QoL and the high rate of morbidities, the question for GR-MPM is markedly complex: what is the best treatment for the subclinical disease (usually have a minimal disease with an indolent biological behavior for several years), in healthy patients with a long-life expectancy? The current possible options are P/D or first-line chemotherapy. We have no data for answering the difficult question about a predictable response to therapy and for identifying who can benefit from immediate therapy. An ongoing trial (82) expecting to accrue 800 participants with the BAP1 cancer syndrome in 10 years who will undergo uniportal video-assisted thoracic surgery (VATS) and laparoscopy every 3 years for individuals more than 33 years old: patients in whom early-stage mesotheliomas are detected may be eligible for clinical protocols. The information derived from this protocol should address the open questions about the importance of implementing screening programs and targeting epigenetic drivers to induce regressions or to prevent/delay the progression of these neoplasms.

Differences in prognosis and identification of prognostic factors

The prognosis for MPM remains poor. MPM has an extremely short survival rate, about 8 to 14 months following diagnosis (83). Histological subtype in MPM has been widely recognized as a prognostic factor, with non-epithelioid histology considered as a predictor of poor survival

Table 5 State of art in immunotherapy for "wt" MPM

Immunotherapy	Rationale	Reference
Immune checkpoints	MPM is associated with relevant chronic inflammation. CTLA-4 and PD-L1 are upregulated and expressed on effectors T-cells	Cedres S, *et al.* 2021, (73); Calabrò L, *et al.* 2021, (88)
Mesothelin-targeted approaches	Mesothelin is overexpressed in epithelial MPM cells but not in normal cells	Baldo P, *et al.* 2017, (75)
Oncolytic viruses	Oncolytic viruses have the capacity to destroy tumor cells	Danson S, *et al.* 2017, (76)
WT1	WT1 is overexpressed in MPM	Krug LM, *et al.* 2010, (77)
Vaccination with tumor cells lysate	Generate specific-tumor immunity that causes regression of tumor	Powell A, *et al.* 2006, (78)

wt, wild type; MPM, malignant pleural mesothelioma; PD-L1, programmed cell death 1.

in two main prognostic scores [European Organization for Research and Treatment of Cancer (EORTC); Cancer and Leukemia Group B (CALGB)] (73). Furthermore, biphasic forms of non-epithelioid mesothelioma can exhibit a variable percentage of epithelioid differentiation. Vigneswaran *et al.* found that this percentage acts as an independent predictor of survival (84). Additionally, a recent study showed that patients with MPM carrying *BAP1* loss-of-function variants have better prognoses compared to non-germline mutants, with 5-year OS of 47% and 7%, respectively (85). Using localized therapy and systemic therapy [chemotherapy and/or programmed cell death 1 (PD-1)/programmed death-ligand 1 (PD-L1) targeted immunotherapy], Murrone *et al.* (85) assessed the relationship between genetic changes in MPM tumors and clinical outcomes. Compared to tumors with *BAP1* or *NF2* variants, patients with *TP53*-mutated tumors exhibited lower OS and PFS with treatment. According to research by Pass *et al.* 2013, carriers of *BAP1* variants had an average survival of 5 years, which was significantly longer than the benefit of any available therapy (86). This study also revealed that current therapies only significantly extended patients' median survival (which in the control group was 1 year) by 11 weeks. The same authors conducted an additional study in which patients with mesothelioma who had a family history of the disease and/or of other cancers, as well as patients with early-onset mesothelioma (at age 50 years), were more likely carriers of inherited germline variants, and these patients had a significantly improved survival rate. A total of 79 patients met these recruitment criteria. Inherited germline variants were found in 28 of 50 probands (56%) (17). Patients with mesothelioma who carried germline variants experienced significantly prolonged survival of 5 to ≥10 years, only 28% reported possible asbestos exposure, and the M:F and pleural *vs.* peritoneum ratios were 1:1, underscoring the uniqueness of this subgroup of patients. Among them, 43 of 79 patients had deleterious germline *BAP1* variants: their median age at diagnosis was 54 years, and the median survival was 5 years (17). Although only small cohorts of patients have been evaluated to date, mesotheliomas in carriers of different germline variants seem to follow a similar trend. Markowitz *et al.* (87) correlated genomic alterations and clinical data in 17 patients with MPM who performed next-generation sequencing (NGS) analysis. The most common alterations involved, in order, *NF2*, *BAP1*, *CDKN2A*, and *TP53* proved that patients with *TP53* mutated tumors had worse OS as well as PFS with chemotherapy compared to tumors with *BAP1* or *NF2* variants. Median PFS with anti-PD-1/PD-L1 monotherapy was poor at only 1.5 months (*Table 5*). This finding is similar to other studies that have reported these as the frequently altered inactivating variants in tumor suppressor genes in MPM tumors (89).

