Virchows Archiv
https://doi.org/10.1007/s00428-025-04250-y

ORIGINAL ARTICLE

Perivascular epithelioid cell tumors of the urinary bladder: a multi-institutional clinicopathologic and molecular analysis of 21 cases

Ankur R. Sangoi[1] · Anandi Lobo[2] · Ankit Tiwari[3] · Mahmut Akgul[4] · Shivani Kandukuri[5] · Andres M. Acosta[6] · Khaleel I. Al-Obaidy[7] · Shilpy Jha[8] · Seema Kaushal[9] · Swati Satturwar[10] · Jasreman Dhillon[11] · Adeboye O. Osunkoya[12] · Sean R. Williamson[13] · Dinesh Pradhan[14] · Rajal B. Shah[15] · Anil V. Parwani[10] · Liang Cheng[16] · Arndt Hartmann[17] · Sambit K. Mohanty[18] · Abbas Agaimy[17]

Received: 29 July 2025 / Revised: 29 July 2025 / Accepted: 25 August 2025

Abstract

While perivascular epithelioid cell tumor (PEComas) have been described in most organ systems, only a few bladder PEComas have been reported. Although most behave in an indolent fashion, a subset may develop metastasis. Herein, we describe the clinicopathologic and molecular characteristics of 21 bladder PEComas, including biomarker analysis and comprehensive sequencing. Patients included 13 females and 8 males, with age ranging from 17–81 years (mean = 47.6 years). Clinical follow-up data was available for 17 patients (ranging 5–60 months; mean = 19.4 months). The morphologic features significantly associated with metastatic disease included ≥ 2 mitoses/10 high-power fields (p = 0.0023), atypical mitoses (p = 0.0152), and necrosis (p = 0.0023); the presence of ≥ 70% atypical epithelioid cells and vascular invasion did not meet statistical significance. The Biomarker profile (p16, p53, TRIM63 ISH, ATRX, RB1) found no statistical significance with metastasis. TRIM63 ISH showed high sensitivity (86%) with poor specificity (11%) for *TFE3* rearrangements. NGS revealed *TFE3* fusions in 8/17 cases (47%): 7 with *SFPQ::TFE3* fusions and 1 with *NONO::TFE3* fusion). Overall, mTOR pathway mutations were detected in 9 cases (53%): *TSC1/2* mutations in 6 (35%), *MTOR* mutation in 1 (6%), and co-mutations of *TSC/MTOR* in 2 (12%) cases. Additionally, co-mutations involving *p53* were noted in 2 tumors (1 *SFPQ::TFE3/p53*; 1 *MTOR/p53).* Metastasis was identified in 5 *TFE3*-rearranged PEComas (OR = 8.7509) and 2 *TSC/MTOR*- mutated tumors (OR = 0.1143). *TFE3*-rearranged bladder PEComas show a higher propensity towards aggressive behavior compared to *TSC/MTOR*- mutated tumors. Awareness of the molecular signature may be important for prognostic stratification and targeted therapeutic approaches.

Keywords PEComa · Perivascular · Epithelioid · Bladder · Urinary · Molecular

Introduction

Perivascular epithelioid cell tumors (PEComas) are uncommon mesenchymal neoplasms of unknown histogenetic origin that display combined smooth muscle and melanocytic differentiation to a variable extent and exhibit a variety of distinct histologic and immunophenotypic features [1]. PEComas are infrequently seen in the genitourinary tract and are typically encountered in the kidney (seemingly synonymous with renal epithelioid angiomyolipoma [2]). In the urinary bladder, PEComas are extraordinarily rare, with the original depiction under the label "clear cell myomelanocytic tumor" published in 2003 [3]. Since then, less than 50 bladder PEComas have been reported, mostly in the form of single case reports [4–7]. Those cases arising in the bladder often pose diagnostic challenges due to morphologic overlap with other spindle and epithelioid neoplasms. Given the rarity of bladder PEComas, limited data exist regarding their molecular features, behavior, and optimal management.

Although a majority of the reported genitourinary tract PEComas exhibit indolent clinical behavior, a subset may show aggressive behavior including metastasis [4–7].

Ankur R. Sangoi and Anandi Lobo are co-first authors.

Sambit K. Mohanty and Abbas Agaimy are co-senior authors

Extended author information available on the last page of the article

Published online: 04 October 2025

Prognostic studies of PEComa have primarily relied on select histopathologic criteria tailored to specific anatomic sites (e.g., kidney [2, 8–10] and soft tissue/gynecologic tract [10–14]). Additionally, a subset of studies has explored the role of immunohistochemistry (IHC) and/or molecular profiling to aid in risk stratification, particularly for renal PEComas [2, 15, 16], and, to a lesser extent, those arising in the bladder [16], and soft tissue/gynecologic tract [12]. Among genitourinary tract PEComas, data on the proposed genetic dichotomy [tuberous sclerosis complex (*TSC*) alteration versus TFE3-mediated rearrangement] resulting in activation of the mTOR versus the microphthalmia transcription factor (MiTF) pathways, respectively, have been studied almost exclusively in the kidney [2]. However, to our knowledge, a clinicopathologic study evaluation including prognostic and/or molecular characteristics solely of urinary bladder PEComas has not been previously performed, providing the rationale for the current study, which aims to systematically evaluate both clinicopathologic parameters and molecular alterations in a cohort of bladder PEComas, with a particular emphasis on identifying features associated with aggressive clinical behavior.

Methods

An international cohort of 21 bladder PEComas was compiled from 17 different institutions, with slides re-reviewed by experienced genitourinary pathologists. Morphologic inclusion criteria were defined by the 5th edition World Health Organization (WHO) classification of an extrarenal PEComa composed of epithelioid to spindled tumor cells with melanocytic/muscle differentiation [17]. Available clinicopathologic features were recorded for all tumors. Additionally, the presence of the following pathologic features was specifically assessed: known clinical history of TSC and/or prior chemotherapy exposure, ≥ 70% atypical epithelioid cells (defined as atypical polygonal cells with abundant cytoplasm, vesicular nuclei, prominent nucleoli, and nuclear size exceeding at least twice that of adjacent nuclei), ≥ 2 mitotic figures/10 high power fields, atypical mitotic figures, necrosis, and vascular invasion. Follow-up data was sought for each patient, with an adverse outcome defined as metastasis.

