REVIEW ARTICLE

Medical and Surgical Care of Patients With Mesothelioma and Their Relatives Carrying Germline BAP1 Mutations

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ABSTRACT

The most common malignancies that develop in carriers of *BAP1* germline mutations include diffuse malignant mesothelioma, uveal and cutaneous melanoma, renal cell carcinoma, and less frequently, breast cancer, several types of skin carcinomas, and other tumor types. Mesotheliomas 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. Some *BAP1* carriers have asymptomatic mesothelioma that can be followed by close clinical observation without apparent adverse outcomes: they may survive many years without therapy. Others may grow aggressively but very often respond to therapy.

Detecting *BAP1* germline mutations has, therefore, substantial medical, social, and economic impact. Close monitoring of these patients and their relatives is expected to result in prolonged life expectancy, improved quality of life, and being cost-effective. The co-authors of this paper are those who have published the vast majority of cases of mesothelioma occurring in patients carrying inactivating germline *BAP1* mutations and who have studied the families affected by the BAP1 cancer syndrome for many years. This paper reports our experience. It is intended to be a source of information for all physicians who care for patients carrying germline *BAP1* mutations. We discuss the clinical presentation, diagnostic and treatment challenges, and our recommendations of how to best care for these patients and their family members, including the potential economic and psychosocial impact.

Keywords: Mesothelioma; BAP1; Cancer genetics; Germline mutations; Tumor predisposition syndromes; Asbestos

Introduction: The BAP1 Cancer Syndrome and Mesothelioma

`The discovery that heterozygous germline *BAP1* pathogenic mutations—that is, "null variants"—confer an increased risk for a variety of cancers has created new opportunities for early detection and therapy of diffuse malignant pleural pericardial and peritoneal mesothelioma, referred to in this manuscript as "mesothelioma."[1–3] In the clinically ascertained families, carriers of a heterozygous nonfunctional BAP1 allele, the lifetime penetrance has approached 100%; approximately one-third of carriers develop two to seven cancers during their lifetime and mesotheliomas are frequent (Fig. 1).[4–12] Pathogenic germline *BAP1* mutations are autosomal dominant: because family members have a 50% chance to inherit the same mutation, they should be tested, as they will benefit from screening and early detection. Pathogenic germline mutations, mostly *BAP1* mutations, were found in approximately 9.7% to 12% of all patients with mesothelioma; they are much more prevalent among young patients and in those with a family history of mesothelioma.[13–17] Specifically, pathogenic germline mutations are found in more than 50% of mesotheliomas developing in patients 50 years old or younger and in almost all patients with mesothelioma with a family history of mesothelioma and/or uveal melanoma (UVM) or clear cell renal cell carcinoma (ccRCC).[18] In *BAP1* mutation carriers, pleural and peritoneal mesotheliomas may develop synchronously or several years apart, likely representing different primaries developing in a background of diffuse atypical mesothelial hyperplasia and mesothelioma in situ, lesions typically found in the pleura and peritoneum of carriers of pathogenic mutations.[2,3]Affected individuals

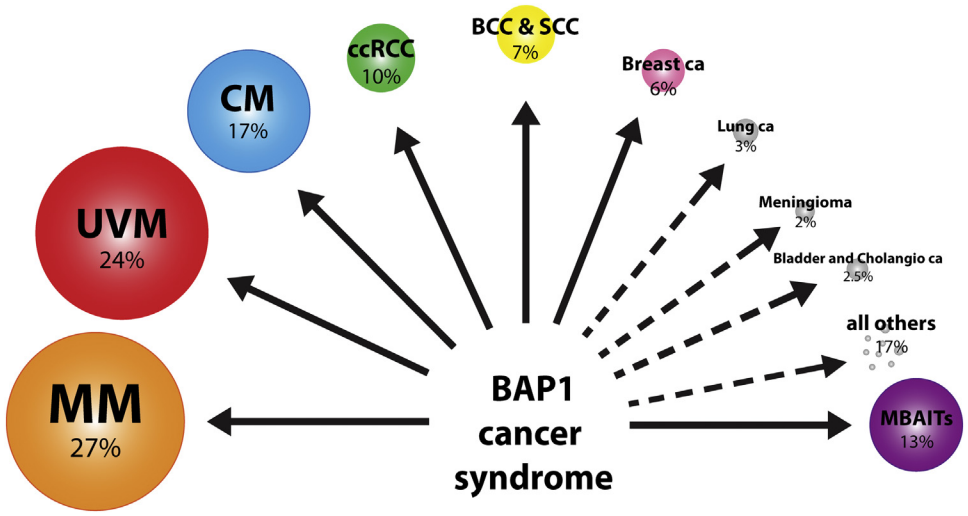

Figure 1. Incidence of different cancer types in carriers of germline *BAP1* mutations. Compiled from 97 papers from PubMed from 2011 to January of 2022, including a total of 689 individuals (309 females, 268 males, and 112 unknown), in which 553 developed cancer: 27% had 2 to 7 tumor types. Percentage of tumors indicated in the figure represents the percentage of carriers of germline *BAP1* mutations who develop that specific tumor type. Age range: 12 years old with meningioma, 84 years old with mesothelioma. Median age of mesothelioma diagnosis was 55 years old. MM, malignant mesothelioma; UVM, uveal melanoma; CM, cutaneous melanoma; ccRCC, clear cell renal cell carcinoma: BCC, basal cell carcinoma; SCC, squamous cell carcinoma; ca, cancer; MBAITs, melanocytic BAP1-mutated atypical intradermal tumors.

develop cancer approximately 20 years earlier than observed when the same malignancies develop sporadically,[18–20] and they also develop benign melanocytic intradermal tumors.[7,8,21–23]

Men and women exposed to asbestos have the same risk of developing mesothelioma.[24] Because men are more likely to work in trades in which asbestos exposure occurs, sporadic (not genetically related) pleural mesothelioma occurs with a male/female ratio of approximately 5:1 and 2:1 in peritoneal mesotheliomas that are less frequently associated with asbestos exposure.[3] Accordingly, the overall ratio of pleural to peritoneal mesothelioma is 5:1.[3] In contrast, in *BAP1* mutation carriers, pleural and peritoneal mesotheliomas occur with a male/female ratio of 1:1 and with a pleural:peritoneal ratio of 1:1, as they often occur in patients with no or minimal asbestos exposure.[2,3,13–15,25]

Cancer screening in *BAP1* mutation carriers should start early in life. The earliest cancers were found in two 8-year-old children who developed cutaneous melanoma (N.K.H., unpublished observations). In the United States, the youngest *BAP1* mutation carrier who developed mesothelioma was aged 28 years (peritoneal malignant mesothelioma) and the oldest at 84 years (M.C. et al. unpublished observations). In a cohort of 72 Dutch germline *BAP1* mutation carriers, six developed pleural and two peritoneal mesothelioma. Among their genetically untested relatives, five developed pleural and four peritoneal mesothelioma, with age range of 39 to 71 years.[26]

Some malignancies in germline *BAP1* mutation carriers, mesotheliomas in particular, are much less aggressive.[2,19] Median survival for mesothelioma in these patients is approximately 5 to 7 years from diagnosis with 26% of patients surviving 10 or more years—some are alive and well 20 years after diagnosis and therapy (Ref. 18 and M.C. unpublished observations); hopefully, some of them will not die of it. This is significantly different than the 6 to 24 months median survival for sporadic—that is, not genetically related—mesothelioma, depending on histology.[3] Two studies reported a 5 to 7 years of median survival in both pleural and peritoneal mesotheliomas[18,19]; one study found an improved median survival of 7.9 years for pleural but not for peritoneal mesothelioma.[14] Resolving these discrepancies will require evaluation of more patients. At present, we do not know why mesotheliomas in carriers of germline *BAP1* mutations are less aggressive.