There are several reasons to justify genetic testing for patients with mesothelioma in comparison to the majority of mesotheliomas that form in older people with asbestos exposure, the prognosis of mesothelioma patients who carry germline variants is much better. Also, in carriers of germline variants of genes required for DNA repair (*BAP1*, *TP53*, *BRCA1/BRCA2*, etc.) (90,91), magnetic resonance imaging (MRI) should be preferred to X-ray imaging, which uses ionizing radiation and can cause secondary malignancies. These patients should be screened in order to obtain an early diagnosis that might increase their OS. They, like their relatives who inherited the same variants (the transmission rate of heterozygous variants is about 50%), are all at risk of developing multiple malignancies. Screening programs can help to detect early different types

of cancers: such as melanoma, renal cell carcinoma, breast carcinoma (tumor forms that are common in carriers of heterozygous *BAP1* variants), as well as colon, ovarian, and endometrial cancers (frequent in carriers of heterozygous *MLH1* variants, associated with Lynch syndrome).

Screening, genetic testing, and surveillance of patients with BAP1 germline variants

Although pathogenic variants in several genes have been associated with high susceptibility to MPM, *BAP1*-TPDS1 is the only condition with a recognizable pattern of inheritance that includes MPM among its clinical features. As discussed before, *BAP1*-TPDS1 is characterized by an autosomal dominant pattern of inheritance, therefore, subjects with germline pathogenic variants in *BAP1* should receive genetic counseling regardless of the diagnosis of MPM. Considering the variability in the clinical presentation of this syndrome, the lack of large studies on MPM incidence among carriers of *BAP1* germline variants, and the possibility of incomplete penetrance, every individual with a pathogenic *BAP1* variant should be managed as a patient with *BAP1*-TPDS1, even in the absence of signs and symptoms compatible with the clinical diagnosis of this condition. Genetic testing should be proposed for all first-degree relatives since they may be carriers of the same variant. We suggest that genetic screening for *BAP1* variants should be considered for individuals exposed to asbestos, since the genetic background may influence the risk associated with environmental factors. Moreover, *BAP1* loss has a very important clinical implication in the diagnosis of MPM: detection of the BAP1 protein is by far the most important biomarker in the distinction between benign and malignant mesothelial proliferations with a complete specificity since BAP1 loss in mesothelial cells is indicative of malignancy. In addition, BAP1 staining loss is particularly helpful in confirming MPM from metastases from other neoplasms. Even if GR-MPMs have a better prognosis than AR-MPMs (42), patients should follow a strict surveillance protocol based on periodic imaging (preferably MRI) and laboratory tests. This protocol should be suggested to unaffected carriers of *BAP1* as well, due to the aggressive course of the disease. The surveillance protocol for carriers of germline *BAP1* pathogenic variants should be extended to the other types of cancers reported in *BAP1*-TPDS1: uveal melanoma, cutaneous melanoma, renal cell carcinoma, and basal cell carcinoma (39), while for the tumors for which the increased risk is less validated—hepatocellular carcinoma, cholangiocarcinoma, and meningioma—the clinical management should be evaluated on the base of the presence of clinical features or abnormal laboratory markers. Unfortunately, the involvement of germline variants in genes other than *BAP1* is not as deeply characterized, and the available information is insufficient to develop and implement guidelines for tailored genetic screening and/or clinical surveillance. However, we suggest discussing the potential risk of developing MPM, among other cancers, in the genetic counseling of individuals carrying germline variants in cancer-predisposing genes like *TP53* or *CDKN2A*.