One representative formalin-fixed paraffin-embedded tissue block from select cases was selected for whole-slide IHC analysis using the following markers (interpretation patterns; clone): p16 (positive or negative; E6H4), p53 (wild type or mutant; DO-7), TRIM63 in situ hybridization (ISH; > 10% as positive or < 10% as negative; RNA scope), ATRX (retained or lost; polyclonal), RB1 (retained or lost; G3-245), cathepsin K (> 10% as positive or < 10% as negative; 3F9), and TFE3 (> 10% as positive or < 10% as negative; MRQ-37). Additionally, molecular evaluation was performed on 17 cases including an assessment of next generation sequencing (NGS), microsatellite instability (MSI, and tumor mutational burden (TMB), as previously described [18]. Statistical analysis was performed using GraphPad Prism 10. A meta-analysis of previously-reported molecular alterations among bladder PEComas was also performed.

Results

The 21 bladder PEComa patients included 13 females and 8 males with an age range of 17–81 years (median = 46 years, mean = 47.6 years). No patients had a history of TSC or known prior chemotherapy exposure, although data on some cases might be incomplete. Clinical follow-up was available for 17 patients (range 5–60 months, mean 19.4 months). Figure 1 depicts detailed summarized clinicopathologic characteristics of the bladder PEComas, including noted pathologic features, IHC results, and molecular findings. Significant cytoplasmic dark brown pigmentation was not identified in any case. Notable IHC results from stains performed on all select cases yielded the following results: p16 positive in 3/15 (20%), p53 mutant pattern in 4/15 (27%), TRIM63 ISH positive in 14/16 (88%), ATRX loss in 4/15 (27%), RB1 retained in 15/15 (100%), TFE3 positive in 9/19 (47%), and cathepsin K positive in 17/17 (100%). Figure 2 depicts representative cytomorphology and select IHC staining for study tumors.

Molecular findings by NGS in our cohort yielded driver genetic alterations identified in all 17 tumors tested. All PEComas showed mutations in either *TSC/MTOR* (9/17; 53%) or had *TFE3* gene rearrangement (8/17; 47%). Of the 9 *TSC/MTOR*- mutated PEComas, 3 involved *TSC2*, 3 involved *TSC1*, and 1 involved *MTOR*; 2 tumors showed co-mutations (*TSC2* and *MTOR*). Of the 8 *TFE3* rearranged PEComas, 7 showed *SFPQ::TFE3* fusions and 1 showed *NONO::TFE3* fusion.

Among the PEComas, in terms of IHC and molecular correlation, all the 4 PEComas (100%) with mutant p53 staining were confirmed to harbor *TP53* mutation by NGS; notably, 1 of these *TP53* mutated PEComas also showed a concurrent *MTOR* mutation. Of the 4 PEComas that showed aberrant loss of ATRX staining on IHC, 3 (75%) showed *ATRX* mutation by NGS. Additionally, of the 14 PEComas that demonstrated positive TRIM63 ISH staining and underwent molecular testing, 6 (43%) were found to have *TFE3* gene rearrangements. All (7/7, 100%) PEComas with *TFE3* rearrangement that had TFE3 IHC performed showed positive staining.

A statistical analysis conducted to evaluate the association between IHC and the development of metastatic disease

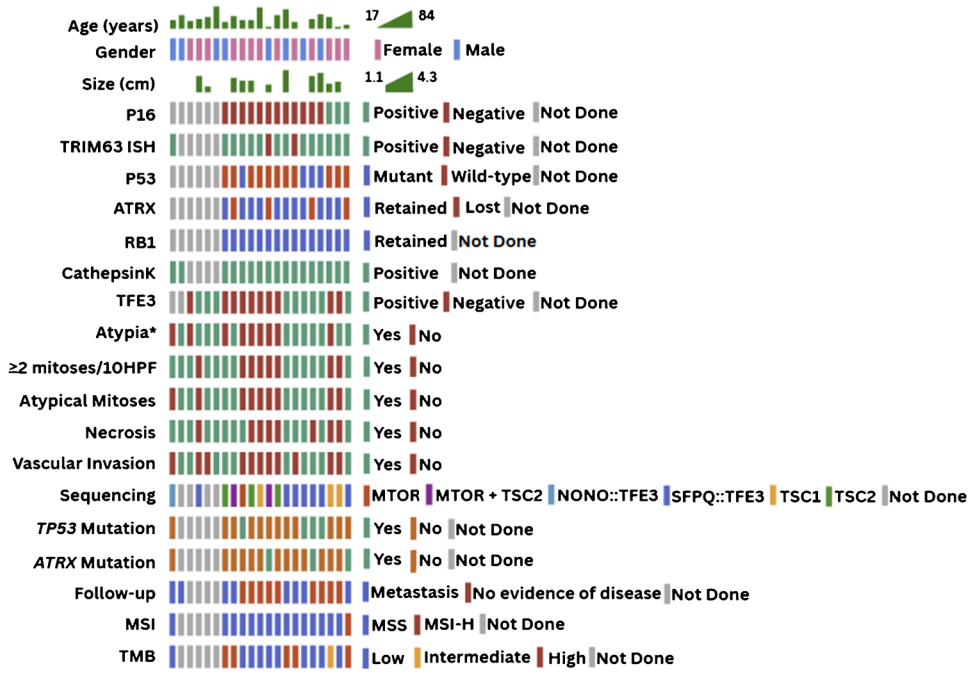

Fig. 1 Detailed clinicopathologic characteristics of urinary bladder PEComas including morphologic features, immunoprofile, and molecular findings. Each bar represents a study case. IHC, immunohistochemistry; ISH, in situ hybridization; NGS, next generation sequencing; MSI, microsatellite instability; TMB, tumor mutational burden; * = ≥ 70% atypical epithelioid cells

found no statistically significant association for any of the performed biomarkers (p16, p53, TRIM63 ISH, ATRX, RB1). Additionally, the study examined various clinicopathologic features for their association with 8 PEComas with metastatic disease (Table 1). The morphologic features significantly associated with metastatic disease included ≥ 2 mitoses/10 high-power fields (n = 8/10, 80%; p = 0.0023), atypical mitoses (n = 7/9, 78%; p = 0.0152), and necrosis (n = 8/10, 80%; p = 0.0023). Furthermore, 5 tumors harboring TFE3 rearrangements developed metastasis (OR = 8.7509) suggesting a potential association with aggressive behavior, while 2 *TSC/MTOR*-mutated tumors had metastatic disease (OR = 0.1143). Overall aggressive behavior was observed in 5/7 (71%) of TFE3-rearranged versus 2/9 (22%) of mTOR-altered cases with follow-up.

