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BAP1 Tumor Predisposition Syndrome

Synonyms: *BAP1* Cancer Syndrome; Cutaneous/Ocular Melanoma, Atypical Melanocytic Proliferations, and Other Internal Neoplasms (COMMON Syndrome)

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Summary

Clinical characteristics

BAP1 tumor predisposition syndrome (*BAP1*-TPDS) is associated with an increased risk for a specific skin lesion, *BAP1*-inactivated melanocytic tumors (BIMT; formerly called atypical Spitz tumors), and the following cancers, in descending order of frequency: uveal (eye) melanoma (UM), malignant mesothelioma (MMe), cutaneous melanoma (CM), renal cell carcinoma (RCC), and basal cell carcinoma (BCC). Hepatocellular carcinoma, cholangiocarcinoma, and meningioma may also be associated with *BAP1*-TPDS. Affected individuals can have more than one type of primary cancer. In general, the median age of onset of these tumors is younger than in the general population. UM tends to be a more aggressive class 2 tumor with higher risk for metastasis and reduced survival compared to UM occurring in the general population. Due to the limited number of families reported to date, the penetrance, natural history, and frequencies of *BAP1*-associated tumors are yet to be determined. Other suspected but unconfirmed tumors in *BAP1*-TPDS include (in alphabetic order): breast cancer, neuroendocrine carcinoma, non-small-cell lung adenocarcinoma, thyroid cancer, and urinary bladder cancer.

Diagnosis/testing

The diagnosis of *BAP1*-TPDS is established in a proband by identification of a heterozygous germline pathogenic variant in *BAP1* on molecular genetic testing.

Management

Treatment of manifestations: Treatment of CM and BCC per established clinical guidelines. UM: because of the increased aggressiveness of *BAP1*-related UM, management should be the same as the more aggressive class 2 or

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monosomy 3 tumors. MMe treatment per oncologist familiar with *BAP1*-MMe; RCC treatment per established management guidelines.

Prevention of primary manifestations: UM: avoid arc-welding. MMe: avoid asbestos exposure (including naturally occurring tremolite and erionite) and smoking. CM and BCC: limit sun exposure, use sunscreen and protective clothing, and have regular dermatologic examinations.

Surveillance: BIMT, CM, BCC: annual full-body dermatologic examinations beginning around age 18 years. Baseline whole-body imaging in those with a large number of lesions; repeat as needed. Biopsy of BIMT is not recommended unless lesions grow or change in shape or color. UM: yearly dilated eye examinations and at least baseline fundus imaging beginning around age 11 years. Refer any pigmented intraocular lesion to an ocular oncologist for follow up and management. MMe: no screening modalities exist; however, annual physical examination is recommended. If an abdominal MRI is to be performed as recommended for RCC, consider evaluation of the peritoneum and pleura as well. While some physicians recommend spiral chest CT for asymptomatic persons with a history of exposure to asbestos, others do not, given the possible increased risk of cancer from radiation exposure. RCC: annual clinical examination; abdominal ultrasound every two years alternating with MRI every two years starting at age 30 years.

Agents/circumstances to avoid: Arc welding, asbestos including naturally occurring tremolite and erionite, smoking, unnecessary and prolonged sun exposure, routine chest x-ray and CT examinations.

Evaluation of relatives at risk: Clarify the genetic status of at-risk relatives by molecular genetic testing for the *BAP1* pathogenic variant in the family in order to identify as early as possible those who would benefit from prompt initiation of screening and preventive measures.

Genetic counseling

BAP1-TPDS is inherited in an autosomal dominant manner. To date, most individuals diagnosed with *BAP1*-TPDS have an affected parent; the proportion of *BAP1*-TPDS caused by a *de novo* pathogenic variant is unknown. Each child of an individual with *BAP1*-TPDS has a 50% chance of inheriting the *BAP1* pathogenic variant; however, penetrance appears to be incomplete and the types of *BAP1*-related tumors can vary among different members of the same family. Once the germline *BAP1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No diagnostic criteria have been published for the *BAP1* tumor predisposition syndrome (*BAP1*-TPDS). In one review, 90% of families reported with a germline *BAP1* pathogenic variant met the criteria outlined in Suggestive Findings [Rai et al 2016].