Gene mutations are not equivalent. Pathogenic mutations in tumor suppressor genes, such *BAP1* and *TP53*, that simultaneously impair (1) DNA repair and transcription, (2) mechanisms regulating cell death, and (3) cellular metabolism, are much more potent cancer inducers than tumor suppressors that alter only one of these activities.[4] Heterozygous *BAP1* and *p53* mutations cause cancer, and often multiple cancers,[4,8–10,27,28] in approximately 100% of affected carriers, evidence of haploinsufficiency; thus, the term "cancer syndrome" reflects the medical conditions they cause.[4] For pathogenic mutations that increase the risk of cancer only in a fraction of mutation carriers, "tumor predisposition syndrome" seems more appropriate.[4]

The interplay between *BAP1* mutations and carcinogens remains incompletely defined. In vitro and in vivo studies indicate that germline mutations of *BAP1* and of some DNA repair and tumor suppressor genes increase sensitivity to asbestos, ionizing radiation, and ultraviolet light.[4,29–32] This evidence, however, comes from experiments in tissue culture and in mice where the exposure doses are limited in time and significantly higher than in humans. Currently, there is no evidence that ionizing radiation from typical exposures, such as airplane travel or medical imaging, increases cancer risk in humans with BAP1 germline mutations.

Clinicians are often unaware of patients carrying germline *BAP1* mutations, and most do not know the clues to suspect or investigate carriers. Moreover, many clinicians are unaware of the unique clinical characteristics of malignancies arising in *BAP1* mutation carriers, and the needs of these patients and their family members. Thus, many patients and their affected family members may not receive ideal therapies and the necessary follow-up. This may negatively affect their quality of life and survival. In this manuscript, we provide information based on our collective experience and the published literatures, pertaining to surveillance of healthy individuals and patients with cancer carrying germline *BAP1* pathogenic mutations, and regarding the management of mesotheliomas arising in these individuals.[3,6,33,34]

This paper focuses on *BAP1*; however, the concepts discussed may apply more widely to individuals carrying other pathogenic germline mutations that cause other tumor predisposition syndrome/cancer syndromes, as in these individuals mesothelioma may occasionally develop and may also be associated with prolonged survival.[4,13,14,18,32]

Clinical Examples of Patients Carrying *BAP1* Germline Mutations and Challenges in Their Clinical Management

To explain the challenges clinicians face when dealing with mesothelioma in carriers of germline *BAP1* mutations and in advising family members who inherited these same mutations, we will review three representative examples. The selection of these patients was based on the collective experience of the co-authors who

together have diagnosed/treated most of the published cases of mesotheliomas developing in carriers of germline *BAP1* mutations. In our experience, these three cases represent well the diagnostic and therapeutic challenges in this particular group of patients, who are usually young, do not have evidence of asbestos exposure, seem to respond to therapy, and often have an excellent survival. These three patients are from the same family, carry the same *BAP1* mutation, and have no history, radiologic or histologic evidence of asbestos exposure (Fig. 2). Written informed consent was received from all patients. Collection and use of patient information and samples were in accordance with the Declaration of Helsinki (1995) and the World Medical Association (2013 revision), approved by the University of Hawaii (institutional review board number CHS14406). After a brief synopsis of the patients' situation, related issues in the context of hereditary BAP1 cancer syndrome are discussed.

Patient 1 (I-01, Sister of Proband)

A 43-year-old woman known to carry a *BAP1* germline mutation presented in March 2016 with recurrent abdominal pain. Laparoscopy result revealed multiple peritoneal nodules diagnosed as malignant mesothelioma, epithelioid type with tubulopapillary and trabecular architecture. The malignant cells seemed bland and well-differentiated, and they infiltrated the surrounding tissues. This patient was treated with cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, and adjuvant cisplatin/pemetrexed therapy.[35] This therapy is associated with major complications in approximately 40% of patients and a median of 12 days of hospitalization. The 60 days' mortality can be as high as 6%. As of January 2022, almost 6 years post-diagnosis and therapy, she remains tumor free with an excellent quality of life. This patient is clearly doing exceptionally well. Now, let us consider her sister (Figs. 2 and 3).

Patient 2 (I-03, Sister of Proband)

A 46-year-old female with history of stage IIB breast cancer, ER/PR positive and HER2 negative. In 2015, she underwent elective laparoscopic oophorectomy for ovarian ablation in light of her ER-expressing breast cancer, which revealed multiple peritoneal nodules. Biopsy and pathologic examination of these nodules revealed malignant mesothelioma, epithelioid type with tubulopapillary architecture: the same histology as found in her sister. This patient, however, elected not to receive any further treatment. Her mesothelioma did not progress: as of January 2022, 6 years postdiagnosis, she is asymptomatic and lives a normal life, and she remains on adjuvant aromatase inhibitor for her breast cancer (Figs. 2 and 3).

This sister initially manifested a less frequent malignancy for this inherited cancer syndrome, breast cancer (Fig. 1). Only through an incidental finding on therapeutic laparoscopy was she diagnosed with