Discussion

Among the larger series investigating PEComas of the genitourinary tract, most attention has been focused on PEComas of the kidney ("renal epithelioid angiomyolipomas"), as detailed in three prior studies [2, 8, 9]. Of these, only the study by Sangoi et al. [2] incorporated both detailed clinicopathologic features as well as molecular testing to identify prognostic risk factors in renal epithelioid angiomyolipomas. In contrast, PEComas of the urinary bladder have been far less extensively studied, and, to date, only two prior larger (> 2 cases, to exclude mostly case reports) series of PEComas have been described (n = 3 [19] and n = 11 [20]). Of these, only one study formally incorporated and systematically applied prognostic histologic features (as described by Brimo et al. [9]). Moreover, molecular characterization of bladder PEComas has been limited, predominantly in the form of *TFE3* rearrangement testing by FISH, with only a handful of studies incorporating results of sequencing data (Table 1). In this study, representing to our knowledge the largest series of bladder PEComas to date (n = 21) as well as the largest series subjected to molecular testing (n = 17), we performed an integrated assessment of select purportedly unfavorable clinicopathologic features alongside a select focused panel of IHC markers with prognostic relevance as well as NGS to investigate those PEComas that may show poor outcome as well as further elucidate the biologic underpinnings of aggressive disease behavior.

Several key findings emerge from this study. First, the histologic features predictive of malignancy and validated in the studies by Brimo et al. [9] and Sangoi et al. [2] for renal PEComas (≥ 70% atypical epithelioid cells, ≥ 2 mitotic figures/10 high power fields, atypical mitotic figures, necrosis, and vascular invasion) are applicably relevant to the urinary bladder PEComas evaluated in this study, with all but two showing a statistically significant association with the development of metastasis including distant sites (Table 2). Moreover, the smaller bladder PEComas series by Neumann et al. [20], which similarly applied the Brimo et al. criteria, also demonstrated the utility of these cytomorphologic parameters, further supporting their applicability in the bladder setting.

Second, in this study we also investigated whether a subset of IHC markers could complement morphologic assessment in the prognostication of bladder PEComas.

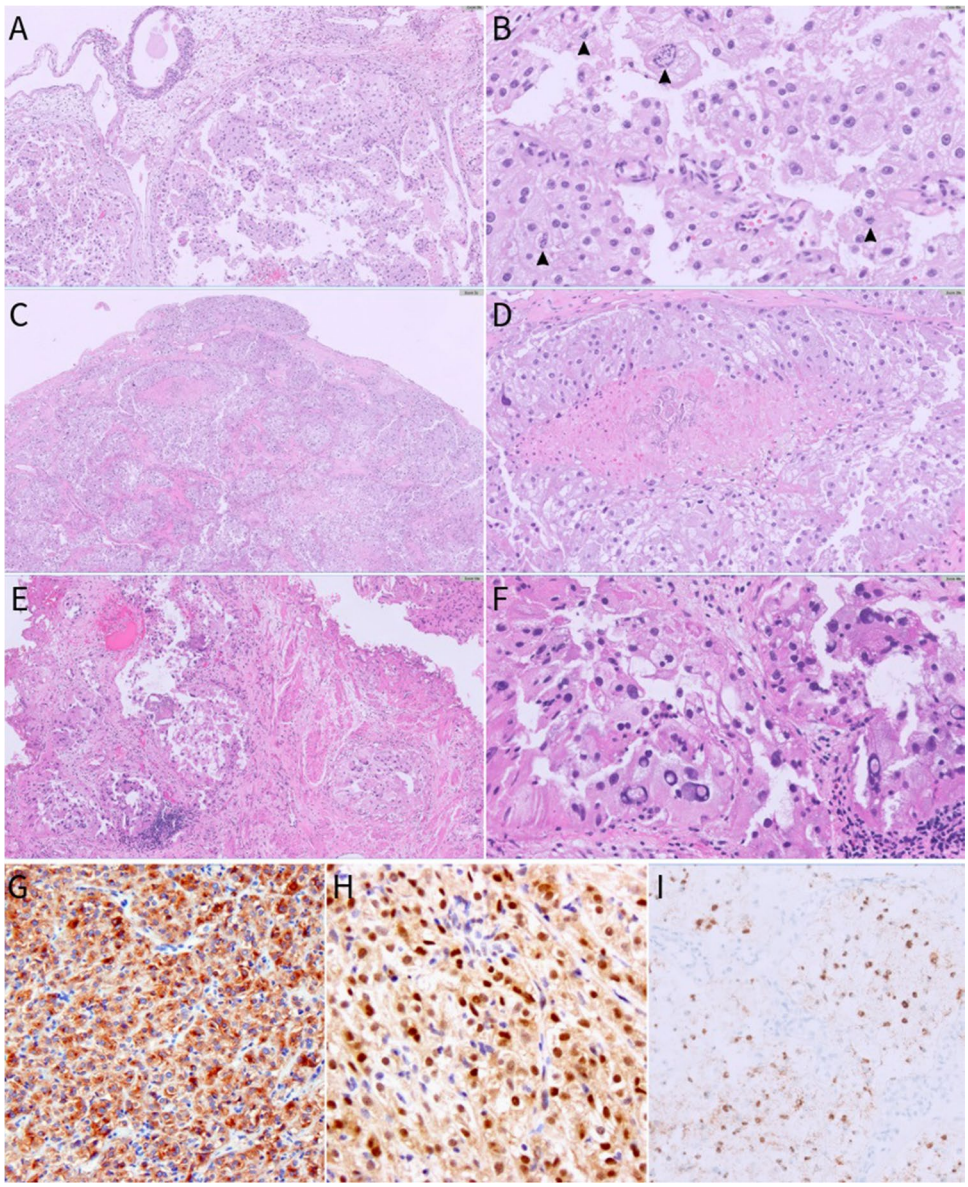

Fig. 2 Representative images of urinary bladder PEComa from transurethral resection specimens. The tumor cells show an infiltrative growth pattern in sheets and nests composed of epithelioid cells with clear to eosinophilic cytoplasm, variable atypia, and interspersed thin vasculature (H&E, **A**–**F**). Some of the notable morphologic features associated with metastasis included ≥ 2 mitotic figures/10 high power fields (**B**) and necrosis (**D**); the presence of ≥ 70% atypical epithelioid cells (**F**) did not meet the statistical threshold. Representative positive immunostains included cathepsin K (G; × 200), TFE3 (H; × 200), and TRIM63 ISH (I; × 200). H&E, hematoxylin and eosin stain