Suggestive Findings

BAP1-TPDS **should be suspected** in an individual who has EITHER of the following:

- Two or more confirmed *BAP1*-TPDS tumors*
- One *BAP1*-TPDS tumor and a first- or second-degree relative with a confirmed *BAP1*-TPDS tumor*

* Excluding two basal cell cancers and/or cutaneous melanomas, given their high frequency in the general population

Confirmed *BAP1*-TPDS tumors include the following (in descending order of likelihood):

- *BAP1*-inactivated melanocytic tumors (BIMT). Formerly called atypical Spitz tumors, these may be the most common manifestation of *BAP1*-TPDS, and may result in the initial identification of a proband.

BIMT are skin colored to reddish brown, averaging 5 mm in diameter; the histologic findings are between those of a Spitz nevus and a melanoma. Both copies of *BAP1* are inactivated, leading to loss of staining for the BAP1 protein on immunohistochemistry; in addition, BIMT usually have somatic *BRAF* pathogenic variant p.Val600Glu.

- Uveal (eye) melanoma (UM)
- Malignant mesothelioma (MMe)
- Cutaneous melanoma (CM)
- Renal cell carcinoma (RCC)
- Basal cell carcinoma (BCC)
- Hepatocellular carcinoma, cholangiocarcinoma, and meningioma. These now appear to be less common manifestations of *BAP1*-TPDS.

Unconfirmed tumors (with conflicting evidence regarding inclusion in the *BAP1*-TPDS spectrum) include the following (in alphabetic order):

- Breast cancer
- Neuroendocrine tumors
- Non-small-cell lung adenocarcinoma
- Thyroid cancer
- Urinary bladder cancer

Establishing the Diagnosis

The diagnosis of *BAP1*-TPDS **is established** in a proband by identification of a heterozygous germline pathogenic variant in *BAP1* on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *BAP1* is performed. The identification of partial and whole-gene deletions in a subset of individuals supports the benefit of doing gene-targeted deletion/duplication analysis concurrently, or if no *BAP1* pathogenic variant is found on sequence analysis.

- **A multigene panel** that includes *BAP1* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in *BAP1* Tumor Predisposition Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
BAP1	Sequence analysis [3]	>87.5% [4]
	Gene-targeted deletion/duplication analysis [5]	<12.5% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Haugh et al [2017], Carlo et al [2018], Huang et al [2018], Walpole et al [2018], Boru et al [2019]

Clinical Characteristics

Clinical Description

BAP1 tumor predisposition syndrome (*BAP1*-TPDS) is associated with increased risk for a number of cancers and a specific skin lesion, *BAP1*-inactivated melanocytic tumor (BIMT; formerly called atypical Spitz tumor). Affected individuals can have more than one type of primary cancer [Abdel-Rahman et al 2011, Testa et al 2011, Wiesner et al 2011, Popova et al 2013, Walpole et al 2018].

Because of the limited number of families reported to date and ascertainment bias of groups focusing on uveal melanoma, malignant mesothelioma, and cutaneous melanoma, the penetrance and frequencies of the various *BAP1*-associated tumors are yet to be determined. In an attempt to adjust for ascertainment bias, Walpole et al [2018] (as noted below) compared the prevalence of each component tumor in probands with *BAP1*-TPDS to the prevalence in relatives known to also have a *BAP1* pathogenic variant. It has been well established, however, that the following tumor types are associated with *BAP1*-TPDS.

***BAP1*-inactivated melanocytic tumor** (BIMT; formerly called atypical Spitz tumor). The natural history of these lesions is not clearly known. It appears that individuals with *BAP1*-TPDS typically have multiple lesions [Haugh et al 2017]. BIMT are skin colored to reddish brown, averaging 5 mm in diameter; the histologic findings are between those of a Spitz nevus and a melanoma. Both copies of *BAP1* are inactivated, leading to loss of staining for the BAP1 protein on immunohistochemistry; in addition, BIMT usually have somatic *BRAF* pathogenic variant p.Val600Glu.