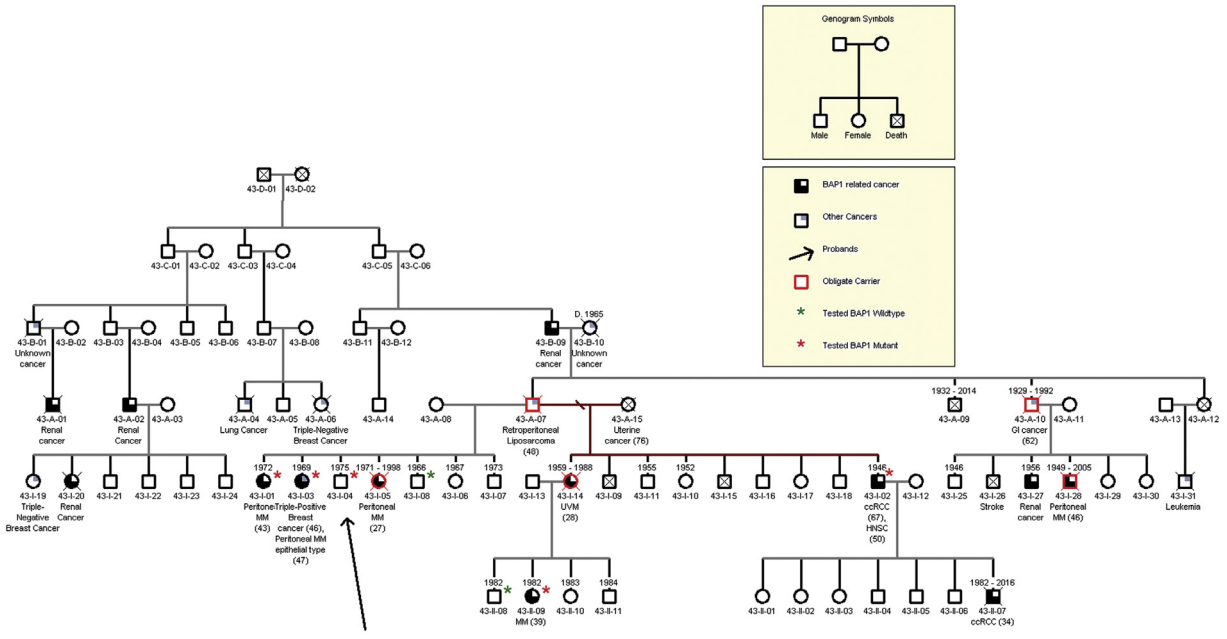

Figure 2. Pedigree of the P-family. Date of birth and date of death are indicated when known. The diagnoses are based on review of medical records and information from treating physicians; the diagnoses of mesothelioma were further verified by the review of the histology and of the immunostains. Information about some of the patients in this pedigree can be found in Kittaneh and Berkelhammer.[35] MM, malignant mesothelioma, ccRCC, clear cell renal cell carcinoma, UVM, uveal melanoma.

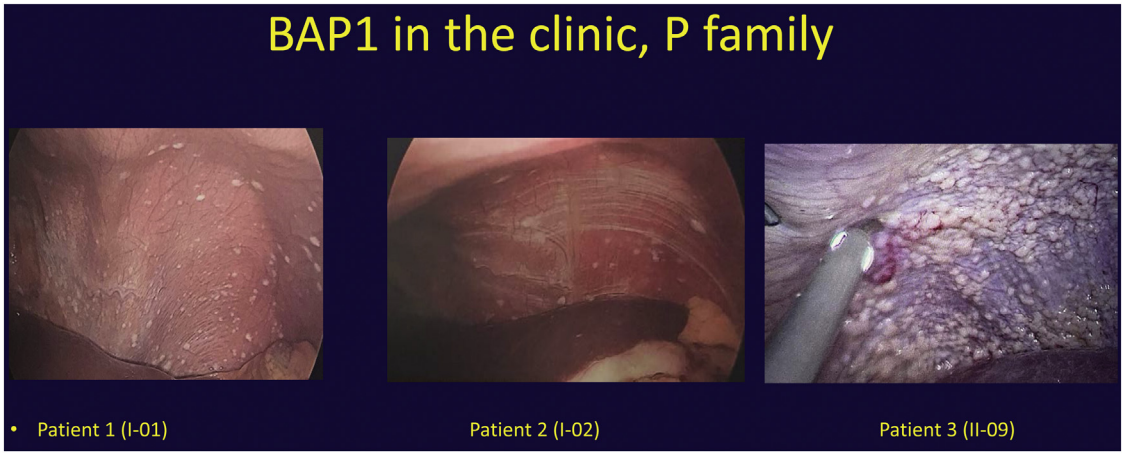

Figure 3. Early mesothelioma nodules in carriers of germline *BAP1* mutations from the P-family. These nodules were identified during laparoscopy (patients 1 and 2) and VATS (patient 3, see histology in Supplementary Figure 1). These nodules are common in carriers of germline *BAP1* mutations, and they often have an indolent biological behavior for several years. VATS, video-assisted thoracoscopy.

mesothelioma, with a low peritoneal carcinomatosis index. In her case, despite no therapy, her outcome from her mesothelioma at 6 years is identical to that of her sister who underwent extensive and potentially toxic therapies. The obvious issue here is the inability to advise patients with *BAP1* germline mutations as to the natural history of their mesothelioma so that they can make informed decisions regarding watchful waiting versus aggressive therapy. Nevertheless, in these same patients, other malignancies that are frequent in carriers of *BAP1* germline mutations, such as UVM, cutaneous melanoma, and ccRCC, can instead be aggressive, and they require early detection and prompt ablation/removal, measures that can be life-saving. The situation with the third relative in the family is a little different.

Patient 3 (II-09 Half-Niece of Proband)

A 39-year-old woman with an 8-year history of recurrent "benign reactive," right pleural effusion. In December 2020, she underwent video-assisted thoracoscopy (VATS) revealing multiple pleural nodules that were diagnosed as diffuse malignant mesothelioma, epithelioid type, with trabecular architecture. After debating whether and how to treat her, it was decided to treat her with 6 cycles of cisplatin/pemetrexed. Her follow-up imaging result revealed a partial response with resolution of her pleural effusion (Figs. 2 and 3 and Supplementary Fig. 1).

This is a young woman, with minimal disease, with the options of watchful waiting, pleurectomy decortication (risk of death 1%–2%, morbidity 20%, hospitalization 7 d), or first-line chemotherapy for which, for patients with sporadic mesothelioma, median overall survival is 12 to 15 months and there is 1% risk of death and 5% chance of complications. She presented with surgically resectable disease, and probably she had mesothelioma for 8 years, when she started developing pleural effusions. She waited 8 years to have a thoracoscopy and biopsy. Would it have made any difference if treatment had been administered 8 years prior?

These examples reveal the complexity of this cancer syndrome, especially for patients diagnosed with having mesothelioma. Although most patients with mesothelioma carrying germline mutations have significantly prolonged survival compared with sporadic—that is, non-genetically related—mesotheliomas, there are no biomarkers to identify which patients will have a long-term survival and which may benefit from immediate therapy with attendant potential morbidity. Indeed, there are no models that accurately predict who is going to respond to therapy either in germline—although most of them do—or sporadic mesotheliomas. If a mesothelioma patient with a germline mutation decides to have surveillance only, there is no consensus on how to follow these patients, either by frequency or mode (computed tomography [CT], magnetic resonance imaging [MRI]) of follow-up. Moreover, present data do not indicate that specific *BAP1* mutations influence the type(s) of cancer that will develop or the aggressiveness of the malignancies. To address these issues, the U.S. National Cancer Institute (NCI) has opened two clinical trials to prospectively study frequency of mesotheliomas and other cancers in individuals with germline *BAP1* mutations (see subsequent discussion).

Germline *BAP1* Mutations

To date, with one exception,[36] all pathogenic *BAP1* mutations resulted in loss of BAP1 nuclear localization,

where BAP1 regulates DNA repair, chromatin assembling, and transcription.[2] The nuclear localization signal is located at the carboxyterminus of the BAP1 protein; therefore, all truncating mutations are pathogenic because the nuclear localization signal is lost[1,18,20] and the truncated BAP1 protein remains in the cytoplasm where it is degraded to amyloid.[37] Accordingly, most families affected by the BAP1 cancer syndrome carry truncating mutations (Fig. 4). Determining the pathogenicity of nonsynonymous *BAP1* variants is more challenging; however, their location is helpful. In fact, to translocate from the cytoplasm to the nucleus, BAP1 has to deubiquitylate itself.[38] Therefore, nonsynonymous mutations in the UCH domain (the deubiquitylating BAP1 domain) may also be pathogenic when they cause loss of the deubiquitylating activity (this can be tested in vitro[29]). Mutations in other portions of the protein are less frequently pathogenic (Fig. 4). Because the BAP1 cancer syndrome is a novel medical entity, CLINVAR, and other tools available on the internet to predict the impact of a given mutation, are often not helpful to assess whether a variant is or is not pathogenic, as historical information to make such predictions is rarely available.

