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The Importance of Multidisciplinary Approach in Early Detection of BAP1 Tumor Predisposition Syndrome: Clinical Management and Risk Assessment

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ABSTRACT: Germline BAP1 (BRCA1-associated protein-1) mutations are involved into a novel specific cancer syndrome and strictly associated with a high cancer susceptibility. Recent data suggest that BAP1 has activity toward target substrates explaining why loss of BAP1 causes a pro-tumorigenic deregulation of gene expression. The recently published data reviewed raise the hypothesis that BAP1 regulates a common subset of substrates, which in turn causes a pro-tumorigenic deregulation of gene expression, and alternatively suggest the role of BAP1 as tumorigenesis suppressor/promoter also by independent mechanisms. The clinical phenotype of BAP1 alterations includes MBAITs (melanocytic BAP1-mutated atypical intradermal tumors), uveal melanoma (UM), cutaneous melanoma (CM), renal cell carcinoma (RCC), mesothelioma (MM), and possibly several other tumors. In clinical practice, early diagnosis is crucial for curative resection of all these tumor types. The uniformed and unambiguous definition of MBAITs as clinical/pathological predictive markers could provide physicians means to identify patients who may carry germline BAP1 mutations and thus could be at high risk of developing CM, UM, MM, RCC, and possibly other tumors. As part of a novel multidisciplinary approach, physicians, pathologists, and clinicians involved into diagnostics should be aware of the histological features and the spectrum of tumors associated with BAP1 loss. Further clinical, epidemiological, and functional studies are required to fully explain the roles of BAP1 and its interaction partners in neoplasia, to define mechanisms behind shared and non-shared clinical and pathological criteria.

KEY WORDS: Bap1, cancer syndrome, melanoma, mesothelioma, MBAITs

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Background

BAP1 (BRCA1-associated protein-1) emerged as an enzyme localized in the nucleus, containing the signature motifs and the activity of an ubiquitin carboxyl-terminal hydrolase (UCH). BAP1 is a 90-kD protein (729 a.a.) that initially was thought to bind BRCA1 in vitro and in vivo, releasing ubiquitin from it, similar to other members of UCH enzyme family, and enhance the growth-suppressive properties of BRCA1.[1] The human BAP1 locus was mapped to chromosome 3p21.3, a region of the genome that is commonly deleted or rearranged in many cancers.[1,2] Loss of BAP1 by deletion, deleterious frame-shift mutation, truncation, or rearrangement may be associated with these genomic changes, particularly when high-penetrance, multi-neoplastic, heredity is observed. The evidence reported to date suggests that BAP1 may be considered much more than a tumor suppressor gene, also given the strong evidence that this gene has an emerging role in influencing cancer cell growth. In the next paragraph, we will review the current knowledge about the BAP1 gene functions and its role in regulating cell-cycle progression (see Table 1).

BAP1 and Cellular Function(s)

The definition of BAP1 as a member of UCH family implicates the ubiquitin-proteasome pathway as a potential, direct effector and/or regulator of BRCA1 cellular functions. Regulated ubiquitination of proteins, followed by subsequent proteasome-dependent proteolysis, plays a central role in almost all cellular processes related to growth, differentiation, and homeostatic.[3] The UCH family members are cytoplasmic or

Table 1. BAP1 major cellular functions.

BAP1 MAJOR CELLULAR FUNCTIONS	REFERENCES
1. As part of the Ubiquitin-Carboxy-terminal Hydrolase (UCH) system	1–5
BAP1 can lead to the following functions:	
a)Proteasome-dependent proteolysis	
b)Cell cycle regulation	
c)Gene expression	
d)Signal transduction	
e)Protein trafficking	
2. Deubiquitination of histones leading to chromatin rearrangement	5
3. Regulation of cell cycle progression by interaction with HCF-1	6,7,38
4. Chromatin modulation and gene transcription	8,9
5. dsDNA repair by regulation of BRCA1/BARD1 complex	11,12
6. Promotion of DNA double-strand break repair	52

nuclear-localized 50–300 kD proteins that generally cleave ubiquitin or ubiquitin-conjugates from large substrates. Their enzymatic activity is closely associated with the 26S proteasome. The UCH system has commonly been characterized as a set of small cytoplasmic proteins (25–30 kD) with preference to cleave ubiquitin from ubiquitin-conjugated small substrates and is also involved in the co-translational processing of pro-ubiquitin. As part of these UCH family members, BAP1 may affect several biochemical pathways.[1] All the deubiquitinating enzymes (DUBs), including BAP1, are highly specialized and specifically involved in different cellular processes such as cell-cycle regulation, gene expression, DNA repair, signal transduction, and protein trafficking.[4] Notably, DUBs appear to be involved in several genetic alterations of DUB genes in various types of cancer.[5] Despite these recent insights, physiological functions of most of the human DUBs remain still unknown. BAP1 broadens the potential roles of this family of proteases, because it is the first large nuclear-localized UCH to be identified.[1] Given that BAP1 is a UCH strictly associated with the BRCA1 complex of proteins, its loss or inactivation may affect a variety of signaling pathways in the cell as discussed below.