Gene therapy targeting BAP1 variants

As previously reported, no effective targeted therapies are available for MPM (*Table 6*); possible alternatives have been investigated, looking for germline variants affecting pathways that may be responsive to targeted protocols. In particular, Sculco *et al.* (74) performed an NGS analysis to identify predisposing genes susceptible to targeted therapies and suggested a primary role for germline variants of genes involved in the DNA repair mechanisms (*BRCA1*, *BRIP1*, *CHEK2*, *SLX4*, *FLCN*, and *BAP1*), suggesting that in case of variants, lower asbestos exposure was needed to develop MPM. As already said, BAP1 modulates DNA damage repair mechanism. It has been suggested that BAP1-altered MPM might be susceptible to poly (ADP-ribose) polymerase inhibitors (PARPi) (101). PARP enzymes play a major role in DNA single-strand break repair and base excision repair pathways and PARPi are approved across many cancer types. In a single-center, non-randomized, phase 2 trial (102), in which patients with previously treated mesothelioma were given olaparib, the rationale for the study was that patients with somatic BAP1 mutations or deficiencies of others DNA repair genes could benefit from olaparib monotherapy. This study reported that olaparib monotherapy has a limited activity in MPM [overall response rate (ORR) of 4%, median PFS 3.6 months, median OS 8.7 months]; the median PFS of germline BAP1 mutants (n=4) was 2.3 months (95% CI: 1.3–3.6) and the median OS was 4.6 months (95% CI: 3.1–4.9). In this study, the analysis of BAP1 mutation status gives an antithetic result: patients with BAP1 mutations had a shorter OS and PFS if they received Olaparib in monotherapy. Recently, Tazemetostat, a selective oral enhancer of zeste homolog 2 (EZH2) inhibitor, has shown antitumour activity in several

Table 6 State of the art in targeted therapies for "wt" MPM

Target therapy	Rationale	Reference
Cell cycle	Cancers cells might be susceptible to pharmacological disruption of the G2 checkpoint	Krug LM, *et al.* 2014, (79)
Arginine deaminase	Arginine succinate deficiency renders mesothelioma cells sensitive to arginine deprivation; Adi-PEG is an arginine-degrading enzyme	Szlosarek PW, *et al.* 2017, (92)
NF2	NF2 is a tumor suppressor gene encoding for the merlin protein. Merlin inactivation has a critical role in the pathogenesis of MPM	Kinoshita Y, *et al.* 2020, (93)
PI3K/AKT/mTOR pathway	The inhibition of this pathway, crucial in cell proliferation, in vitro induces apoptosis of MPM cells	Zhou S, *et al.* 2014, (94)
Tyrosine kinase	Many growth factors are activated in MPM (like EGFR, PDGFR, VEGFR) (imatinib-erlotinib)	Porta C, *et al.* 2007, (95); Edwards JG, *et al.* 2006, (96)
Angiogenesis and blood vessels	VEGF levels are increased in patients with MPM (thalidomide-bevacizumab-sorafenib)	Buikhuisen WA, *et al.* 2013, (97); Ceresoli GL, *et al.* 2013, (98); Strumberg D, *et al.* 2005, (99)
HSP90	HSP90 stabilizes proteins required for tumor growth and survival of mesothelioma	Okamoto J, *et al.* 2008, (100)

wt, wild type; MPM, malignant pleural mesothelioma; Adi-PEG, pegylated arginine deiminase; PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase B; mTOR, mammalian target of rapamycin; EGFR, endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptors; VEGFR, vascular endothelial growth factor receptor; HSP90, heat shock protein 90.