Uveal melanoma (UM) is the cancer most commonly reported in persons with *BAP1*-TPDS (36% of probands and 16% of relatives reported with *BAP1*-TPDS have UM), and it is the cancer with the earliest reported age of diagnosis (age 16 years) [Walpole et al 2018]. Median age of onset of UM in persons with *BAP1*-TPDS is 53 years, which is younger than the onset of UM in the general population (62 years). The tumors are generally more aggressive class 2 (i.e., high metastatic risk) tumors with reduced survival [Njauw et al 2012, Rai et al 2016]. In one study, mean length of survival in persons whose UM lacked BAP1 expression was 4.74 years compared to 9.97 years in persons whose tumors expressed BAP1 [Kalirai et al 2014].

Malignant mesothelioma (MMe) is the second most frequent cancer (25% of probands and 19% of relatives) identified in individuals with *BAP1*-TPDS [Walpole et al 2018]. Several studies have shown that the median age of onset of MMe in individuals with *BAP1*-TPDS was significantly earlier (55 to 58 years) than that of sporadic MMe (68-72 years) [Baumann et al 2015, Ohar et al 2016, Walpole et al 2018]. In the general population, pleural

MMe accounts for about 80% and peritoneal MMe constitutes most of the remaining MMe. However, in individuals with *BAP1*-TPDS the ratio of peritoneal to pleural involvement is significantly higher [Carbone et al 2015, Cheung et al 2015, Ohar et al 2016, Walpole et al 2018]. In *BAP1*-TPDS the majority of peritoneal MMe occurs in women, in contrast to the general population, in which men are more likely to have this tumor type [Walpole et al 2018].

In contrast to survival in persons with *BAP1*-related cutaneous melanoma, UM, or renal cell carcinoma, survival in persons with *BAP1*-related MMe may be significantly longer, especially in those with pleural mesothelioma [Baumann et al 2015, Pastorino et al 2018, Wang et al 2018, Hassan et al 2019].

Growing evidence suggests that *BAP1* pathogenic variants interact with environmental asbestos exposure to increase the risk for MMe [Xu et al 2014, Kadariya et al 2016].

Cutaneous melanoma (CM). First reported in association with *BAP1*-TPDS in 2011, CM is now known to be the third most common cancer in *BAP1*-TPDS, occurring in 13% of affected individuals [Wiesner et al 2011]. Interestingly, Walpole et al [2018] found CM in 45% of probands but in no relatives affected with *BAP1*-TPDS [Walpole et al 2018]. Multiple primary cutaneous melanomas are common. The median age of onset of CM in individuals with *BAP1*-TPDS is earlier than in the general population (39 vs 58 years). While it is possible that *BAP1*-related CM is more aggressive than CM in the general population, the data are currently inconsistent [Gupta et al 2015, Kumar et al 2015, Rai et al 2016, Liu-Smith & Lu 2020].

Renal cell carcinoma (RCC). Heterozygous *BAP1* germline pathogenic variants are specifically associated with an increased risk for RCC, in particular those with clear cell morphology [Haas & Nathanson 2014]. Walpole et al [2018] found RCC in 10% of probands and relatives with *BAP1*-TPDS, although the specific histology was not always known and additional morphologies including papillary and chromophobe cell tumors were also observed. Median age of RCC diagnosis appears to be younger in persons with *BAP1*-TPDS than in the general population (47-50 vs 64 years), and length of survival is decreased in persons with *BAP1*-related RCC [Rai et al 2016]. Histology of these tumors is distinct from tumors not associated with pathogenic variants in *BAP1*, with higher grade at diagnosis and lack of somatic *PBRM1* pathogenic variants (which are common in RCC not associated with pathogenic variants in *BAP1*) [Peña-Llopis et al 2012].

Basal cell carcinoma (BCC) has recently been confirmed as a tumor in the *BAP1*-TPDS spectrum [de la Fouchardière et al 2015b, Mochel et al 2015, Wadt et al 2015]. Multiple primary basal cell carcinomas are common. Walpole et al [2018] found that the median age of diagnosis for non-melanoma skin cancer (primarily BCC) was 44 years.