BAP1's role in regulating cell-cycle progression. Confirming the complexity of functions performed by this gene, Machida et al showed that BAP1 plays positive roles in cell proliferation.[6] The interaction with host cell factor-1 (HCF-1), a cell-cycle regulator composed of HCF-1N and HCF-1C, is critical for the BAP1-mediated growth regulation. The HCF-1 binding motif of BAP1 is required for interaction with HCF-1N and mediates deubiquitination of HCF-1N by BAP1 (see Figure 1A). HCF-1 is a chromatin-associated protein thought to both activate and repress transcription by linking appropriate histone-modifying enzymes to a subset of transcription factors. One known specific role of HCF-1 is to promote cell-cycle progression at the G1/S boundary by recruiting H3K4 histone methyltransferases to the E2F1 transcription factor to transcribe the genes required for S-phase initiation.[7] Promoted by these evidences, it is reasonable to speculate that BAP1 influences cell proliferation at G1/S by coregulating transcription from HCF-1/E2F-governed promoters. Considering the strong association between BAP1/HCF-1 and HCF-1/E2Fs described above, we can conclude that ubiquitination of HCF-1 prevents activation of E2F-responsive promoters. The deubiquitination by BAP1 relieves this inhibitory effect, promoting cell proliferation. Presently, however, direct evidence of BAP1 interacting with ubiquitinated E2F transcription factors is still lacking.

BAP1 and chromatin modulation. It was shown that BAP1 deubiquitinase activity toward histone H2A as polycomb repressive deubiquitinase (PR-DUB) complex together with ASXL1, which is also the most ancient function of BAP1, preserved in its Drosophila ortholog Calypso.[8] BAP1 knockdown has been demonstrated to significantly modify expression of several known polycomb target genes, a family of proteins that form multi-protein complexes involved in transcriptional regulation.[8] These complexes are critical to physiological processes such as embryonic pluripotencial development, self-renewal, and differentiation.[9] These findings implicate not only that BAP1 associates with several proteins involved in chromatin modification and gene transcription but also that transcriptional dysregulation is a potential pathogenetic mechanism in BAP1-mutated tumors. It is therefore deducible that BAP1 could get many other pleiotropic effects on cell growth by interaction with other protein partners and/or regulation of several genes.

BAP1 and the BRCA1/BARD1 complex. As previously stated, BAP1-mediated tumor suppression is carried out by accelerating progression through the G1-S checkpoint. This leads to an accumulation of DNA damage and cell death.[10] It was initially suggested that BAP1-bound BRCA1 cleaves ubiquitin, and enhances the growth-suppressive effects of BRCA1.[1] Later studies casted doubts on the role played by BAP1 considering the BRCA1 pathway. It was shown that BAP1 did not appear to be involved in the deubiquitination of the BRCA1/BARD1 complex.[11] BRCA1 and BARD1 form a heterodimeric tumor suppressor complex,[12] and formation of the BRCA1/BARD1 complex is required for ubiquitin E3 ligase activity.[13] This reveals important roles in dsDNA repair. According to this hypothesis, Nishikawa et al showed that BAP1 interacts with BARD1 to inhibit the E3 ligase activity of the BRCA1/BARD1 complex, and that BAP1 and BRCA1/BARD1 mutually regulate ubiquitination in the cell cycle and in the DNA damage response pathway.[14] According to the present state of knowledge, it is reasonable to speculate that BAP1 may exert a regulatory role in the DNA damage response. Thus, it appears clear from these studies that BAP1

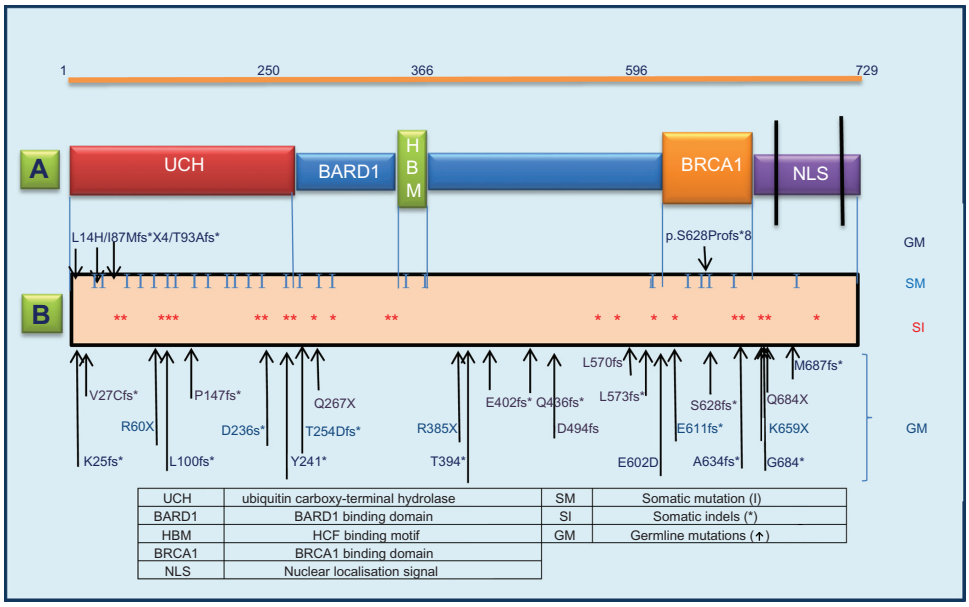

Figure 1. (**A**) Functional domains and regions of interaction of the 729 a.a BAP1 protein, consisting of an N-terminal UCH domain (1–250), an HCF-1-binding domain (HBM, 363–366), and a two-part NLS (656–661 and 717–722). Simplified BAP1 interaction with BARD1 (182–365), HCF-1 (365–385), BRCA1 (596–721) is also illustrated. Numbers at the beginning and at the end refer to amino acids positions. (**B**) Distribution of BAP1 mutations in UM, MM, and RCC specimens to date. Inactivating germline mutations identified in previous studies[17,19,23–25,29,30,32,47–51] are indicated by arrows. Reported somatic missense mutations (SM – blue I) and indels (SI—red*) from UM specimens (COSMIC database; http://www.sanger.ac.uk/genetics/CGP/cosmic/)[21] and germline variants (black lines) from other families are also shown.

has also a relevant role in BRCA1-regulated processes as well as in having BRCA1-independent functions.