Given the overall rarity of the most frequent tumor types found in the BAP1 cancer syndrome in the general population (e.g., mesothelioma, UVM, ccRCC, and melanocytic BAP1-mutated atypical intradermal tumors, Fig. 1), personal and family histories are very powerful, allowing a clinical diagnosis of BAP1 cancer syndrome that can be verified by genetic testing. Furthermore, if the novel *BAP1* variant segregates in a patient and/or family members with tumors highly specific to the BAP1 cancer syndrome, this provides strong evidence for pathogenicity of the variant. For example, because there are approximately 3200 mesotheliomas/yr in the U.S. population, in a U.S. family with two male and two female siblings, the probability of one male and one female developing mesothelioma by chance is 2.8E−10 (0.00000000028% or 0.000000028%). Efforts to collate all *BAP1* variants from cases around the world will make these interpretations easier over time. We recommend that, whenever possible, the decision of whether a given *BAP1* mutation is pathogenic should be integrated and supported by a family history of multiple cancers, in particular those most frequently associated with the BAP1 cancer syndrome.

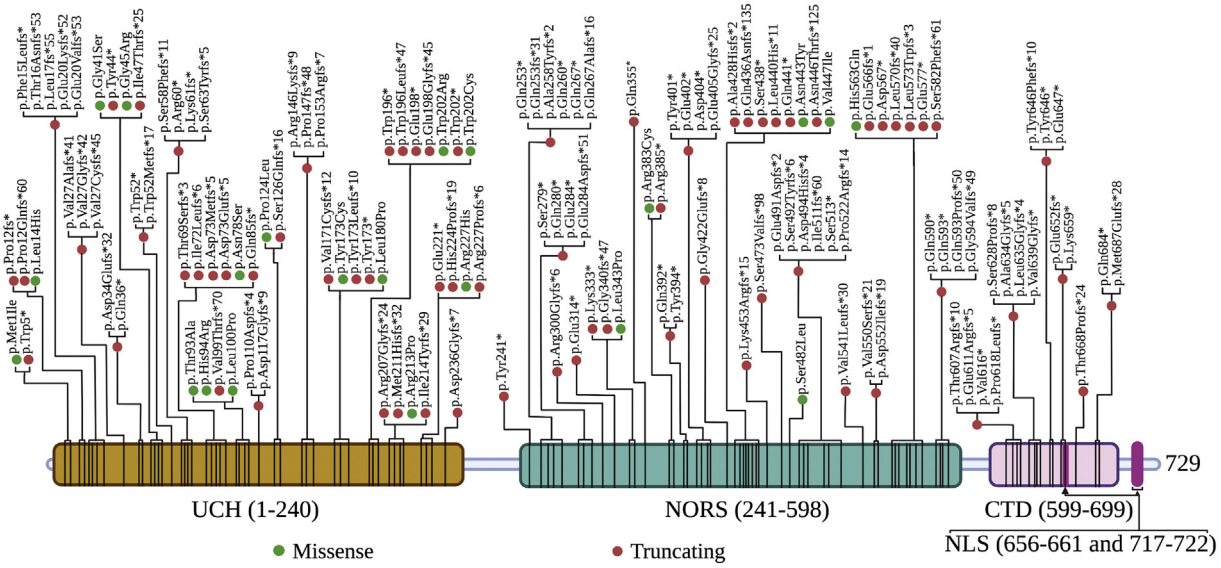

Figure 4. Schematic representation of the BAP1 protein with pathogenic and likely pathogenic variants reported as of February 2022. The previously reported, and some unreported (M.C. et al, unpublished), *BAP1* variants were classified according to the ACMG model. The deubiquitylating enzyme, BAP1, contains a catalytically active ubiquitin carboxyterminal hydrolase domain (UCH 1-240), an unstructured nonorganized region (NORS 241-598), a C-terminal domain (CTD 599-699), and a nuclear localization signal (NLS 656-661 and 717-722). The locations of pathogenic and likely pathogenic variants are found on the BAP1 protein in their associated domains. Missense mutations are marked with a green dot, and truncating variants are marked with a red dot. Graphical representation does not include large germline deletions found in four families, including two families affected by multiple malignancies carrying a whole heterozygous *BAP1* gene deletion (Walpole et al.[6] and MC et al., unpublished observations), variants lacking protein structure prediction, VUS (as classified using the ACMG model), benign variants, and others that did not meet the cutoff criteria for ACMG scoring owing to high population frequency or lack of critical information. For additional information of the variants, see Supplementary Table 1. Fs, frame shift; *, stop codon; splice, aberrant splicing. ACMG, American College of Medical Genetics and Genomics. VUS, variants of unknown significance. Created with Biorender.com.

We use the American College of Medical Genetics and Genomics (ACMG) guidelines to identify *BAP1* mutations as pathogenic, likely pathogenic, variants of unknown significance (VUS), or benign and likely benign.[39] Figure 4 illustrates the locations of all pathogenic *BAP1* mutations that we identified up to January 2022 according to the ACMG guidelines in a total of 234 families and 510 subjects from the United States, Europe, Australia, and Asia based on the previous publications and our study cohorts. The complementary Supplementary Table 1 reports these pathogenic variants and the VUS that were identified based on the ACMG guidelines. Supplementary Table 1 also reports the cancer types associated with these mutations, their Combined Annotation Dependent Depletion (CADD) score and additional details. We anticipate that most VUS with a CADD score more than 18 found in Supplementary Table 1 will be identified as pathogenic in the coming years as more data accumulate. Of note, to date, all *BAP1* germline mutations with a CADD score of 18 or higher have been found to be pathogenic.