Meningioma, particularly a high-grade rhabdoid subtype, has been suggested to be associated with *BAP1*-TPDS [Abdel-Rahman et al 2011, Cheung et al 2015, de la Fouchardière et al 2015a, Wadt et al 2015, Shankar et al 2017]. This is further supported by identification of this tumor in 8.5% of probands with *BAP1*-TPDS and 2.2% of relatives with the *BAP1* pathogenic variant.

Cholangiocarcinoma has also been suggested to be part of *BAP1*-TPDS [Njauw et al 2012, Pilarski et al 2014, Wadt et al 2015]. Walpole et al [2018] found this cancer in 1.4% of probands with *BAP1*-TPDS but in none of the relatives.

Hepatocellular carcinoma (HCC). Germline *BAP1* pathogenic variants have been observed in 0.5% of unselected individuals with HCC [Huang et al 2018]. Walpole et al [2018] identified HCC in 0.7% of probands with *BAP1*-TPDS and 1.6% of relatives with the *BAP1* pathogenic variant.

Other cancers with some evidence (although inconsistent) supporting inclusion in the *BAP1*-TPDS spectrum are the following (in alphabetic order):

- Breast cancer [Testa et al 2011, Njauw at al 2012, Popova et al 2013, Abdel-Rahman et al 2016]. Although breast cancer has been reported in individuals with germline pathogenic variants in *BAP1*, in one individual biallelic inactivation was not observed in the tumor tissue. In addition, no *BAP1* pathogenic variants were detected in any of the 1,078 breast cancers included in The Cancer Genome Atlas (TCGA) project, suggesting that breast cancer is likely not part of the phenotype.
- Neuroendocrine tumors [Abdel-Rahman et al 2011, Wadt et al 2012]
- Non-small-cell lung adenocarcinoma [Abdel-Rahman et al 2011, Njauw et al 2012, Wadt et al 2012, Aoude et al 2013b]
- Thyroid cancer [Popova et al 2013, McDonnell et al 2016]
- Urinary bladder carcinoma. One individual was reported with a *BAP1* germline pathogenic variant and evidence of biallelic inactivation in the tumor [Tesch et al 2020].

Genotype-Phenotype Correlations

To date no genotype-phenotype correlations for *BAP1*-TPDS have been published.

Most families (104 of 141) have had a unique *BAP1* pathogenic variant; a number of recurrent pathogenic variants have been reported [Walpole et al 2018] (see Molecular Genetics).

Penetrance

The penetrance of the *BAP1*-TPDS appears to be high based on the published literature, with 88% of probands and 82.5% of relatives with a heterozygous germline *BAP1* pathogenic variant having had a cancer diagnosis. However, ascertainment biases in favor of both testing and reporting affected versus unaffected individuals may have inflated this figure. For example, in more than half of the reported families only the proband had been tested. Also, the majority of the study participants were ascertained based on their strong family history of cancer. Given these biases, an accurate estimate of penetrance cannot be determined at this time. In attempting to adjust for this, Walpole et al [2018] found a significantly lower prevalence of *BAP1*-related tumors in affected relatives compared to probands (see Prevalence).

Nomenclature

BAP1-inactivated melanocytic tumors have also been called the following:

- Atypical Spitz tumors
- Nevoid melanoma-like melanocytic proliferations (NEMMP) [Njauw et al 2012]
- Melanocytic *BAP1*-mutated atypical intradermal tumors (MBAITS) [Carbone et al 2012]
- BAPoma [Author, personal observation]

Prevalence

The prevalence of *BAP1*-TPDS is unknown. Based on data from the Genome Aggregation Database (gnomAD), the carrier frequency is 1:26,837 in the general population. In the cancer cohort from the TCGA, the frequency was 8:10,389 (1:1,299).