BAP1 and Cancer Susceptibility

BAP1 gene mutations, including rearrangements, homozygous deletions, and missense mutations, were initially described in lung and breast carcinomas.[1,15] BAP1 is located in 3p21.3, a region of chromosome 3 that commonly harbors deletions, sometimes encompassing BAP1. This region undergoes frequent copy-number loss and loss-of-heterozygosis in 80% of breast carcinomas, 90% of lung carcinomas, and almost all renal carcinomas.[1,2] For example, the NCI-H226 non-small cell lung carcinoma line carries a homozygous BAP1 deletion (BAP1-/-),[1] and recently a relevant suppression both in tumor formation in mice and growth in monolayer cultures using this cell line by lentiviral-based restoration of BAP1 was shown.[10] It is reasonable to speculate that these tumor suppressor properties are highly dependent on localization of BAP1 to the nucleus and aberrations affecting its active site, particularly cysteine residue. As mentioned earlier, germline BAP1 mutations are associated to a novel cancer syndrome characterized, at least in the affected families so far studied, by benign melanocytic skin BAP1-mutated tumors with an early age of the onset, and later in life by a high incidence of mesothelioma (MM), uveal melanoma (UM), cutaneous melanoma (CM), clear cell renal carcinoma (RCC), and possibly additional cancers, as reported in recent findings.[16,17] Here we describe the emerging BAP1's role as a cancer regulator in relation to a high tumor susceptibility.

Gene alterations. Although the function of BAP1 remained elusive for some time, several pieces of evidence suggest that BAP1 is not just a probable tumor suppressor capable of specifically inhibiting tumor growth in vitro[18] and in an animal model.[10] Different alterations in the BAP1 gene have been described, including coding sequence deletions (leading to loss of the N-terminal region or to premature protein termination), base substitutions leading to nonsense and missense mutations, focal deletions, frame-shift mutations, deletions, and large chromosomal insertions or splice site mutations.[19,20] The latter together with frame-shift mutations have been reported to occur as the most common sequence alterations[21] (see Figure 1B, Table 2). By virtue of the complex functions of BAP1, it is reasonable to suppose that the types of mutation and the gene regions in which they occur will lead to different functional consequences. For instance, truncating mutations frequently result in loss of the nuclear localization signal (NLS) and/or the C-terminal protein-binding domain, while missense mutations affect the ubiquitin hydrolase function of BAP1.[22] Furthermore, BAP1 mutations, depending on the cell type in which they occur and/or the nature of other co-existing mutations, may harvest different tumor phenotypes. Related to BAP1 tumor suppressive function, loss-of-function BAP1 mutations in a diverse array of solid tumor types have been identified,[13,18,19,23–26] including frequent somatic mutations in MM,[24,25] UM,[19,23] and RCC[13,26] (see Tables 3 and 4). Recently, Dey et al identified a somatic heterozygous BAP1 mutation in a patient with de novo myelodysplastic

Table 2. Here we show all the published BAP1 germline mutation cases reported to date.

REFERENCES	PEDIGREE	TUMOR TYPES	GERMLINE DNA CHANGE	MUTATION TYPE AND LOCATION IN GENE	PREDICTED EFFECT ON PROTEIN
17	Family	RCC	c.41T>A	Missense (or splice) exon 1	p.L14H
47	Family	UM, CM	c.75insG	in/del exon 3	p.K25fs*43
34	Family	MM, CM	c.79delG	in/del exon 3	p.V27Cfs*45
30	714 (individual)	CM	c.178C>T	nonsense exon 4	p.R60*
32	Family	RCC	c.256_277 and c.277A>G	In/del exon 5	p.I87Mfs*X4 and p.T93Afs*
51	Family	UM	c.299 T>C(mother)	missense Exon5	pL100fs*
			c.299 T>C(son-monosomy of 3)	missense Exon5	pL100fs*
24	Family	MM	W c.438-2A>G	splice intron 6	p.P147fs*48
50	Family	UM	c.581-2A>G	splice exon 8	Premature truncation
30	FAM562 (family)	UM, CM	c.706_707insG	in/del exon 9	p.D236Gfs*7
48	Family	MM, UM, CM	c.723T>G	nonsense exon 9	p.Y241*
49	Family	MM, UM	c.758_759insA	in/del exon 9	p.T254Dfs*30
23	FUM036 (family)	MM, UM, CM	c.799C>G	nonsense exon 10	p.Q267*
30	FAM729 (family)	UM, CM	c.1153C>T	nonsense exon 12	p.R385*
29	FUM103	AdenoK (rib)	c.1182C>G	nonsense exon 12	p.T394*
19	MM087 (individual)	UM	c.1318-1319insA	in/del exon 12	p.E402fs*2
25,34	Family 1	UM, CM	c.1305delG	in/del exon 13	p.Q436Nfs*135
50	Individual #1	UM	c.1480_1481delGA	in/del exon 13	p.D494fs*
33	Family	MM, UM, CM	c.1708C>G	splice exon 13	p.L570fs*40
24	SP-002 (individual)	MM, UM	c.1832delC	in/del exon 13	p.L573fs*3
50	Individual #2	UM	c.1806G>C	missense(or splice)exon 14	p.E602D (or truncation)
30	3123 (individual)	UM	c.1831_1834del4	n/del exon 14	p.E611Rfs*5
24	SP-008 (individual)	MM, UM	c.2008-2011delTCAC	in/del exon 14	p.S628fs*8
29	FUM104	RCC	c.1882_1885delTAC	In/del exon12	pS628Profs*8
30	2734 (individual)	UM	c.1899_1900ins5	in/del exon 15	p.A634Gfs*5
30	3101 (individual)	UM	c.1975A>G	nonsense exon 15	p.K659*
29	FUM064	UM	C2050C>T	nonsense exon 16	pG684*
24	Family L	MM, UM, CM	c.2050C>T	nonsense exon 16	p.Q684*
25,34	Family 2	MM, UM, CM	c.2057-2A>G	splice intron 16	p.M687Efs*28