The IHC stains selected were based on a literature review of previously described biomarkers showing aggressive behavior in PEComas across various sites [2, 12, 15, 16, 21, 22]. Having encountered an index bladder PEComa in which TRIM63 ISH was positive, we also explored the potential utility of this stain as a surrogate screening tool for *TFE3* fusions (akin to that recognized in MiTF renal cell carcinoma [23]), with at least some studies suggesting *TFE3*-rearranged PEComas may be associated with a more aggressive clinical behavior. [12, 16, 20, 24–27]. While we did not compare other differential diagnostic entities of PEComa, we were guided by one recent study highlighting differential TRIM63 ISH expression levels as a putative diagnostic tool of alveolar soft part sarcoma (showing "high staining" for TRIM63) versus PEComa (showing "intermediate/spectrum" TRIM63 reactivity) [28] in investigating the diagnostic sensitivity of TRIM63 ISH among our cohort. Although none of the biomarkers tested in our study showed statistically significant correlation with metastasis (and may not prove a reliable alternative to conventional morphologic assessment of select features), it should be noted that while TRIM63 ISH demonstrated high sensitivity (86%) for *TFE3*-rearranged PEComa, it showed poor specificity (11%). These findings similarly overlap with prior observations highlighted by Sangoi et al. in their assessment of TRIM63 ISH positivity and *TFE3* rearrangement among renal PEComas [2]. In contrast, *TFE3* testing by IHC showed perfect concordance with *TFE3* evaluation by NGS in our cohort (100% sensitivity and specificity for *TFE3* rearrangement). However, we recognize the known challenges in validating and evaluating TFE3 IHC [29–32], precluding its incorporation in

Table 1 Meta-analysis of urinary bladder PEComas with molecular characterization

Reference	Age	Sex	Molecular alteration by sequencing
Argani et al. [16]	27	M	*SFPQ::TFE3*
Argani et al. [16]	82	F	*NONO::TFE3*
Papke et al. [25]	35	F	*SFPQ::TFE3*
Agaram et al. [35]	44	M	*RASSF1::PDZRN3*
Chen et al. [49]	27	M	*SFPQ::TFE3*
current study	17	M	*SFPQ::TFE3*
current study	43	F	*MTOR* missense mutation
current study	29	F	*SFPQ::TFE3*
current study	51	F	*TSC1* nonsense mutation
current study	37	M	*TSC2* missense mutation
current study	46	F	*SFPQ::TFE3*
current study	23	F	*TSC1* nonsense mutation
current study	54	F	*MTOR* duplication, *TSC2* frameshift mutation
current study	42	F	*TSC2* missense mutation
current study	81	F	*TSC1* nonsense mutation
current study	75	M	*SFPQ::TFE3*
current study	24	M	*MTOR* duplication, *TSC2* frameshift mutation
current study	60	M	*SFPQ::TFE3*
current study	58	F	*TSC2* frameshift mutation
current study	37	F	*SFPQ::TFE3*
current study	43	M	*NONO::TFE3*
current study	46	F	*SFPQ::TFE3*
Reference	**Age**	**Sex**	**Molecular alteration by TFE3 FISH**
Russell et al. [26]	27	F	TFE3 FISH positive
Vannucchi et al. [6]	66	F	TFE3 FISH positive
Williamson et al. [24]	55	F	TFE3 FISH positive
Wu et al. [50]	78	F	TFE3 FISH negative
Wu et al. [50]	37	F	TFE3 FISH negative
Wu et al. [50]	31	F	TFE3 FISH negative
Wu et al. [50]	26	M	TFE3 FISH negative
Wu et al. [50]	55	F	TFE3 FISH negative
Wu et al. [50]	34	F	TFE3 FISH negative
Wu et al. [50]	30	M	TFE3 FISH negative
Neumann et al. [20]	60	M	TFE3 FISH negative
Neumann et al. [20]	24	M	TFE3 FISH positive
Neumann et al. [20]	41	F	TFE3 FISH negative
Neumann et al. [20]	50	F	TFE3 FISH positive
Neumann et al. [20]	56	F	TFE3 FISH positive
Neumann et al. [20]	61	F	TFE3 FISH negative
Neumann et al. [20]	31	F	TFE3 FISH positive

many laboratories. Moreover, some studies have reported discordance with TFE3 positivity by IHC version fusion status, further complicating its interpretive reliability [33, 34].

Third, the molecular findings from this study support the dogma that for most PEComas, genetic dichotomy comes in the form of *TSC/MTOR* alterations or *TFE3* rearrangements [35, 36] (Fig. 3), leading to activation of the mTOR and the MiTF pathway, respectively. However, it should be noted that perhaps given the rarity of PEComas in the bladder, there has been a paucity of studies incorporating molecular testing beyond FISH for bladder PEComas (Table 1) compared to those arising in other anatomic sites outside the bladder. While NGS testing in our cohort exhibits a near equal distribution of *TSC/MTOR* alteration (53%) to *TFE3* rearrangement, which mirrors the findings in one of the largest comprehensive reports of genetic studies of PEComas across various sites (showing

Table 2 Pathologic features of urinary bladder PEComas with metastasis

Patient#	Molecular alterations	Atypia*	> 2 Mitoses/10 HPF	Atypical mitoses	Necrosis	Vascular invasion	MSI	TMB	Follow-up
1	*SFPQ::TFE3*; *TP53*	Yes	Yes	Yes	Yes	Yes	MSS	Low (1.34 mut/MB)	Liver and bone metastasis (5 months)
3	*SFPQ::TFE3*; *ATRX*	Yes	Yes	Yes	Yes	Yes	MSI-H	High (54.15 mut/MB)	Died of extensive visceral and bone metastasis (9 months)
5	*TSC2* missense mutation	No	Yes	Yes	Yes	Yes	MSS	High (14.5 mut/MB)	Liver metastasis (14 months)
8	*MTOR* duplication; *TSC2* frameshift mutation	Yes	Yes	Yes	Yes	Yes	MSS	High (41.2 mut/MB)	Died of extensive visceral and bone metastasis (17 months)
11	*SFPQ::TFE3*	Yes	Yes	Yes	Yes	Yes	MSS	High (16.1 mut/MB)	Lung and liver metastasis (9 months)
15	*SFPQ::TFE3*	Yes	Yes	Yes	Yes	No	MSS	High (15.5 mut/MB)	Liver, lung, lymph node, bone metastasis (7 months)
16	*NONO::TFE3*	No	Yes	No	Yes	No	MSS	Low (4 mut/MB)	Liver and lymph node metastasis (8 months)
17	N/A	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Lung metastasis (6 months)

**Atypia* ≥ 70% atypical epithelioid cells, *MSI* microsatellite instability, *MSS* microsatellite stable, *MSI-H* microsatellite instable high, *mut/MB* mutations per megabase

a slight predominance in *TSC/MTOR* alteration compared to *TFE3* rearrangement [35]), future studies are needed to specifically evaluate the genetic landscape of bladder PEComas.