The prevalence of *BAP1*-TPDS ranges from 1%-2% in persons with UM,1%-3% in persons with MMe [Huang et al 2018, Panou et al 2018], 1%-1.5% in those with RCC [Carlo et al 2018, Wu et al 2019], and 0.5% in persons with HCC. Several large studies showed that *BAP1*-TPDS is rare in those with CM (0.1%) [Aoude et al 2015, O'Shea et al 2017]. The prevalence of *BAP1*-TPDS in persons with other cancers is unknown.

UM. The prevalence of germline *BAP1* pathogenic variants in unselected individuals with UM is 1%-2% [Aoude et al 2013a, Gupta et al 2015, Repo et al 2019]; in contrast, the frequency is 20%-30% in persons with UM who have a family history of UM [Turunen et al 2016, Rai et al 2017].

MMe. Germline *BAP1* pathogenic variants have been identified in 1%-3% of simplex cases and 6%-7.7% (9:153) of individuals with familial MMe [Betti et al 2015, Ohar et al 2016, Betti et al 2018].

CM. Germline *BAP1* pathogenic variants were observed rarely in two large studies of sporadic CM with a prevalence of 3:1,197 (0.25%) and 0:1109 [Aoude et al 2015, O'Shea et al 2017]. Also, germline *BAP1* pathogenic variants are rare in familial CM (0%-0.7%), particularly in those with no other cancers observed in the family [Njauw et al 2012, Boru et al 2019, Potjer et al 2019].

Genetically Related (Allelic) Disorders

Germline *de novo* heterozygous *BAP1* pathogenic variants have been reported in 11 individuals with developmental delay and/or intellectual disability and various additional features including hypotonia, seizures, behavior disorders, dysmorphic facial features, skeletal malformations, short stature, and congenital anomalies of the eyes, heart, and urinary system [Küry et al 2022].

Sporadic tumors (including cholangiocarcinoma, hepatocellular carcinoma, mesothelioma, renal cell carcinoma, uveal melanoma, and *BAP1*-inactivated melanocytic tumors) occurring as single tumors in the absence of any other findings of *BAP1* tumor predisposition syndrome frequently harbor somatic variants in *BAP1* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

Pathogenic variants in genes other than *BAP1* can be associated with uveal melanoma, cutaneous melanoma, malignant mesothelioma, and renal cell carcinoma; however, no other gene is known to be associated with increased risk for the **combination of these cancers**, as is seen in *BAP1* tumor predisposition syndrome (*BAP1*-TPDS).

Table 2. Genes to Consider in the Differential Diagnosis *BAP1* Tumor Predisposition Syndrome

Cancer Type	Gene / Genetic Mechanism	Comments/References
Uveal melanoma	*BRCA1* *BRCA2* *MBD4* *PALB2*	Sinilnikova et al [1999], Iscovich et al [2002], Scott et al [2002], Moran et al [2012], Abdel-Rahman et al [2020a], Abdel-Rahman et al [2020b]
Malignant mesothelioma	*CDKN2A* [1]	Panou et al [2018]
Cutaneous melanoma	*CDKN2A* *CDK4* *MC1R* *MITF*	Pancreatic cancer is assoc w/*CDKN2A* pathogenic variants [Marzuka-Alcalá et al 2014].

Table 2. continued from previous page.

Cancer Type	Gene / Genetic Mechanism	Comments/References
Hereditary renal cell carcinoma	*VHL*	See Von Hippel-Lindau Syndrome.
	Xp11 translocation	Xp11 translocation renal cell carcinoma (OMIM 300854)
	FH	Hereditary cutaneous leiomyomatosis, renal cell cancer, uterine leiomyomas (fibroids); see *FH* Tumor Predisposition Syndrome.
	FLCN	• Renal tumors: hybrid oncocytic, chromophobe, oncocytoma, papillary, clear cell renal cell carcinoma • Cutaneous: fibrofolliculomas/trichodiscomas • Pulmonary: lung cysts, spontaneous pneumothoraces; see Birt-Hogg-Dubé Syndrome.
	MET	Hereditary papillary renal cell carcinoma (OMIM 605074)

Monogenic disorders included in this table are inherited in an autosomal dominant manner.
1. Panou et al [2018] describe several additional genes; however, only *BAP1* and *CDKN2A* remain significant if the Bonferroni correction is applied.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *BAP1* tumor predisposition syndrome (*BAP1*-TPDS), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended in a multidisciplinary team approach [Rai et al 2016, Star et al 2018].