syndrome (MDS) and deletion of 20q as the sole additional somatic abnormality.[27] Interestingly, although only a total cohort of 32 patients was sequenced for BAP1 mutations, down-regulation of BAP1 expression in CD34 þ cells from patients with de novo MDS compared with age-matched counterparts was identified.[28] Confirming its emerging role in the oncogenic processes, Harbour and colleagues[19] identified inactivating mutations in BAP1 in 47% of UMs. A high metastatic potential was observed in the vast majority of these tumors, many of which also showed monosomy of chromosome 3.[13,25] Therefore, one allele of BAP1 is lost via monosomy of chromosome 3 and the second allele is non-functional because of an inactivating BAP1 mutation, in keeping with Knudson's two-hit model. Up to date, a broad spectrum of other tumors associated with germline and somatic mutations in BAP1 has been described, and the biological and clinical significance of BAP1-associated tumors is the subject of intensive ongoing studies.

BAP1 Cancer Syndrome

Carbone et al[16] first investigated the presence of melanocytic tumors in two families, to verify if germline BAP1 mutations were associated with distinct syndromes or with a single syndrome exhibiting a wide phenotypic range. A pooled analysis of individuals from studies reporting BAP1-mutated families[23–25,30] to compare cancer risk in 63 BAP1-mutated compared to 55 non-mutated individuals was conducted. After review of published morphology, histology and review of the original tissue sections for melanocytic skin lesions in members of the BAP1-mutated families with either MM or UM,

Table 3. Distribution of BAP1 somatic mutations reported to date (source: COMMON; http://cancer.sanger.ac.uk/cosmic/gene/analysis?ln = BAP1#histo).

MUTATION TYPE	MUTANT SAMPLES	PERCENTAGE(S)
Substitution nonsense	44	14.86
Substitution missense	113	38.18
Substitution synonymous	14	4.73
Insertion inframe	0	0.00
Insertion frameshift	12	4.05
Deletion inframe	8	2.70
Deletion frameshift	71	23.99
Complex	3	1.01
Other	40	13.51
Total	296	100

Table 4. Tumors associated with BAP1 germline mutations.

TUMORS ASSOCIATED WITH BAP1 GERMLINE MUTATION	REFERENCES
Uveal melanoma**	19,23–25,30,33,50,29,53
Epithelioid/spitzoid cutaneous melanocytic naevi/tumours**	25
Cutaneous melanoma**	23,25,33,34,30,53,29
Mesothelioma**	24,34,29
Lung adenocarcinoma**	23
Meningioma**	23
Renal Cell Carcinoma	32,29,17
Paraganglioma	33,53
Neuroendocrine carcinoma	23
Other: Ovarian, Pancreatic cancers, Hepatic cholangiocarcinoma, ***	24,29

Notes: **Tumors reported on OMIM: #614327 – tumor predisposition syndrome (http://omim.org/entry/614327). ***Germline mutations occurred at BAP13p21–22 locus, on a small region congruent with a smaller linkage region founded in a family, assuming that all individuals with kidney, ovary cancers, and early onset breast carcinomas carried the same risk allele.[24,29]

the skin tumors were shown to be indistinguishable.[16] Interestingly, to describe these skin tumors (pink to tan of about 0.2–1.0 cm in diameter) found in affected family members, variable nomenclature was used by pathologists mostly because the lesions macroscopically resembled dermal nevi, but histologically and molecularly did not fit any previous diagnostic definition. Therefore, they proposed the term MBAITs (melanocytic BAP1-mutated atypical intradermal tumors) for all the described BAP1-mutated atypical melanocytic proliferations with common histology and common molecular characterization.[16] Pink polypoid papules, raised pink papules, and lightly pigmented papules were reported to describe the variable clinical presentations of MBAITs. The entity of AST (atypical Spitz tumor) has become a catch-all phrase to clinically and histologically describe a very heterogenous group of lesions: MBAITs have "Spitzoid features," such as large epithelioid, spindle cells, pleomorphisms, but are sufficiently distinct morphologically, cytologically, and clinically. Lumping different melanocytic lesions, such as MBAITs, under the nomenclature used to describe ASTs may hinder both pathologists to identify and classify this subgroup of lesions and clinicians in selecting patients who may benefit from testing for BAP1 mutations. However, uniform and shared amendments by consensus of the actual nomenclature for these new lesions described a need to be confirmed preferable by future characterization of ASTs. Other pathologists do not completely agree with this interpretation: the use of the terms MBAITs and/or NEMMPs (nevoid melanoma-like melanocytic proliferations)[30] proposed for these tumors, when they occur in a familial setting, could be inaccurate. As MBAITs are not exclusively intradermal without junctional involvement, and as the term NEMMPs is similar to nevoid melanomas, aggressive growth is implied inappropriately for these types of tumors. Notably, in contrast to AST that occasionally masks a melanoma, these lesions are benign in appearance and behavior with a history of being stable in morphology, per the patient, and rarely directly evolve into a CM.[16] At a molecular level, the BAP1-associated lesions are also significantly different from traditional ASTs previously described, confirming that that they should not be grouped together. These lesions are molecularly characterized by BAP1 inactivation and almost always by concurrent BRAF mutation, features absent or rare in Spitz and/or ASTs. In the MBAITs cells, but not in the nearby smaller nevus cells, IHC showed negative BAP1 nuclear staining with variable cytoplasmic staining, suggesting loss of heterozygosity of the wild-type BAP1 allele.[16] BRAF analysis was performed on all the MBAITs diagnosed, and BRAF V600E mutations were identified in all of them, confirming the extremely high prevalence of this mutation as originally reported[25] and subsequently confirmed.[30] The overall prevalence of cancer was significantly higher (63.5 and 9.1%, respectively, $P<0.001$) in the BAP1-mutated cohort compared with the non-mutated cohort.[16] MM, UM, CM, and MBAITs prevalence was significantly higher in the BAP1-mutated cohort, while no significant difference was found between the two cohorts concerning the rates of other cancers.[16] All these findings revealed that germline BAP1 mutations cause a novel autosomal dominant hereditary cancer syndrome, characterized predominantly by MM, UM, and CM, by MBAITs, and possibly by other cancers. Recently, some other studies extended the spectrum of tumors related to BAP1 germline mutations.[16,31] For example, a screening for germline BAP1 deleterious mutations in familial BAP1-associated syndromes, including UM, malignant pleural MM, and CM, 6 families with 9 RCC-affected individuals within 11 families screened confirmed a significantly increased risk for RCC.[32] This finding strictly presumes not