haematological cancers and solid tumours. Authors tested an enhancer of the *EZH2* inhibitor tazemetostat on a three-dimensional-MPM cell model that had a defect in the ataxia telangiectasia mutated (*ATM*) gene. This targeted therapy significantly reduced the size and viability of *ATM*-silenced spheroids, inducing apoptosis in the MPM mutated cells. Similar results were reported by Pandey *et al.* (103), who investigated the *BAP1*-loss-associated chromatin and expression changes in mouse and human mesothelioma, mostly related to the polycomb repressive complex (PRC)-mediated silencing. To test the role of variants in this pathway, an *EZH2* inhibitor was tested, confirming the better response in *Bap1*-deficient mouse and human cell lines. Moreover, the authors described that *Bap1*-deficient mesothelioma cells are sensitive to the loss of kinases belonging to a major metabolic pathway involved in mevalonate and cholesterol biosynthesis. They also tested the potential role of a mevalonate pathway inhibitor, zoledronic acid (ZA), finding that *Bap1*-deficient mouse mesothelioma cell lines are more sensitive to ZA treatment than the *Bap1* wild-type cell line. This result was confirmed also using human MPM cell lines. Finally, the association of the two inhibitors, ZA and tazemetostat, prolonged survival in *Bap1*-deficient mesothelioma mice.

In June 2022, a clinical trial published in *The Lancet Oncology* (104) examined the effectiveness of tazemetostat, an EZH2 inhibitor, for treating malignant mesothelioma. The study involved 74 adult patients with relapsed or refractory malignant mesothelioma from multiple clinical sites. Divided into two parts, the study focused on pharmacokinetics in Part 1, analyzing plasma samples for tazemetostat's concentration, and efficacy and disease control rate in BAP1-deficient malignant mesothelioma in Part 2. In Part 1, patients received a single dose of 800 mg tazemetostat on Day 1, followed by twice-daily doses on Day 15. Pharmacokinetic measurements were taken from plasma samples on Day 15, including Cmax, Tmax, AUC0–t, AUC0–∞, and t1/2. In Part 2, the primary endpoint was determining the disease control rate at week 12, while secondary endpoints assessed response rates, survival, pharmacokinetics, and pharmacodynamics. In patients with BAP1-inactivated MPM, the disease control rate was 54% (95% CI: 42–67%; 33 of 61 patients) at week 12 after a median follow-up of 35.9 week; no patients had a confirmed complete response and two patients had a confirmed partial response. Serious adverse events were reported in 34% of patients. Further phase II/III studies are needed to validate the possibility of the development and adoption of targeted therapies in MPM and test the efficacy of these target agents. It is plausible to assume that future therapies for MPM associated with *BAP1* variants may benefit from targeted protocols applied to cancers associated with genes

affecting similar pathways, like *BRCA1/2*-associated breast carcinoma or colon adenocarcinoma caused by epimutations in *MLH1*.

Conclusions

MPM is a very aggressive disease and its etiology is strongly related to asbestos exposure, despite only a small number of exposed people developing MPM. A minority of cases seem to be not clearly related to asbestos exposure and the incidence of these cases has been increasing in recent years, suggesting that genetic predisposing factors may play a crucial role (GR-MPM). Moreover, familial cases of MPM have been largely evaluated in the recent past, suggesting that heredity may be an important and underestimated feature in MPM development. By analyzing the genetic susceptibility in MPM, approximately 20% of cases may be related to genetic predisposition: genes involved in DNA repair mechanisms are the most frequently involved. In the present review, we described different clusters of MPM based on the predominant etiological factor: asbestos exposure or predisposing genetic variants. In sum, the AR-MPM usually occurs in old age with a skewed prevalence towards the male gender and is often diagnosed at an advanced stage and associated with symptoms, such as pleural effusion. On the other hand, GR-MPM occurred in younger patients with no gender predilection and presented with no symptoms and early stage at diagnosis.

We have herein also highlighted that pathogenic germline variants in the *BAP1* gene segregate in an autosomal dominant pattern in the familial cases. MPMs in subjects carrying such variants are significantly less aggressive and the clinical management of these cases requires a multidisciplinary approach.

Finally, we have summarized the therapeutic frontiers in MPM, including the potentiality of a gene-targeted therapy, which is promising but far to be validated in clinical practice at the moment.

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Footnote

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