Genetic Testing

Genetic testing for mesothelioma has been increasingly offered in university hospitals in the United States and is also offered by several private companies. Clinical genetic testing panels for hereditary cancer frequently include approximately 40 to 300 genes, including *BAP1*, and allow simultaneous detection of multiple germline mutations that have been associated with an increased risk of cancer, including mesothelioma.[13,14,18] When pathogenic germline mutations are detected, family members should also be tested, as they may benefit from screening and early detection (see subsequent discussion). It is generally agreed that to decrease ascertainment bias, all first-degree relatives should be genotyped. Turnaround time of these tests may vary from one to several weeks depending on the hospital setting or commercial test used. For example, all patients with mesothelioma presenting at The University of Chicago Mesothelioma Clinic since April 2016 have been approached for consent to research-based germline genetic testing.[13] Through January 2021, 439 of 462 (93%) patients consented. Of these, 431 (98%) wished to hear actionable cancer risk findings if any were identified and 46 of 439 (10%) had an actionable finding. This positive genetic testing proportion is similar to the proportions found in other patients with multiple other cancer types, such as breast (6%), pancreas (4%–7%), prostate (5%–12%), and ovarian (18%) carcinomas in which guidelines recommend history based or, increasingly, universal germline genetic testing.[13,16,40–43] Recontact and disclosure were successful for 28 of 46 (61%) with actionable findings, including 25 patients and three designated family members for patients deceased before disclosure. Nevertheless, of these, only seven (25%) wished to confirm their results clinically and allow the finding to be part of their medical records. Major themes emerging from disclosure included lack of exploration of family history of cancer ("I thought this cancer was caused by asbestos") and major concerns regarding potential implications on current or future asbestos litigation, limiting acceptance of clinical testing.[13]

Somatic *BAP1* Mutations

Carriers of heterozygous germline *BAP1* mutations prevalently develop mesothelioma, UVM, cutaneous melanoma, and ccRCC, and their tumor cells carry biallelic *BAP1* mutations[2,3] (Fig. 1). Underscoring the pathogenic role of BAP1 loss in these malignancies, somatic *BAP1* mutations are much more common in these same tumor types than in other malignancies.[2,3] More than 60% of sporadic mesotheliomas and 100% of those developing in carriers of germline *BAP1* mutations have biallelic inactivation of *BAP1* in their tumor cells.[1,2,44] Nevertheless, the significant improved survival of patients with mesothelioma in carriers of germline *BAP1* mutations is not observed in patients with mesothelioma carrying somatic biallelic *BAP1* mutations: this suggests that heterozygous germline BAP1 mutations influence the microenvironment, including possibly the immune response, rendering the host more resistant to mesothelioma growth, a hypothesis that is being investigated with support of NCI R01 funding.

Next-generation sequencing approaches to find nucleotide-level mutations, integrated with multiplex ligation-dependent probe amplification or high-density CGH arrays to reveal minute and large chromosomal *BAP1* deletions, identify most *BAP1* mutations, including germline heterozygous *BAP1* mutations.[44,45] BAP1 immunohistochemistry (IHC) nuclear loss is very sensitive to detect *BAP1* biallelic inactivation because approximately 100% of pathogenic *BAP1* mutations are either truncating mutations causing deletion of the nuclear translocation signal located at the carboxyterminus of the BAP1 protein or these mutations impair BAP1 deubiquitylating activity which is required for BAP1 protein nuclear translocation[38] (Fig. 4). Of note, cells with heterozygous *BAP1* mutations contain one normal allele that produces nuclear staining. Therefore, IHC cannot be used to identify germline *BAP1* mutations. BAP1 IHC is instead very helpful in the differential diagnosis of mesothelioma. Benign mesothelial cells, including benign atypical mesothelial hyperplasia, reactive mesothelial cells in chronic pleuritis and in various

types of benign peritoneal inflammatory processes that cause adhesions and cystic formations which at times can be difficult to distinguish from malignant mesothelioma, always retain BAP1 nuclear staining (Fig. 5). Instead, loss of BAP1 nuclear staining is evidence of malignancy.[44,46,47] Moreover, loss of BAP1 nuclear staining is helpful as a supportive evidence to diagnose mesothelioma from other malignancies.[44,46–48] Representative examples to help pathologists interpret BAP1 IHC are revealed (Fig. 5).

Screening and Surveillance of *BAP1* Mutation Carriers and Cost/Benefit Considerations

Primary surveillance for carriers of pathogenic germline *BAP1* mutations is critical as it can be lifesaving. The main issues are when to start testing; how to do the testing in the least invasive fashion to avoid excess radiation or invasive biopsies; and how to harmonize different screening protocols for different cancers, including UVM and cutaneous melanoma, mesothelioma (pleural, pericardial, or peritoneal), and other cavitary malignancies, in particular the quite frequent ccRCC (Fig. 1). In 2016, a consensus report in *JTO* proposed screening for *BAP1* germline mutations in families with high-risk features, such as three or more cases of any of the following cancers within two generations: malignant mesothelioma, UVM, ccRCC, and cholangiocarcinoma. Moreover, recommendations for *BAP1* germline mutations carriers and their affected relatives included the following: (1) annual dermatologic screening for early detection of melanoma at age 18 years or older; (2) annual eye examination/ophthalmoscopy for UVM at age 18 years or older; and (3) skin and eye examinations every 6 months after age of 30 years when the frequency of cancer among carriers of germline *BAP1* mutations starts to increase, with supportive genetic counseling.[33] In 2016, Pilarski et al.,[34] reviewed this issue and suggested that screening for UVM should start when carriers are 11 years old and screening for mesothelioma and ccRCC at age 30 years. There are other publications discussing recommendations for surveillance,[6,18,26,34,49–51] and these were reviewed.[6] The Dutch Oncogenetics Society recommends yearly surveillance for skin and UVM starting at age 16 years and yearly MRI imaging to detect mesothelioma and ccRCC starting at age 30 years in a research setting.[26] In 2021, the Australia NSW Cancer Institute government eviQ website created a BAP1 cancer risk management page with a proposed surveillance plan.[51] Presently, based on our collective experience, we recommend adopting the guidelines regarding age at which to start screening and the frequency of screening as per the ongoing NCI clinical study (NCT03830229) described in detail in Table 1. These protocol-specific screenings were based on the available scientific literature regarding the age of onset of the different tumor types in individuals with pathogenic germline mutations in BAP1. The radiologic imaging using MRI starts at age 30 years except for MRI of the brain that starts at age 18 years given recent reports of meningiomas in children and young adults and the fact that meningiomas in these patients are more aggressive.[52,53] A related trial (NCT04431024) that is focused primarily on mesothelioma detection uses CT screening beginning at age 30 years (see subsequent discussion).

Screening and follow-up for early cancer detection should be cost-effective and improve survival. In 2021, Walpole et al.[54] created a Markov microsimulation health state transition model of *BAP1* germline carriers to predict whether active surveillance for the four most common malignancies (mesothelioma, UVM, cutaneous melanoma, and ccRCC) influences survival and reduced costs. They found that surveillance of *BAP1* carriers was associated with an increased survival of 4.9 years at an additional cost of US $6197 for the health care system, including surveillance costs (US $1265 per life-year gained). The nonsurveillance arm had more cancers diagnosed at a late stage (62.8% versus 10.7%) and a higher rate of *BAP1*-related deaths (50.2% versus 35.4%; 29.5% increase). The model was cost-effective under all sensitivity analyses. A robustness analysis estimated that 99.86% of 100-sample iterations were cost-effective, and 19.67% were cost-saving. These findings support the inclusion of a surveillance regimen for *BAP1* germline mutation carriers in the health care system, as this model suggests that it will improve survival and be cost-effective.