only that BAP1 is a RCC-predisposition gene but also that RCC belongs to the BAP1 syndrome. In addition, also meningioma, lung adenocarcinoma, neuroendocrine carcinoma, and abdominal (suspected to be ovarian) adenocarcinoma were identified[23] in a family with BAP1 germline mutations. Previous and recent data,[17,23,24,29,32,33] together with the evidence of biallelic BAP1 inactivation, confirmed that several other tumors such as paraganglioma and neuroendocrine tumors could be part of the BAP1 tumor predisposition syndrome. Moreover, members of two families with germline BAP1 mutations, who developed MM and UM, also developed other tumors.[24] A recent screening of 46 previously untested, unrelated UM patients and 4 additional patients with a personal or family history suggestive of BAP1 hereditary cancer syndrome identified 3 patients with germline pathogenic mutations in BAP1.[29] Two of these three patients presented with UM and the third with a metastatic adenocarcinoma, likely a hepatic cholangiocarcinoma. The families' pedigrees included cases of UM, MM, RCC, CM, and several other internal malignancies. The results of this study confirmed the association between germline BAP1 mutation and predisposition to UM, MM, CM, and RCC. In addition, other cancers such as cholangiocarcinoma and breast carcinoma may be part of the phenotype of this hereditary cancer predisposition syndrome (Table 5). Still, these findings do not exclude the involvement of other genes in contributing to the hereditary predisposition in BAP1 cancer syndrome. In the clinical practice, the presence of epithelioid ASTs/MBAITs appears to be a readily recognizable phenotype, providing potentially useful screening markers. Clinically, these markers may enable the detection of the characteristic dome-shaped or pedunculated, non-pigmented, often multiple tumors. Pathologically, appearance of the predominantly intradermal ASTs with characteristic epithelioid cells may offer the means to identify patients with a higher likelihood of harboring a BAP1 germline mutation. The screening of ASTs, particularly those with a prominent epithelioid cell component, should be performed for BAP1 and BRAF status by IHC and/or by mutation assay. If BAP1 mutations are identified in the tumors, testing for germline BAP1 mutations should be considered, preferably in the context of a familial cancer genetic screening unit. These patients require close monitoring for early detection and curative resection of uveal and CM, and awareness of risk of MM and other malignancies.

Clinical and Pathological Skills

Clinical skills and implications. "The learning and knowledge that we have, is, at the most, but little compared with that of which we are ignorant." The key to everything is to know. Knowledge unlocks doors. In clinical terms, this motto translates into the requirement of an early detection of a BAP1 germline mutation to prevent later, more serious, malignancies. It is clinician's responsibility be aware of the possible existence of this syndrome, once detected in affected individuals, extending screening to all the members of his family and identifying clinical risks together with pathological, diagnostic, and therapeutic courses. In the light of the discovery of the novel, autosomal dominant BAP1 cancer predisposition syndrome described, there is a clinically relevant focus on the importance of multidisciplinary approach in early detection of BAP1-mutated lesions. The development of benign melanocytic tumors in BAP1-mutation carriers during the second decade of life, with tendency to increase in numbers by age, was showed and confirmed in several BAP1-mutant families reported to date.[16,25] The occurrence of CM in some BAP1-mutation carriers, including those that reasonably derive from these benign melanocytic tumors,[34] suggests that these tumors occasionally may undergo malignant transformation, and should therefore be removed. A clinical practice to recognize specific phenotypic markers, similar to other autosomal dominant cancer syndromes, such as adenomas or hypertrophy of the retinal pigment epithelium in familial adenomatous polyposis families or café-au-lait spots in families with neurofibromatosis type 1, is recommended. Despite lack of consensus among pathologists, melanocytic tumor-defined MBAITs[16] are proposed as BAP1-mutation carrier-specific phenotypic markers. The presence of specific and characteristic skin lesions could become an important clinical feature to identify BAP1-mutation carriers. Removal and testing of suspicious lesions may identify patients with germline and/or somatic BAP1 mutations. Regardless, to fulfill the requirements for a useful, early clinical marker, there is a need for further clinical, pathological, and correlation studies. For example, in a setting of CMs reported showing biallelic BAP1 inactivation, one of the tumors was associated with an epithelioid naevus. Both the naevus and melanoma components showed loss of BAP1 expression by IHC,[34] suggesting that some BAP1-mutated epithelioid melanocytic tumors may progress to melanoma. It is essential to broaden knowledge not only about BAP1 differential expression in mutated/wild-type tumor tissues and its biological and functional behaviors but also about tumors with BAP1 mutations. Further studies validating the clinical impact of BAP1 mutation and future development of therapeutics are warranted. Oncologists, dermatologists, ophthalmologists, surgeons, pathologists, clinical geneticists, researchers, and possibly even more other specialists need to be aware of the multidisciplinary nature of this syndrome (see Figure 2A). Optimally, a patient with a BAP1 mutation is closely followed from the first clinical visit, passing to the morphological diagnosis and molecular testing, the genetic counseling, the risk assessment, and the prognosis estimation, until the curative treatment or treatments.