Determining tumor genetics may be clinically relevant as we found that *TFE3*-rearranged bladder PEComas show a higher propensity towards aggressive behavior compared to *TSC/MTOR* mutated counterparts (OR = 8.7509 vs OR = 0.1143, respectively). While the odds ratios indicate a possible trend, larger cohorts are needed to validate these associations and define their clinical relevance. Importantly, this genetic dichotomy may also carry therapeutic implications, as some studies have shown that *TFE3*-rearranged PEComas treated with *MTOR* inhibitors fail to show a response [16]. This is however somewhat controversial, as other studies have shown *TFE3*-rearranged PEComas may show at least partial benefit in select cases for *MTOR* targeted therapies [37–39]. Despite this variability, *MTOR*-targeted therapies are now recognized as a viable and effective treatment option for malignant PEComas [40, 41]. Given this potential, it may be worth considering molecular testing of an encountered bladder PEComa, at least for one showing some of the notable clinicopathologic features highlighted in this study.

This study is not without limitations, the most notable being our inability to formally compare the PEComa prognostic criteria cited by Folpe et al. (for gynecologic tract/soft tissue PEComas) to those referenced by Brimo et al. [9] and subsequently validated by Sangoi et al. [2] (for renal PEComas). The primary barrier was the lack of tumor size data for the majority of our case cohort, many of which were received as consultation specimens or transurethral resections without associated imaging. Tumor size > 5 cm is one of the key parameters in the Folpe et al. [11] stratification model, which also includes infiltrative growth pattern, high nuclear atypia, mitotic count > 1/50 HPF, necrosis, and vascular invasion, with > 2 features considered worrisome for malignancy. Nonetheless, as four of these six Folpe et al. [11] features are effectively enveloped within the criteria originally depicted by Brimo et al. [9] and later validated by Sangoi et al. [2], it may be prudent to apply one or both of these prognostic models when encountering a bladder PEComa (the second largest bladder PEComa study [20] also utilized Brimo et al.'s criteria [9]). Moreover, our findings highlight the need for future studies to assess whether a "genitourinary tract" specific risk stratification model for PEComas is warranted (only rare PEComas of the prostate, testis, ureter, urethra,

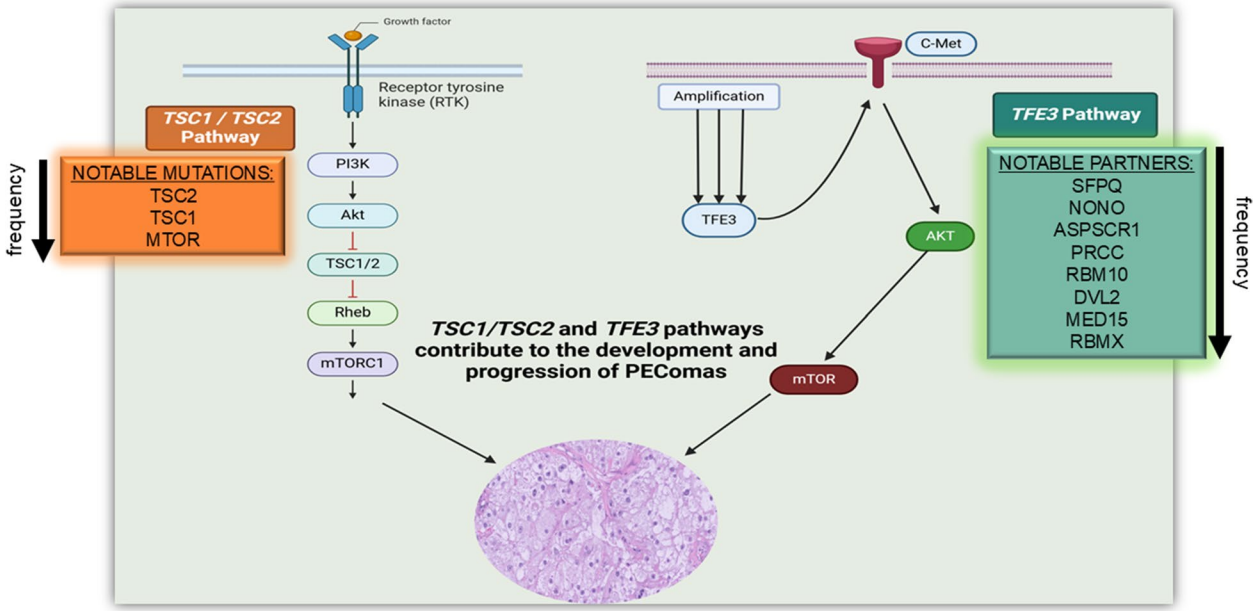

Fig. 3 Illustration of the two primary molecular subtype pathways of urinary bladder PEComas (prepared on Biorender.com). *TSC1/TSC2*-mutated subtype: loss-of-function mutations in the *TSC1* or *TSC2* genes disrupt the TSC1-TSC2 protein complex, leading to constitutive activation of Ras homolog enriched in brain (*RHEB*). Activated *RHEB* stimulates *mTORC1*, which in turn phosphorylates downstream effectors and promotes unchecked cell growth and proliferation. *TFE3*-rearranged subtype: this less common subtype is characterized by transcriptional upregulation of *TFE3*, often due to gene fusions or amplifications. Elevated *TFE3* activity induces the c-Met proto-oncogene and activates downstream signaling pathways, including *AKT* and *mTOR*, as well as other partially defined effectors, contributing to tumorigenesis and enhanced cell proliferation