Screening for Mesothelioma

No clear consensus for mesothelioma surveillance exists, a limitation that the ongoing clinical trials at the NCI for patients with mesothelioma and their relatives carrying germline *BAP1* mutations hopes to address; see subsequent discussion. Imaging by CT[33,35,34,55–58] and ultrasound[59] has not been proven useful. Among noninvasive blood-based biomarkers, mesothelin (also known as soluble mesothelin-related peptides) has been extensively studied. Although there is statistically significant evidence that soluble mesothelin-related peptides can be elevated in the year before diagnosis,[60] its sensitivity is too low for early detection.[61,62] Other biomarkers include high-mobility group box 1, fibulin-3, calretinin, and osteopontin. Studies revealed significantly higher total and acetylated high-mobility group box 1 blood levels in patients with mesothelioma and in asbestos-exposed patients, compared with healthy controls, but this test relies

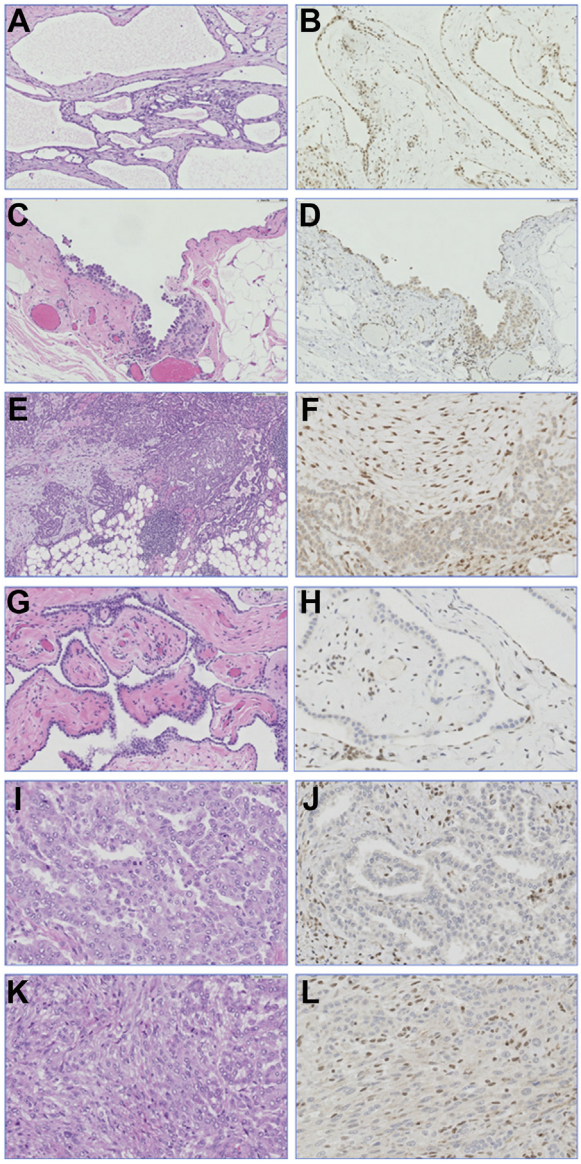

Figure 5. BAP1 immunostaining. (*A*, *B*) Benign mesothelial hyperplasia. (*A*) Cystic mesothelial inclusion in a patient who had previous surgery for ectopic pregnancy and developed peritoneal adhesions (H/E stain). (*B*) The single layer of mesothelial cells revealing nuclear BAP1 staining, an evidence that this is a benign lesion. (*C*–*F*) Peritoneal epithelioid mesothelioma. (*C*) Single layer of benign mesothelial cells forming a nodular area known as "in situ" mesothelioma (H/E stain). (*D*) BAP1 nuclear expression is retained in normal and lost in malignant cells (nodule) supporting a diagnosis of mesothelioma in situ (preinvasive malignant lesion). This patient had another focus of frankly invasive mesothelioma whose cells had lost BAP1 nuclear expression. (*E*, *F*) Malignant peritoneal epithelioid mesothelioma (*E*, H/E staining) with BAP1 loss and adjacent fibrosis with benign spindle-reactive mesothelial cells and fibroblasts in which nuclear BAP1 staining is retained (*F*). (*G*, *H*) Pleural biopsy. Same patient as E and F who developed a year later mesothelioma in the pleura. (*G*) H/E stain reveals a microcystic papillary pleural mesothelioma that seems to be a very early lesion (new primary seems more likely than spread from previous peritoneal mesothelioma). (*H*) BAP1 immunostaining reveals normal mesothelium with retained BAP1 next to malignant mesothelium with BAP1 loss. (*I*–*L*) Malignant biphasic pleural mesothelioma, epithelioid component (*I*, *J*), sarcomatoid component (*K*, *L*). There is BAP1 nuclear loss in both epithelioid and sarcomatoid components, evidence that both round and spindle cells are malignant. Note that BAP1 is retained in the nuclei of background reactive benign mesothelial spindle cells; the latter can be distinguished by the malignant cells because of their smaller size and bland nuclear features. H/E, hematoxylin and eosin.

on Western blotting, which is not suitable for screening, whereas validation of mass spectrometry and enzyme-linked immunosorbent assay has proved difficult.[63] Fibulin-3, encoded by the SPP1 gene, is an extracellular glycoprotein expressed in most tissues in the early embryonic stage, and it is selectively elevated in patients with mesothelioma. Ongoing studies elucidated possible reasons for inconsistent readings depending on the tube that the blood is harvested owing to FBLN3 proteolysis.[60] Despite excellent discrimination between patients exposed to asbestos and patients with mesothelioma, osteopontin specificity limits its usefulness for mesothelioma screening.[64] Calretinin is expressed in mesothelial cells and mesothelioma.[65] Blood calretinin levels were able to prediagnose mesothelioma in an asbestos-exposed population with an area under the curve of 0.77 one to 15 months prior definitive diagnosis.[66] Novel methods being explored for screening include breath analyses,[67,68] circulating tumor DNA, and microRNAs.[60]

Clinical Trials for Patients With Mesothelioma and Their Relatives Carrying *BAP1* Germline Mutations

In the United States, the NCI has two open clinical trials specifically tailored for these patients and their relatives. These trials offer eligible individuals free cancer prevention and cancer therapy in one of the most advanced medical centers in the United States. Moreover, because, as briefly summarized previously, there are no proven effective screening tests for mesothelioma, one of the main objectives of these trials is the identification of a reliable screening methodology.

The first trial—Long Term Follow-up of Mesothelioma Patients With Germline Mutations in *BAP1* and Other Genes[69] (ClinicalTrials.gov NCT03830229)—is seeking to noninvasively detect malignancies arising in these individuals using periodic MRI scans and breast, skin, and ocular examination. The primary objective is to study the natural history of patients and their family members with germline mutations involving *BAP1* and other DNA repair genes. The secondary objective is to define the risk of developing mesothelioma and other cancers in this cohort. For eligible patients, see Table 1.