Anamnesis, genetic screening, and counseling. Awareness of detailed and correct anamnestic history, at least covering the spectrum of tumors that occur in the setting of germline BAP1 mutations, is crucial for pathologists and clinical geneticists. Considering the wide variability of clinical presentation in BAP1 germline-mutated patients, it is important

Table 5. BAP1 cancer syndrome.

CATEGORY	SUBCATEGORY	FEATURES	REFERENCES
Inheritance	–	Autosomal dominant	–
Head and Neck	Eyes	Uveal melanoma	19,23–25,30,53
Respiratory	Lung	Mesothelioma, malignant, after asbestos exposure	23,24
		Lung adenocarcinoma	23
Skin, Nails, Hair	Skin	Melanocytic skin	16,25
		tumors/papules, skin-colored to	
		reddish-brown, dome-shaped or	
		pedunculated, well	
		circumscribed with an average	
		size of 5 mm/ASTs/MBAITs[53]	23,25,29,30,34,53
		Cutaneous melanoma	
Urinary	Kidney	Renal Cells Cancer	29,17
Neoplasia	–	Mesothelioma	24
		Uveal melanoma	19,23–25,29,30,33,51,53
		Cutaneous melanoma	23,25,29,30,33,34,53
		Meningioma	23
		MBAITs	25
		Lung adenocarcinoma	23
		Renal Cells cancer	29,17
		Breast Cancer	23
		Meningioma	23
		Paraganglioma	33,53
		Colon Cancer	21,39,46
Miscellaneous	–	Tumor predisposition syndrome	17,23–25,29,30

Notes: This tumor predisposition syndrome[49] is inherited in an autosomal dominant pattern. Individuals carrying heterozygous BAP1 mutations are at high risk for the development of a variety of tumors,[23,25,26,35,40] including benign melanocytic tumors as well as several malignant tumors (including UM, CM, and MM on exposure to asbestos), and other cancer types, such as lung adenocarcinoma, meningioma, and colon cancer or RCC.

to collect familial and pathological history information for family members. It would be useful to know if they could be involved into other not cancer-related disease processes, and here we would like to stress the importance of collecting also a detailed non-oncological history to deepen the knowledge even on the plane of not cancer disease, from a medical point of view, and to define if BAP1 mutations could be also associated with specific metabolic disorders or other internal disease predispositions. Henceforward for this reason, to reach the goal more multidisciplinary clinical studies are needed. In practical terms, in the current state of knowledge, patients who are offered BAP1 testing on their tumors should first have genetic counseling so that the occurrence of an inherited predisposition syndrome is evaluated. If a germline mutation is later identified, the patient, as well as the rest of family members, can be offered further counseling, investigation, and follow-up monitoring. Further molecular genetic studies are also needed to help us divide the entity of MBAITs/ASTs associated with BAP1 mutations into subgroups based on genetics and ultimately behavior. These progresses could be then valuable in guiding clinical management: once established full pathological diagnostic criteria and matched them with phenotypic presentations, would be also possible identify clinical criteria, as set forth by the World Health Organization (WHO) for other heritable syndromes.

BAP1 testing. If family members or an individual patient is suspected to carry a BAP1 germline mutation on the basis of their familial pedigree and/or clinical phenotype, following detailed genetic counseling, absence/presence of a mutation can be confirmed by direct (Sanger) sequencing using blood or salivary-derived DNA. When no blood or salivary DNA is obtained, tumor tissues may also be directly sequenced. Preferably, this type of analysis should be made early, in parallel with the removal of the first suspected lesion. When we talk about molecular diagnostic testing, we should also pay attention to processing time, costs, and sensitivity/specificity of method(s) in question. A second, cheap and rapid, alternative way is screening tumors with BAP1 IHC, as