and urachus have been reported [42–48]). Because the amassed study slides/photomicrographs from our bladder PEComa were housed with one of our senior authors who unfortunately passed away during manuscript preparation (and to whom this study is dedicated), we were not able to incorporate morphologic assessment of study cases compared to molecular alterations identified. Anecdotally, we did observe that *TSC/MTOR* mutated PEComas showed more of a spindled to epithelioid configuration compared to that of *TFE3*-rearranged PEComa, which exhibited a more nested architecture of epithelioid cells with cleared cytoplasm (Fig. 2). These comparative morphology/molecular differences have been analogously highlighted in a recent study by Argani et al. [16], suggesting that *TFE3*-rearranged PEComas may be biologically distinct from conventional (*TSC/MTOR* mutated) PEComas and warrant separation (coining the term "*TFE3*-rearranged PEComa-like neoplasms"). The study by Argani et al. [34] highlights that these *TFE3*-rearranged PEComa-like neoplasms present more often in younger patients, may be associated with prior chemotherapy exposure, often show desmin/SMA negativity or weak/focal positivity and are often HMB45 positive but minimally melanA positive, and may behave more aggressively with limited response to *MTOR* inhibitors. However, the nosology of separately categorizing *TFE3*-rearranged PEComas has been challenged regarding whether these tumors should be considered a distinct entity [25]. Future studies are also needed to evaluate the ideal label for bladder PEComas based on their molecular characterization to ensure diagnostic accuracy, prognostic assessment, and therapeutic strategies tailored to the molecular subtype.

In summary, in this study (the largest series of urinary bladder PEComas reported to date) we identified several histopathologic features significantly associated with metastatic disease including the presence of ≥ 2 mitotic figures/10 high power fields, atypical mitotic figures, and necrosis. Our molecular analysis lends support to the genetic dichotomy of PEComas characterized either by *TSC/MTOR* pathway alterations or *TFE3* gene rearrangements. In this regard, *TFE3*-rearranged bladder PEComas show a higher propensity toward aggressive behavior compared to *TSC/MTOR* mutated tumors, and that awareness of the molecular signature may be important for prognostic stratification and targeted therapeutic approaches.

Acknowledgements With the untimely death of Dr. Sambit Mohanty during the final phases of this study, this manuscript is dedicated to him and written in his memory and honor.

Author contribution AA, SKM, and AL designed the study. ARS, AL, and SKM interpreted the data. ARS wrote the original manuscript. All authors reviewed the manuscript draft for approval.

Funding Open Access funding enabled and organized by Projekt DEAL.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval Samples were used in accordance with ethical guidelines for the use of retrospective tissue samples at our institutions.

Conflict of interest AA is Editor-in-Chief of Virchows Archiv.

References

1. Folpe AL, Kwiatkowski DJ (2010) Perivascular epithelioid cell neoplasms: pathology and pathogenesis. Hum Pathol 41(1):1–15. https://doi.org/10.1016/j.humpath.2009.05.011
2. Sangoi AR, Lobo A, Jha S, et al (2025) Renal epithelioid angiomyolipoma: prognostic implications of targeted immunohistochemical and molecular markers in conjunction with clinicopathologic features. Am J Surg Pathol. https://doi.org/10.1097/PAS.0000000000002411
3. Pan CC, Yu IT, Yang AH, Chiang H (2003) Clear cell myomelanocytic tumor of the urinary bladder. Am J Surg Pathol 27(5):689–692. https://doi.org/10.1097/00000478-200305000-00013
4. Adriaenssens Z, Lamoury RPA, Tilborghs S, Wachter S, Brits T (2024) Bladder perivascular epithelioid cell neoplasm: review on clinical features of this rare tumor. Urol Ann 16(1):28–35. https://doi.org/10.4103/ua.ua_40_23
5. Hamza A, Guo CC (2020) Perivascular epithelioid cell tumor of the urinary bladder: a systematic review. Int J Surg Pathol 28(4):393–400. https://doi.org/10.1177/1066896919895810
6. Vannucchi M, Minervini A, Salvi M, Montironi R, Raspollini MR (2020) TFE3 gene rearrangement in perivascular epithelioid cell neoplasm (PEComa) of the genitourinary tract. Clin Genitourin Cancer 18(6):e692–e697. https://doi.org/10.1016/j.clgc.2020.04.004
7. Martignoni G, Pea M, Zampini C et al (2015) Pecomas of the kidney and of the genitourinary tract. Semin Diagn Pathol 32(2):140–159. https://doi.org/10.1053/j.semdp.2015.02.006
8. Nese N, Martignoni G, Fletcher CD et al (2011) Pure epithelioid PEComas (so-called epithelioid angiomyolipoma) of the kidney: a clinicopathologic study of 41 cases: detailed assessment of morphology and risk stratification. Am J Surg Pathol 35(2):161–176. https://doi.org/10.1097/PAS.0b013e318206f2a9
9. Brimo F, Robinson B, Guo C, Zhou M, Latour M, Epstein JI (2010) Renal epithelioid angiomyolipoma with atypia: a series of 40 cases with emphasis on clinicopathologic prognostic indicators of malignancy. Am J Surg Pathol 34(5):715–722. https://doi.org/10.1097/PAS.0b013e3181d90370
10. Gantzer J, Toulmonde M, Severac F et al (2024) PEC-PRO: a new prognostic score from a series of 87 patients with localized perivascular epithelioid cell neoplasms (PEComas) treated with curative intent. Cancer 130(13):2304–2314. https://doi.org/10.1002/cncr.35277
11. Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL, Weiss SW (2005) Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. Am J Surg Pathol 29(12):1558–1575. https://doi.org/10.1097/01.pas.0000173232.22117.37
12. Bennett JA, Ordulu Z, Pinto A et al (2022) Uterine PEComas: correlation between melanocytic marker expression and TSC alterations/TFE3 fusions. Mod Pathol 35(4):515–523. https://doi.org/10.1038/s41379-021-00855-1
13. Shukla PS, Xia R, Lin LH, Schwartz CJ (2021) Gynaecological perivascular epithelioid cell tumour (PEComa): comparative analysis of proposed algorithms for prediction of clinical outcome. Histopathology 79(5):847–860. https://doi.org/10.1111/his.14434
14. Schoolmeester JK, Howitt BE, Hirsch MS, Dal Cin P, Quade BJ, Nucci MR (2014) Perivascular epithelioid cell neoplasm (PEComa) of the gynecologic tract: clinicopathologic and immunohistochemical characterization of 16 cases. Am J Surg Pathol 38(2):176–188. https://doi.org/10.1097/PAS.0000000000000133
15. McCarthy MR, Nichols PE, Sharma V et al (2023) Molecular and immunophenotypic correlates of metastatic epithelioid angiomyolipoma include alterations of TP53, RB1, and ATRX. Arch Pathol Lab Med 147(7):817–825. https://doi.org/10.5858/arpa.2022-0127-OA
16. Argani P, Gross JM, Baraban E et al (2024) TFE3 -rearranged PEComa/PEComa-like neoplasms : report of 25 new cases expanding the clinicopathologic spectrum and highlighting its association with prior exposure to chemotherapy. Am J Surg Pathol 48(7):777–789. https://doi.org/10.1097/PAS.0000000000002218
17. Hes O, Calio A, Martignoni G et al (2022) Extrarenal PEComas. Urinary and Male Genital Tumours WHO Classification of Tumours, 5th Edition, Volume 8, 2022, IARC, Lyons, Paris. Pages 419–420
18. Aggarwal A, Sharma S, Brar Z et al (2024) Comprehensive molecular analysis of driver mutations in non-small cell lung carcinomas and its correlation with PD-L1 expression, an Indian perspective. Pathol Res Pract 253:155013. https://doi.org/10.1016/j.prp.2023.155013
19. Sukov WR, Cheville JC, Amin MB, Gupta R, Folpe AL (2009) Perivascular epithelioid cell tumor (PEComa) of the urinary bladder: report of 3 cases and review of the literature. Am J Surg Pathol 33(2):304–308. https://doi.org/10.1097/PAS.0b013e3181854929
20. Neumann NM, Haffner MC, Argani P, Kao CS, Epstein JI (2021) Histopathologic characterization of bladder perivascular epithelioid cell neoplasms (PEComa): a series of 11 cases with a subset having TFE3 rearrangements. Am J Surg Pathol 45(2):169–177. https://doi.org/10.1097/PAS.0000000000001592
21. Rammal R, Korentzelos D, Skaugen JM, Quiroga-Garza GM (2023) Molecular characterization of malignant renal epithelioid angiomyolipoma: a review of two cases. Am J Clin Pathol 159(3):211–220. https://doi.org/10.1093/ajcp/aqac152
22. Zhang Y, Wei X, Teng X, Chen G (2023) P53 aberration and TFE3 gene amplification may be predictors of adverse prognosis in epithelioid angiomyolipoma of the kidney. Diagn Pathol 18(1):14. https://doi.org/10.1186/s13000-023-01298-9