Table 1. NCI Screening Protocol for Individuals With Pathogenic Germline Mutations in the *BAP1* Gene (NCT03830229)

Eligible Participants (Age ≥ 2 yr)	Evaluation of Germline Mutations	Baseline Screening of Individuals With Germline *BAP1* Mutations (Age at Screening)	Surveillance Screening of Individuals With Germline BAP1 Mutations (Frequency)
Cohort 1: Individuals with mesothelioma carrying pathogenic germline mutations in *BAP1* or other DNA repair/cancer predisposition genes Cohort 2: First- and second-degree relatives of cohort 1 and individuals without mesothelioma carrying germline mutations in *BAP1* or other DNA repair/cancer predisposition	Genetic counseling Saliva, cheek swab, or blood for germline genetic testing	Ophthalmology evaluation (≥2 yr) Dermatology evaluation (≥2 yr) MRI: Chest, abdomen, and pelvis (≥30 yr) MRI: Brain (≥18 yr) MRI: Breast (≥30 yr) Mammogram for women (≥40 yr)	Ophthalmology evaluation (annual) Dermatology evaluation (annual) MRI: Chest, abdomen, pelvis, (every other year) MRI: Brain (every other year) MRI: Breast (every other year) Mammogram for women (annual)

MRI, magnetic resonance imaging; NCI, National Cancer Institute.

BAP1 genetic testing is recommended in children of carriers of *BAP1* mutations when they are 2 years old, and any affected children can be enrolled in the NCI trial for early cancer detection. This young age seems justified by the occurrence of melanomas and meningiomas in children carrying *BAP1* germline mutations. Such early detection efforts are consistent with recommended screening procedures for individuals with Li-Fraumeni syndrome, which also has approximately 100% cancer penetrance.[70]

A parallel complementary NCI surgical trial[71] (ClinicalTrials.gov NCT04431024) seeks to (1) determine the incidence and prevalence of subclinical mesotheliomas, (2) define the natural history of these cancers in individuals with BAP1 CPS, and (3) develop novel treatment strategies for these neoplasms. This protocol is evaluating the potential of photon-counting CT imaging together with serial analysis of cell-free DNA and periodic, thoracoscopic, and laparoscopic assessment of the pleura and peritoneum. It is anticipated that this longitudinal evaluation will identify additional cancers (Fig. 1) in patients with the BAP1 cancer syndrome. Individuals between ages 30 and 40 years will undergo photon-counting CT and analysis of cell-free DNA every 2 years and yearly in more than 40 years of age. Uniportal VATS and laparoscopy will be performed every 3 years for individuals more than 33 years old. The trial is expected to accrue 800 participants in 10 years.

As currently designed, the NCI surgical *BAP1* protocol calls for thoracoscopic surgery (VATS) and laparoscopy every 3 years after initial VATS and laparoscopic assessment performed at the time of enrollment for patients more than age 33 years or at age 33 years for patients enrolled at an earlier age. An objective scoring system has been implemented for interpretation of imaging studies and intraoperative findings. Because patients serve as their own controls, the intent is to better characterize the range of tumor biology found with BAP1-associated versus non–BAP1-associated pleural and peritoneal mesotheliomas.[72] Furthermore, the trial will study the utility and accuracy of cross-sectional imaging, circulating tumor DNA, in addition to proactive minimally invasive surveillance in patients with germline *BAP1* mutations at risk of developing mesothelioma. Patients in whom early stage mesotheliomas are detected may be eligible for clinical protocols currently under development using agents targeting epigenetic drivers in an attempt to induce regressions or to prevent/delay progression of these neoplasms to life-threatening conditions.

Even when performed in centers of excellence, thoracotomies, laparotomies, and cytoreductive surgeries cannot be performed free of potential morbidity and mortality.[73] Are these procedures indicated in subclinical disease? If so, when? As we gain experience with the natural history and relative lethalities of BAP1-associated mesotheliomas, we must address the following questions: (1) Are current standard-of-care procedures for pleural and peritoneal mesotheliomas indicated in patients with subclinical disease? If so, when? (2) Does high risk of mesothelioma ever warrant prophylactic VATS parietal pleurectomies—something already considered for children exposed to high levels of crocidolite asbestos?[74] (3) Can we evaluate novel targeted therapies in patients with subclinical disease without losing the potential for cure by surgery? (4) Given difficulties with implementing screening programs for more common malignancies,[75,76] do potential benefits justify the intensity and psychological burdens of surveillance in individuals affected by the BAP1 cancer syndrome?

The two NCI clinical trials should help to address these questions. The information derived from these protocols should accelerate the development of more efficacious regimens for the treatment and possible prevention of mesothelioma in carriers of *BAP1* and other pathogenic germline mutations. Moreover, the ongoing protocols at the NCI will verify the hypothesis that several years before an invasive mesothelioma develops, germline *BAP1* mutation carriers may already have developed multiple polyclonal early mesothelial nodules[77] that, similar to those found in Figure 3 and Supplementary Figure 1, meet the criteria to diagnose mesothelioma ("subclinical mesothelioma"). Physicians need to be aware that when these minimally infiltrating pleural nodules are detected in carriers of germline *BAP1* mutations, they may remain indolent for years. Eventually, these or other nodules may invade and cause symptoms. Moreover, it is anticipated that *BAP1* mutation carriers may be unusually susceptible to radiation-induced cancers; this hypothesis is supported by the high incidence of melanoma (Fig. 1)[4,7,8] and similar observations in carriers of germline *TP53* mutations affected by the Li-Fraumeni syndrome.[4] Moreover, in vitro studies in primary cells from individuals carrying germline *BAP1* mutations revealed increased susceptibility to DNA damage caused by ultraviolet light and ionizing radiation resulting in cell transformation.[29] Nevertheless, at present, there is no evidence that yearly CT imaging of the chest, abdomen, and pelvis increases cancer risk in individuals carrying germline *BAP1* mutations. Total ionizing radiation exposure from these yearly scans is approximately 1.1 rem, which is well below the guideline of 5 rem per year allowed for adult research subjects by the NIH Radiation Safety Committee, and this exposure is equivalent to radiation exposures during transcontinental airline flights. Nevertheless, until more information is available regarding the efficacies of various standard imaging modalities, it may be prudent to use MRI and ultrasounds rather than CT scans, unless in the context of a well-designed clinical trial for screening and early detection of cancers in individuals carrying germline *BAP1* mutations, particularly children. Of course, for diagnosis and staging, CT scans, positron emission tomography scans, and radiographs should be used.

Targeting *BAP1* Mutations for Therapy

BAP1 has been implicated in the regulation of homologous recombination[29,78,79] being recruited to sites of double-strand DNA breaks and regulating error-free DNA repair.[80] Alterations of BAP1 may influence individual sensitivity to cisplatin chemotherapy, possibly through modulation of apoptosis and transcriptional regulation of the BAP1-HCF1/E2F1 axis. Therefore, it has been proposed that BAP1 status is a useful biomarker to stratify patients for platinum-based chemotherapy.[81] Mesothelioma cells have a characteristic highly unstable karyotype[82] that might be related to chromothripsis.[45,83,84] The frequent inactivation of DNA repair genes, such as *BAP1*, contributes to genomic instability and offers potential for the use of synthetic lethal approaches targeting DNA repair factors. The use of PARP inhibitors has been suggested as a possible strategy for mesothelioma therapy since 2013,[85] followed by various preclinical and clinical studies (Supplementary Table 2). MiST1 (NCT03654833)[86] is a single-arm phase II trial, comprising patients with relapsed mesotheliomas harboring somatic BAP1 deficiency. Although found to have useful activity in mesothelioma, PARP inhibition did not seem to selectively target BAP1-deficient mesotheliomas, necessitating alternative synthetic lethal strategies. In vitro studies reached similar conclusions.[87] The question of whether mesotheliomas in patients with germline mutations in *BAP1* are more sensitive to PARP inhibitors has been recently reported.[88] In a phase II study of olaparib in malignant mesothelioma, tumor response, progression-free survival (PFS), and overall survival were evaluated in patients with mesotheliomas associated with somatic *BAP1* mutation, germline *BAP1* mutation, or no somatic or germline *BAP1* mutation. Surprisingly, patients with germline *BAP1* mutations had no objective tumor responses and the PFS and OS were significantly decreased compared with patients without germline mutation in *BAP1*. This study highlights that patients with germline mutations in *BAP1* should not receive PARP inhibitors outside the context of a clinical trial.