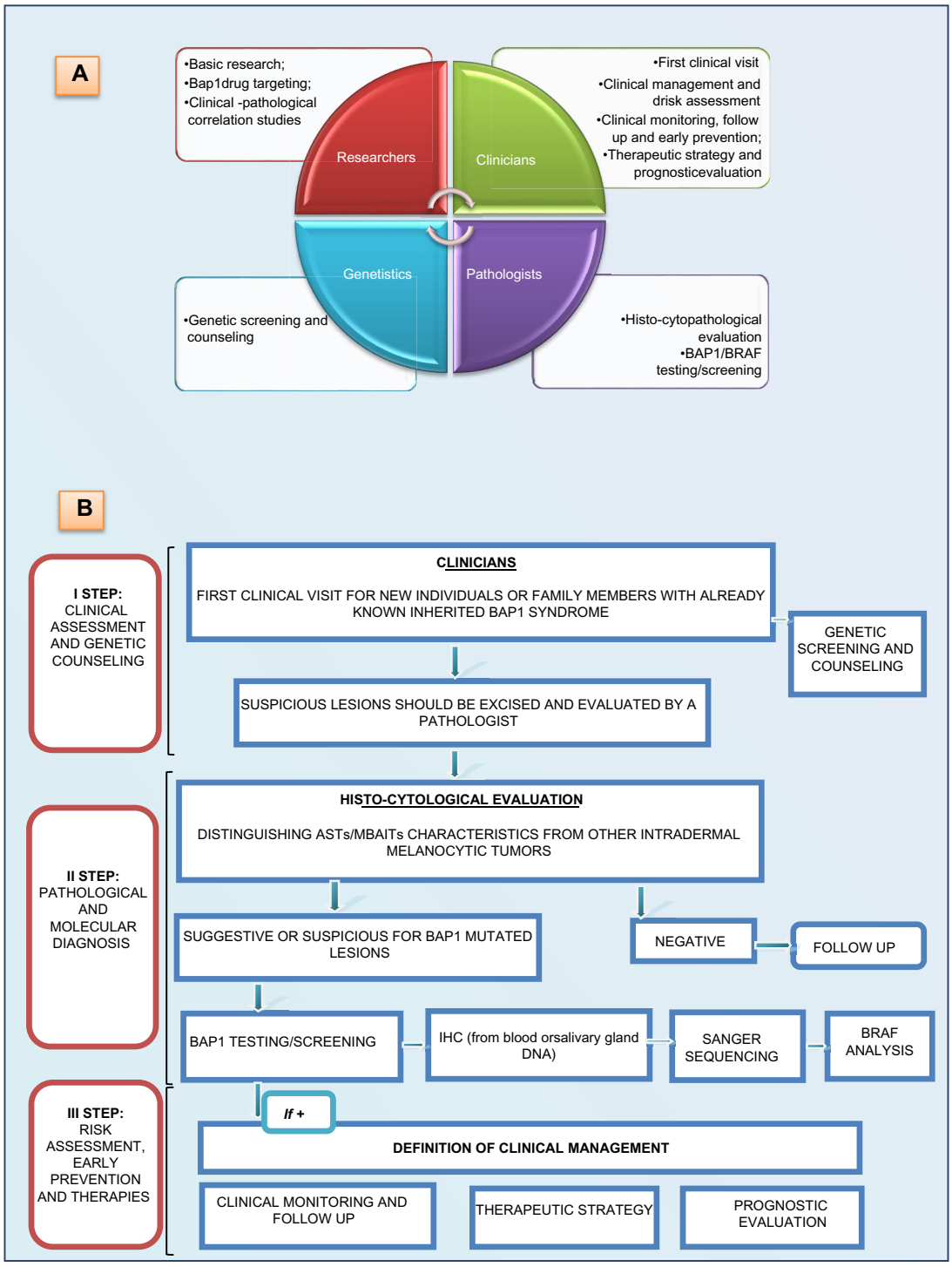

Figure 2. The three-step multidisciplinary (**A**) flowchart showing the major up-to-date clinical-related approaches for early detection of BAP1 tumor predisposition syndrome (**B**).

paraffin-embedded tumor tissue is already available. Tumors that exhibit loss of nuclear BAP1 expression, and those with equivocal IHC results may then undergo subsequent, but more expensive, confirmatory sequencing. False negative BAP1 expression could potentially be a problem in interpretation of BAP1 IHC. However, these problems may be alleviated by the use of concurrent positive controls and negative internal controls. Recently, it was interestingly found a strong correlation between the immunohistochemical and sequencing data, showing how immunohistochemical screening for BAP1 should become routine in the histopathological work-up of UM.[35,36]

Pathological diagnosis. As part of a multidisciplinary model, pathologists have an important role in the identification

of BAP1-associated tumors, most importantly in identification of BAP1 mutation/loss-related morphological markers. BAP1 loss has been described in several studies in association with epithelioid/rhabdoid cytomorphology, in rounded/polygonal cell shape with abundant amphophilic or eosinophilic cytoplasm, and in cutaneous epithelioid/spitzoid tumors, UMs, MMs, and RCCs.[20,24,25,37] These morphological features might help pathologists to identify tumors with a higher likelihood of harboring BAP1 mutation/loss and to initiate screening of the tumor with BAP1 IHC. Furthermore, based on the morphological appearance and the IHC result, pathologists should direct the choice of tumor for DNA extraction for confirmatory genetic testing.

Early prevention and clinical management. As emphasized previously, early diagnosis and clinical monitoring of new patients suspected to carry BAP1 mutations or family members with inherited mutations of BAP1 is central (see Figure 2B). Regarding secondary prevention, a lesion was excised on the base of dermatological or ophthalmological evaluation and confirmed to be mutation positive. Also family members should undergo genetic counseling, periodic follow-up, and clinical monitoring, to reduce the patient's risk of developing tumors or metastasis. The youngest individuals found to carry MBAITs were in their third and fourth decades of life, but all of them described having had lesions for several years.[16] Accordingly, Wiesner et al[25] reported that in the BAP1-mutant families they studied, MBAITs appeared during the first two decades of life, increasing in number with age. Therefore, MBAITs/ASTs may precede the development of MM, CM, and UM. Family members with hereditary BAP1 mutation should undergo early, pre-adolescent, testing as described by other authors.[16] If an individual is found to be a mutation carrier, he/she should be closely monitored with, as an example, bi-annual dermatological and annual ophthalmological examinations (indirect ophthalmoscopy, etc.) and pulmonary/renal evaluations by imaging techniques (CT scan, MRI, ultrasound). Associated evaluation of screening cost efficiency and comparison of the risks/benefits are yet to be fully established. However, shared and accepted clinical guidelines should be available. If this approach was revealed to have clinical relevance, it might enable the early detection of CM, UM, MM, and possibly other cancers. Indeed, both CMs and UMs can be treated and cured when found at an early stage but are fatal when they have metastasized, and early diagnosis also benefits patients with MM when they are diagnosed and treated at a very early stage. Following this concept, it could be possible to identify individuals with personal history of exposure to asbestos to evaluate a high and cumulative risk to develop MM. This could be an important part of the secondary prevention for family members affected by BAP1 germline mutations. Under a speculative molecular model profile, considering the UM management, it could reflect on the possibility of multi-gene screening, based on the detection of BAP1 mutations and other UM-associated susceptibility genes (ie GNAQ, c-KIT, etc.) for all new UM cases or just for members of families with BAP1-inherited mutations, following the MammaPrint® model already used in breast cancers for prognostic and therapeutic purposes.