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *BAP1* Tumor Predisposition Syndrome

System/ Concern	Evaluation	Comment
BIMT, CM, &/or BCC	• Full-body skin exam by dermatologist specializing in melanoma • Consider whole-body imaging if large number of lesions. • Excision of lesions suggestive of BIMT is debated. • Mgmt of other suspicious melanocytic lesions & BCC per established clinical guidelines	Beginning at age ~18 yrs
UM	• Dilated eye exam & baseline dilated fundus imaging • Refer any suspected lesion to ophthalmologist specializing in mgmt of UM (ocular oncologist) for proper diagnosis & mgmt.	Beginning at age ~11 yrs
MMe	• No consensus on screening modalities exists. • Abdominal & respiratory clinical exam w/investigation of any suspected symptoms • Asymptomatic imaging surveillance w/US (renal/abdominal & chest) or MRI (abdominal & chest w/diffusion-weighted sequences)	• Beginning at age 30 yrs • Combined w/RCC eval
RCC	Abdominal exam & investigation of any suspected symptoms	• Beginning at age 30 yrs • Combined w/MMe eval

Table 3. continued from previous page.

System/ Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *BAP1*-TPDS to facilitate medical & personal decision making

BIMT = *BAP1*-inactivated melanocytic tumor; CM = cutaneous melanoma; BCC = basal cell carcinoma; RCC = renal cell carcinoma; MMe = malignant mesothelioma; MOI = mode of inheritance; UM = uveal melanoma
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

The treatments for *BAP1*-TPDS tumors are those used in standard practice.

Table 4. Treatment of Manifestations in Individuals with *BAP1* Tumor Predisposition Syndrome

Manifestation/Concern	Treatment	Considerations/Other
BIMT, CM, &/or BCC	• Annual dermatologic exam & whole-body imaging recommended for stable asymptomatic BIMT lesions • Treatment of CM & BCC per established clinical guidelines	Excision biopsy of BIMT is suggested but not universally recommended for asymptomatic, stable lesions [Star et al 2018].
UM	Manage UMs as more aggressive tumors (i.e., those determined to be Class 2 by expression profiling & those w/monosomy 3)	Because of ↑ aggressiveness of *BAP1*-related UM [Njauw et al 2012]
MMe	Treatment per oncologist familiar with *BAP1*-MMe	• MMe is highly refractory to conventional therapies incl aggressive surgical intervention & multimodality strategies; thus, a cure is unlikely. • Recent studies suggest that *BAP1*-related MMe could respond better to chemotherapy. • Several clinical trials incl w/PARP inhibitor are ongoing.
RCC	Treatment per established management guidelines	Several clinical trials incl w/PARP inhibitor are ongoing.

BIMT = *BAP1*-inactivated melanocytic tumor; CM = cutaneous melanoma; BCC = basal cell carcinoma; RCC = renal cell carcinoma; MMe = malignant mesothelioma; PARP = poly ADP ribose polymerase; UM = uveal melanoma

Prevention of Primary Manifestations

Uveal melanoma (UM). Arc welding has been associated with risk of UM and this should be avoided if possible.

Sunglasses with high UVA and UVB protection can reduce risk of cancer on the eyelids, but data regarding the benefit of sunglasses for UM are lacking.

Malignant mesothelioma. As with all individuals, asbestos exposure (including naturally occurring tremolite and erionite) and smoking should be avoided.

Cutaneous melanoma (CM). Primary prevention is limited to those measures typically used to reduce the risk for CM, including limiting of sun exposure, regular use of sunscreen and protective clothing, and regular dermatologic examinations.

Surveillance

Consensus management recommendations have not been established; however, several groups have proposed variations of the following (see Table 5) [Carbone et al 2012, Battaglia 2014, Rai et al 2016, Star et al 2018].