An ongoing two-part trial in mesothelioma (NCT02860286) with 70 *BAP1* gene-mutated patients using the EZH2 inhibitor tazemetostat reported preliminary results at ASCO 2020 with a 12-week disease control rate of 54% and 24-week disease control rate of 33%.[89] The median patient free survival was 18 weeks and median overall survival was 36 weeks; the results have not been published. Preclinical evidence suggests that *BAP1* wild-type status increases sensitivity to gemcitabine.[90,91] Genomic events associated with the development and progression of different tumors might render certain patients unusually susceptible to therapies that may not have beneficial effects for most.[92–95] For example, if the growth of some mesotheliomas requires the activation of NF-κB, various tyrosine kinases, or certain growth factors, these malignancies may respond to drugs that specifically target these pathways.[96–101] A recent study assessed the efficacy of the anti–PD-L1 antibody durvalumab plus platinum-pemetrexed chemotherapy in 55 patients with

previously untreated, unresectable pleural mesothelioma. The authors revealed that *BAP1*-mutant tumors had a higher degree of CD8+ T cell infiltration and patients harboring deleterious germline mutations in mesothelioma-predisposing genes, including, but not limited to, genes involved in DNA homologous recombination, achieved significantly longer PFS and OS with the chemoimmunotherapy regimen.[102] In summary, by screening patients with mesothelioma for germline and somatic mutations, we may identify those who may benefit from specific therapies.

Conclusions

Germline *BAP1* mutation is the first molecular positive prognosticator discovered in mesothelioma. Improved survival has been found for mesothelioma, not for other malignancies developing in carriers of germline *BAP1* mutations. Improved survival for mesothelioma in these patients may be attributable to several factors.

First, the biology of these mesotheliomas is less aggressive, as found by the low-grade histology of most of them: epithelioid mesothelioma with a trabecular or tubulopapillary architecture (Supplementary Fig. 1). A similar histology in sporadic mesothelioma is associated with only 18 to 24 months of survival.[3]

Second, in some patients, the improved survival may be influenced by early detection, as family members are often imaged at the appearance of the first clinical symptoms. Nevertheless, the extended survival predates the discovery of the BAP1 cancer syndrome—that is, we have patients with mesothelioma who survived 10 or 20+ years in families we studied for more than two decades; eventually studying these families, we discovered that *BAP1* was the mutated gene responsible for mesothelioma.[1,2,4,20] Therefore, it may be possible to achieve even better survival with screening strategies that may enable us to detect these tumors at an earlier stage.

Third, survival is measured from the time of diagnosis. These patients develop multiple pleural and peritoneal nodules years before they are diagnosed. These nodules are often indolent, although, if biopsied, they may meet the histologic criteria for a diagnosis of mesothelioma. For example, "patient 3" had an 8-year history of recurrent pleural effusions, at which time thoracoscopy result revealed several pleural nodules that histologically were diagnosed as mesothelioma (Fig. 3 and Supplementary Fig. 1). Had "patient 3" undergone VATS and biopsy 8 years earlier, she would have likely been diagnosed with mesothelioma, influencing her "survival." The transition from mesothelioma in situ (characterized by lack of BAP1 nuclear staining in the absence of tumor cell invasion) to invasive mesothelioma takes most likely several years, supporting the importance of lead-time bias in patients with germline *BAP1* mutations.[103,104]

Although mesotheliomas are common in carriers of germline *BAP1* mutations, these patients often do not die of mesothelioma; they often die because they develop additional cancers, which can be aggressive (Fig. 1). It is therefore important to closely monitor them to detect additional malignancies at an early stage when they may be amenable to curative resection. Similarly, genetic testing should be offered to their family members, and those found to have inherited the *BAP1* mutation should be screened according to the protocol in Table 1 for early cancer detection. The two clinical trials open at the NCI offer a unique opportunity to study carriers of germline *BAP1* mutations and identify the most effective screening and therapeutic approaches.

Given the evidence, we recommend that germline genetic testing should be offered to all patients diagnosed with having mesothelioma. Concerns about the potential legal implications of a germline mutation in patients pursuing or considering asbestos litigation are unique to patients with mesothelioma and seem to adversely affect the willingness of some of them to undergo formal testing and counseling. Work to address these concerns is necessary.

Prognostic scoring systems for mesothelioma have been developed by the European Organization for Research and Treatment of Cancer,[105] the Cancer and Leukaemia Group B,[106] and others.[107–109] No scoring is universally applied, but the emerging prognostic significance of *BAP1* indicates that it would be beneficial to report this finding in clinical trials to avoid erroneous interpretation—that is, patients carrying germline *BAP1* mutations have a much better prognosis, just a few of them in a phase 1 trial can give the impression of a positive response. Moreover, as nonrandomized phase 2 clinical trials have recently been reported and others are ongoing, BAP1 status would provide additional context to improve the understanding of the outcomes of the enrolled patient population. Given the simplicity to determine BAP1 status, this recommendation could be easily implemented.

Establishment of a worldwide registry that records germline variants in *BAP1* and other cancer predisposition genes in mesothelioma that includes treatment information and clinical outcomes will be pivotal in defining the possibly different roles (causation, prognosis, susceptibility to certain therapies, etc.) of these mutations. The use of an international registry analogous to the mesothelioma international database developed by the International Association for the Study of Lung Cancer would facilitate analyses aimed at a more

comprehensive understanding of *BAP1* mutations in mesothelioma.

In conclusion, there is a subset of patients with mesothelioma identified by the presence of germline mutations of *BAP1* and less frequently other genes that exhibit a prolonged survival and benefit from tailored medical attention aimed at both patients and their family members who have inherited the same mutations.

CRediT Authorship Contribution Statement

Michele Carbone, H. Richard Alexander Jr., Harvey I. Pass, David S. Schrump: Conceptualization and supervision.

All Authors: Data collection, Data curation, and Formal analysis.

Michele Carbone, H. Richard Alexander, Jr., Harvey I. Pass, David S. Schrump with critical input from all co-Authors: Writing original draft, Reviewing and editing subsequent drafts.

Michele Carbone, Thomas Krausz, Luciano Mutti, Michael Minaai, Muaiad Kittaneh, Mika Tanji, Sandra Pastorino, Yasutaka Takinishi, Alicia Zolondick: Visualization.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the Journal of Thoracic Oncology at www.jto.org and at https://doi.org/10.1016/j.jtho.2022.03.014

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