23. Wang XM, Zhang Y, Mannan R et al (2021) TRIM63 is a sensitive and specific biomarker for MiT family aberration-associated renal cell carcinoma. Mod Pathol 34(8):1596–1607. https://doi.org/10.1038/s41379-021-00803-z
24. Williamson SR, Bunde PJ, Montironi R et al (2013) Malignant perivascular epithelioid cell neoplasm (PEComa) of the urinary bladder with TFE3 gene rearrangement: clinicopathologic, immunohistochemical, and molecular features. Am J Surg Pathol 37(10):1619–1626. https://doi.org/10.1097/PAS.0b013e318293729d
25. Papke DJ, Odintsov I, Mahadevan NR, Fletcher CD, Hanna J (2025) Genetic correlates of malignancy in TFE3-rearranged PEComa: a series of 14 cases. Histopathology. https://doi.org/10.1111/his.15476
26. Russell CM, Buethe DD, Dickinson S, Sexton WJ (2014) Perivascular epithelioid cell tumor (PEComa) of the urinary bladder associated with Xp11 translocation. Ann Clin Lab Sci 44(1):91–98
27. Schoolmeester JK, Dao LN, Sukov WR et al (2015) TFE3 translocation-associated perivascular epithelioid cell neoplasm (PEComa) of the gynecologic tract: morphology, immunophenotype, differential diagnosis. Am J Surg Pathol 39(3):394–404. https://doi.org/10.1097/PAS.0000000000000349
28. Taylor AS, Mannan R, Pantanowitz L et al (2024) Evaluation of TRIM63 RNA in situ hybridization (RNA-ISH) as a potential biomarker for alveolar soft-part sarcoma (ASPS). Med Oncol 41(3):76. https://doi.org/10.1007/s12032-024-02305-9
29. Gaillot-Durand L, Chevallier M, Colombel M et al (2013) Diagnosis of Xp11 translocation renal cell carcinomas in adult patients under 50 years: interest and pitfalls of automated immunohistochemical detection of TFE3 protein. Pathol Res Pract 209(2):83–89. https://doi.org/10.1016/j.prp.2012.10.013
30. Kuroda N, Katto K, Tanaka Y et al (2010) Diagnostic pitfall on the histological spectrum of adult-onset renal carcinoma associated with Xp11.2 translocations/TFE3 gene fusions. Med Mol Morphol 43(2):86–90. https://doi.org/10.1007/s00795-008-0423-x
31. Rao Q, Williamson SR, Zhang S et al (2013) TFE3 break-apart FISH has a higher sensitivity for Xp11.2 translocation-associated renal cell carcinoma compared with TFE3 or cathepsin K immunohistochemical staining alone: expanding the morphologic spectrum. Am J Surg Pathol 37(6):804–815. https://doi.org/10.1097/PAS.0b013e31827e17cb
32. Yang B, Duan H, Cao W et al (2019) Xp11 translocation renal cell carcinoma and clear cell renal cell carcinoma with TFE3 strong positive immunostaining: morphology, immunohistochemistry, and FISH analysis. Mod Pathol 32(10):1521–1535. https://doi.org/10.1038/s41379-019-0283-z
33. Argani P, Aulmann S, Illei PB et al (2010) A distinctive subset of PEComas harbors TFE3 gene fusions. Am J Surg Pathol 34(10):1395–1406. https://doi.org/10.1097/PAS.0b013e3181f17ac0
34. Collins K, Bridge JA, Mehra R et al (2024) Renal epithelioid angiomyolipomas overexpress TFE3 and the TFE3-regulated gene TRIM63 in the absence of TFE3 rearrangement. Virchows Arch 485(3):471–478. https://doi.org/10.1007/s00428-024-03855-z
35. Agaram NP, Sung YS, Zhang L et al (2015) Dichotomy of genetic abnormalities in PEComas with therapeutic implications. Am J Surg Pathol 39(6):813–825. https://doi.org/10.1097/PAS.0000000000000389
36. Malinowska I, Kwiatkowski DJ, Weiss S, Martignoni G, Netto G, Argani P (2012) Perivascular epithelioid cell tumors (PEComas) harboring TFE3 gene rearrangements lack the TSC2 alterations characteristic of conventional PEComas: further evidence for a biological distinction. Am J Surg Pathol 36(5):783–784. https://doi.org/10.1097/PAS.0b013e31824a8a37
37. Testa S, Bui NQ, Ganjoo KN (2023) Systemic treatments and molecular biomarkers for perivascular epithelioid cell tumors: a single-institution retrospective analysis. Cancer Res Commun 3(7):1212–1223. https://doi.org/10.1158/2767-9764.CRC-23-0139
38. Purwar R, Soni K, Shukla M, Verma A, Kumar T, Pandey M (2022) TFE3-associated perivascular epithelioid cell tumor with complete response to mTOR inhibitor therapy: report of first case and literature review. World J Surg Oncol 20(1):62. https://doi.org/10.1186/s12957-021-02462-5
39. Saoud R, Kristof TW, Judge C et al (2022) Clinical and pathological features of renal epithelioid angiomyolipoma (PEComa): a single institution series. Urol Oncol 40(2):18–24. https://doi.org/10.1016/j.urolonc.2021.09.010
40. Wagner AJ, Ravi V, Riedel RF et al (2021) Sirolimus for patients with malignant perivascular epithelioid cell tumors. J Clin Oncol 39(33):3660–3670. https://doi.org/10.1200/JCO.21.01728
41. Wagner AJ, Ravi V, Riedel RF et al (2024) Phase II trial of. J Clin Oncol. 42(13):1472–1476. https://doi.org/10.1200/JCO.23.02266
42. De Dominicis G, Boscaino A, Marsilia GM, D'Antonio A, Nappi O (2009) Clear cell "sugar" tumors of urethra: a previously undescribed occurrence and review of published data. Urology 74(3):542–543. https://doi.org/10.1016/j.urology.2009.04.056
43. Lane TM, Masood J, Shah N, Koye B, Hill J (2004) Angiomyolipoma of the testis. J Urol 171(2 Pt 1):794. https://doi.org/10.1097/01.ju.0000107361.95413.a4
44. Pan CC, Yang AH, Chiang H (2003) Malignant perivascular epithelioid cell tumor involving the prostate. Arch Pathol Lab Med 127(2):E96–E98. https://doi.org/10.5858/2003-127-e96-MPECTI
45. Saito M, Yuasa T, Nanjo H, Tsuchiya N, Satoh S, Habuchi T (2008) A case of testicular angiomyolipoma. Int J Urol 15(2):185–187. https://doi.org/10.1111/j.1442-2042.2007.01955.x
46. Zhang H, Wang S, Meng L (2023) Primary Xp11 translocation PEComa of the testis with SFPQ-TFE3 rearrangement: a case report and review of the literature. Diagn Pathol 18(1):6. https://doi.org/10.1186/s13000-023-01288-x
47. Feng R, Tao Y, Zhang T et al (2023) Clinicopathological features of primary malignant perivascular epithelioid cell tumors of ureter: histologic-radiologic correlation. Ann Diagn Pathol 67:152200. https://doi.org/10.1016/j.anndiagpath.2023.152200
48. Liu M, Liang P, Lyu D, Zhu B, Gao J (2024) Case report: urachal perivascular epithelioid cell tumor. Front Oncol 14:1324193. https://doi.org/10.3389/fonc.2024.1324193
49. Chen XF, Yeong J, Chang KTE, Lim AST, Kuick CH, Lim TH, Sudhanshi J, Selvarajan S, Gan VHL, Khor LY (2018) TFE3-expressing epithelioid rich perivascular epithelioid cell neoplasm (PEComa) of the bladder with unusual benign course. Ann Clin Lab Sci 48(1):110–115
50. Wu YL, Lang L, Ma Q, Wu F, Zhang Y, Chen W, Yan XC, Duan GJ (2021) Perivascular epithelioid cell tumor of urinary bladder. Am J Clin Pathol 156(1):56–71. https://doi.org/10.1093/ajcp/aqaa204