Table 5. Recommended Surveillance for Individuals with *BAP1* Tumor Predisposition Syndrome

System/Concern	Evaluation	Frequency
BIMT, CM, &/or BCC	• Full-body skin exam by dermatologist specializing in melanoma • Consider whole-body imaging if large number of lesions. • Excision of lesions suggestive of BIMT is debated. • Mgmt of other suspicious melanocytic lesions & BCC per established clinical guidelines	Annually beginning at age ~18 yrs
UM	• Dilated eye exam & baseline dilated fundus imaging preferably by ophthalmologist trained in diagnosis & mgmt of UM (ocular oncologist) • Alternatively, follow up by ophthalmologist w/referral of suspected lesions to ocular oncologist for proper diagnosis & management	Annually beginning at age ~11 yrs
MMe (pleural & peritoneal)	• No consensus on screening modalities exists. • Clinical eval for signs/symptoms of pleurisy (pleural inflammation), peritonitis, ascites, &/or pleural effusion: chest pain, cough, fever, shortness of breath, dysphagia, hoarseness, weight loss, fever, upper body & face edema, abdominal pain, nausea, vomiting, &/or constipation	• If abdominal MRI is to be performed as recommended for RCC, consider eval of peritoneum & pleura as well. • Some physicians recommend spiral chest CT for asymptomatic persons w/ history of exposure to asbestos; others do not, given possible ↑ risk of cancer from radiation exposure. • Avoid routine surveillance w/chest x-ray or CT exam.
RCC	• Annual clinical exam w/investigation of any suspected symptoms such as abdominal pain &/or hematuria • Asymptomatic imaging surveillance using US (renal/abdominal & chest) & MRI (abdominal & chest w/ diffusion-weighted sequences)	• Beginning at age 30 yrs • MRI every 2 yrs • US every 2 yrs (alternating w/MRIs)

BIMT = *BAP1*-inactivated melanocytic tumor; CM = cutaneous melanoma; BCC = basal cell carcinoma; RCC = renal cell carcinoma; MMe = malignant mesothelioma; UM = uveal melanoma

Agents/Circumstances to Avoid

Avoid the following:

- Arc welding
- Asbestos
- Smoking
- Unnecessary and prolonged sun exposure
- Routine chest x-ray and CT examinations

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of at-risk relatives of an affected individual by molecular genetic testing for the *BAP1* pathogenic variant in the family. Family members who have a *BAP1* pathogenic variant should be offered regular lifelong surveillance. Family members who have not inherited the pathogenic variant and their subsequent offspring have risks similar to the general population.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Currently no open treatment trials specifically target individuals with *BAP1*-TPDS, but several trials are currently open for individuals with somatic *BAP1* pathogenic variants, including PARP inhibitor therapies as single or combination therapies.

One NCI-sponsored trial (NCT01587352) using vorinostat in the treatment of metastatic uveal melanoma is assessing *BAP1* mutation status as a secondary outcome measure.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

BAP1 tumor predisposition syndrome (*BAP1*-TPDS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- To date, most individuals diagnosed with *BAP1*-TPDS have an affected parent. An affected parent may have *BAP1*-related tumors that differ from those of the proband.
- Some individuals diagnosed with *BAP1*-TPDS may have the disorder as the result of a *de novo* germline *BAP1* pathogenic variant. The proportion of *BAP1*-TPDS caused by a *de novo* pathogenic variant is unknown. To date, a *de novo* pathogenic variant has been reported in one individual (both parents tested negative for the variant identified in the proband) [Walpole et al 2018].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* germline pathogenic variant (i.e., a proband who appears to be the only affected family member).
- If the germline *BAP1* pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental leukocyte DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism. (No instances of parental germline mosaicism for a *BAP1* pathogenic variant have been reported to date.)
- The family history of some individuals diagnosed with *BAP1*-TPDS may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative

family history cannot be confirmed unless molecular genetic testing has confirmed that neither of the parents has the germline *BAP1* pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the *BAP1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%. However, penetrance appears to be incomplete (see Penetrance) and the types of *BAP1*-related tumors can vary among different members of the same family.
- If the *BAP1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *BAP1* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for *BAP1*-TPDS because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *BAP1*-TPDS has a 50% chance of inheriting the *BAP1* pathogenic variant. However, penetrance appears to be incomplete and the types of *BAP1*-related tumors can vary among different members of the same family.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the germline *BAP1* pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Predictive testing for at-risk asymptomatic family members requires prior identification of the germline *BAP1* pathogenic variant in the family.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – Health Professional Version (part of PDQ®, National Cancer Institute).