Prognosis and targeted therapies. The role of BAP1 mutations as a prognostic biomarker is still emerging. Interestingly, sequencing efforts demonstrated worse outcomes in patients with BAP1-mutated colorectal cancer (CRC).[39] Multivariate analysis demonstrated that BAP1 expression was an independent prognostic factor for CRC ($P = 0.037$). These findings provide the first evidence that reduced BAP1 expression is associated with poor CRC patients prognosis and that BAP1 mutation could be used as a novel prognostic biomarker for CRC.[39] Using a previously validated immunohistochemical assay, the clinical-pathological significance and oncologic outcomes of BAP1 loss were recently investigated.[40] Immunohistochemistry for BAP1 was performed on tissue microarray sections from 559 non-metastatic RCC cases treated with nephrectomy: BAP1 was negative in 82 of 559 tumors (14.7%), and Cox regression indicated a significantly worse disease-free and overall survival for patients negative for BAP1 protein compared to patients with BAP1 positive tumors.[40] Supporting these results, targeted sequencing was performed in 185 RCCs and matched normal tissues. Pathologic features, baseline patient characteristics, and follow-up data were recorded. BAP1 mutations tended to occur in Fuhrman grades III–IV tumors ($P = 0.052$) and were associated with worse CSS ($P = 0.01$).[41] These recent findings confirmed how immunohistochemistry for BAP1 serves as a powerful tool to predict poor oncologic outcomes and adverse clinicopathological features in patients with non-metastatic RCC similar to UMs or CMs patients. BAP1 assessment using IHC based on a needle biopsy may also benefit preoperative risk stratification and guide treatment planning in the future. Even if results to date of prognostic testing do not significantly influence therapeutic strategies, patients asking for prognostic test may be offered testing of the primary tumor tissue (ie via transscleral or trans-retinal biopsy, or by enucleation).

On the Horizon

Regarding future perspectives, the association of overexpression of BAP1 with tumor progression and prognosis in many other cancer types suggests that inhibition of BAP1 activity (like proteins involved in chromatin modifications such as BMI and EZH2) aberrantly expressed in several tumors[42,43] may have a beneficial therapeutic effect. However, as previously reported, depletion of BAP1 in UM cells induced loss of melanocytic differentiation together with acquisition of a gene expression profile seen in advanced metastasizing tumors.[23] Speculatively, to explain the tumor aggressiveness, we suggest that different types of histone modifications that regulate chromatin structure and transcription may be associated with tumor phenotype. In light of the role of BAP1 in

histone modifications, even if these early findings are yet to be validated with in vivo experiments, HDAC inhibitors (HDACis) were recently tested in UM cell lines, and showed some growth-suppressive effects in vitro.[44] These early data suggest that components of pathways in which BAP1 plays a critical role (eg, chromatin modulation and transcriptional regulation) are potential targets for novel therapeutic agents.[45] Further studies are required to investigate the therapeutic potential of HDAC inhibition in tumors with BAP1 loss. Anyhow, the role of BAP1 as a primary drug target is so far to be evaluated. Currently, the therapeutic strategy is to provide the standard or the experimental protocols specific for each neoplasia of the BAP1 cancer syndrome. If studies will define a therapeutically accessible synthetic lethal target in the setting of BAP1 loss, this could eventually benefit patients whose tumors have BAP1 loss or mutation, and more speculatively, the same synthetic lethal target could be studied as chemoprevention drug targets in individuals with germline BAP1 mutations that predispose to tumor development. The biological insights into pathogenesis emerging from further work on BAP1 mutations could lead to novel, biologically rational treatment strategies.

Overall Conclusions

Germline BAP1 mutations are involved into a novel specific cancer syndrome and are strictly associated with high cancer susceptibility. The recently published data reviewed raise the hypothesis that BAP1 regulates a common subset of substrates, which in turn causes a pro-tumorigenic deregulation of gene expression, and alternatively suggest the role of BAP1 as tumorigenesis suppressor/promoter by direct and independent mechanisms. Distinguishing between these models will be significant for the future therapeutic implications. In clinical practice, early diagnosis is crucial for curative resection of CM and UM, like for MM and RCC. The uniform and shared definition of MBAITs/ASTs as clinical/pathological predictive markers could provide physicians markers to identify individuals who may carry germline BAP1 mutations and thus are at high risk of developing CM, UM, MM, RCC, and possibly other tumors. Next, genetic counseling should be offered and germline DNA should be tested for BAP1 mutations to identify individuals and families at higher risk for one or more of the neoplasms associated with the BAP1 cancer syndrome. Germline BAP1-mutation carriers can be targeted for early detection and therapy that is associated with either a cure or improved prognosis. As part of a novel multidisciplinary approach, physicians, pathologists, and all the clinicians involved into diagnostic assets should be aware of the spectrum of tumors and the histological features associated with BAP1 loss. Extensive clinical, epidemiological, and functional studies are required to fully explain the roles of BAP1 and its interaction partners in neoplasia, to define the consensus clinical/pathological criteria. Studies are also required to identify therapeutical targets in tumors with BAP1 loss. Agents directed at these targets may be useful for treatment of patients with BAP1-loss tumors, and potentially as part of chemo-preventive strategies in individuals with germline BAP1 mutations.

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Author Contributions

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DISCLOSURES AND ETHICS

This paper was subject to independent, expert peer review by a minimum of two blind peer reviewers. All editorial decisions were made by the independent academic editor. All authors have provided signed confirmation of their compliance with ethical and legal obligations including (but not limited to) use of any copyrighted material, compliance with ICMJE authorship and competing interests disclosure guidelines and, where applicable, compliance with legal and ethical guidelines on human and animal research participants.

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