Authors and Affiliations

Ankur R. Sangoi[1] · Anandi Lobo[2] · Ankit Tiwari[3] · Mahmut Akgul[4] · Shivani Kandukuri[5] · Andres M. Acosta[6] · Khaleel I. Al-Obaidy[7] · Shilpy Jha[8] · Seema Kaushal[9] · Swati Satturwar[10] · Jasreman Dhillon[11] · Adeboye O. Osunkoya[12] · Sean R. Williamson[13] · Dinesh Pradhan[14] · Rajal B. Shah[15] · Anil V. Parwani[10] · Liang Cheng[16] · Arndt Hartmann[17] · Sambit K. Mohanty[18] · Abbas Agaimy[17]

✉ Ankur R. Sangoi
asangoi2@yahoo.com

✉ Abbas Agaimy
Abbas.Agaimy@uk-erlangen.de

1 Stanford Medical Center, Stanford Health Care, 300 Pasteur Drive, Stanford, CA 94305, USA

2 Kapoor Center of Urology and Pathology, Raipur, India

3 Cold Spring Harbor Laboratory, Laurel Hollow, NY, USA

4 Brigham and Women's Hospital, Boston, USA

5 University of California Irvine, Irvine, USA

6 Indiana University Health, Indianapolis, USA

7 McLaren Pathology, McLaren Healthcare, Flint, MI, USA

8 Manipal Hospitals, Bhubaneswar, India

9 All India Institute of Medical Sciences, New Delhi, India

10 The Ohio State University Wexner Medical Center, Columbus, USA

11 H. Lee Moffitt Cancer Center & Research Institute, Tampa, USA

12 Emory University School of Medicine, Atlanta, USA

13 Cleveland Clinic, Cleveland, USA

14 University of Nebraska Medical Center, Omaha, USA

15 UT Southwestern Medical Center, Dallas, USA

16 Alpert Medical School of Brown University, Providence, USA

17 Institute of Pathology, University Hospital, Erlangen, Germany

18 CORE Diagnostics, Gurgoan, India