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once a germline *BAP1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for *BAP1*-TPDS are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Cancer Society**
  Phone: 800-227-2345
  cancer.org
- **CancerCare**
  Phone: 800-813-4673
  Email: info@cancercare.org
  cancercare.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. BAP1 Tumor Predisposition Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
BAP1	3p21.1	Ubiquitin carboxyl-terminal hydrolase BAP1	BAP1 @ LOVD	BAP1	BAP1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for BAP1 Tumor Predisposition Syndrome (View All in OMIM)

603089	BRCA1-ASSOCIATED PROTEIN 1; BAP1
614327	TUMOR PREDISPOSITION SYNDROME 1; TPDS1

Molecular Pathogenesis

BAP1 encodes BAP1, a ubiquitin carboxyl-terminal hydrolase. BAP1 is a nuclear-localized deubiquitinating enzyme and acts as a chromatin-associated protein that is part of large multiprotein complexes that both positively and negatively regulate cellular proliferation (reviewed in Daou et al [2015]). It is recruited to promoter regions of genes involved in cellular proliferation to activate transcription and to promote repair at sites of DNA double-strand breaks through homologous recombination [Daou et al 2015]. BAP1 cytoplasmic function is thought to be important in apoptosis [Bononi et al 2017].

Mechanism of disease causation. Loss of function. A pathogenic variant in one *BAP1* allele results in haploinsufficiency of BAP1, a tumor suppressor protein. Tumors develop when the second allele acquires a second pathogenic variant resulting in complete loss of BAP1 tumor suppressor activity. Most *BAP1*-inactivated melanocytic tumors analyzed by Wiesner et al [2012] showed loss of the remaining normal *BAP1* allele by various somatic alterations and all showed loss of BAP1 protein in the nucleus.

Table 6. Notable *BAP1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_004656.4 NP_004647.1	c.1717delC	p.Leu573TrpfsTer3	Founder variant identified in several families from United States w/ common ancestor [Carbone et al 2015, Walpole et al 2018, Boru et al 2019]
	c.1780_1781insT	p.Gly594ValfsTer49	Founder variant in Finland
	c.178C>T	p.Arg60Ter	Observed in multiple subjects from different populations; proven through haplotype studies to have arisen independently multiple times [Walpole et al 2018]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Cancer and Benign Tumors

Sporadic tumors (including cholangiocarcinoma, hepatocellular carcinoma, mesothelioma, renal cell carcinoma, and uveal melanoma) may occur as single tumors in the absence of any other findings of *BAP1*-TPDS and frequently harbor somatic variants in *BAP1* that are not present in the germline (reviewed in Rai et al [2016]). In these circumstances, predisposition to these tumors is not heritable.

Chapter Notes

Author Notes

Authors' website

Our group's research is focused on identifying and characterizing hereditary causes of uveal melanoma. We were one of three groups co-reporting on the identification of *BAP1* tumor predisposition syndrome (*BAP1*-TPDS). We offer research analysis of *BAP1* in families with histories suggestive of *BAP1*-TPDS and are performing exome and other analyses on high-risk UM families without identifiable genetic causes. To discuss enrolling a patient please contact robert.pilarski@osumc.edu.

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Revision History

- 24 March 2022 (aa) Revision: *BAP1*-related neurodevelopmental disorder [Küry et al 2022] added to Genetically Related Disorders
- 17 September 2020 (sw) Comprehensive update posted live
- 9 April 2020 (rp) Revision: clarification of starting age for screening
- 13 October 2016 (bp) Review posted live
- 3 May 2016 (rp) Original submission

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