Histopathology

Histopathology 2025 DOI: 10.1111/his.15482

Assessment and classification of sex cord-stromal tumours of the testis: recommendations from the testicular sex cord-stromal tumour (TESST) group, an Expert Panel of the Genitourinary Pathology Society (GUPS) and International Society of Urological Pathology (ISUP)

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Date of submission 23 December 2024
Accepted for publication 27 May 2025

Acosta A M, Colecchia M, Comperat E, Cornejo K M, Gill A J, Gupta S, Cheville J C, Idrees M T, Kao C-S, Maclean F, Matoso A, Raspollini M R, Michalova K, Mugica M R, Tickoo S K, Tsuzuki T, Ulbright T M, Williamson S R, Siegmund S, Sholl L M, Gonzalez-Peramato P & Berney D M (2025) *Histopathology*. https://doi.org/10.1111/his.15482

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Aims: Testicular sex cord-stromal tumours (TSCSTs) are relatively rare, accounting for ~5% of all testicular neoplasms. They were historically classified into Leydig cell tumour, Sertoli cell tumour, granulosa cell tumour, and unclassified sex cord-stromal tumour. More recently, classification was expanded to incorporate additional histologic types, including some associated with inherited cancer predisposition syndromes. However, the classification of TSCSTs still relies entirely on morphology, with some tumour

types being defined based on their resemblance to ovarian counterparts. In recent years, molecular studies have identified drivers and genomic alterations associated with aggressive behaviour and progression; however, these findings have not yet impacted classification and management.

Methods and results: Under sponsorship of the International Society of Urological Pathology (ISUP) and the Genitourinary Pathology Society (GUPS), a group of genitourinary pathologists was assembled in 2023 with the aim of assessing how to use these new data to improve the classification and management of TSCSTs.

Conclusions: This paper summarizes the recommendations derived from the consensus activities and the first meeting of the *te*sticular *s*ex cord-stromal *t*umour (TESST) group (held at Johns Hopkins Hospital, Baltimore, USA, 3/23/2024).

Keywords: granulosa cell tumour, Leydig cell tumour, myoid gonadal stromal tumour, Sertoli cell tumour, sex cord-stromal tumour, testis

Introduction

Testicular sex cord-stromal tumours (TSCSTs) are rare, accounting for ~5% of all testicular neoplasms overall, with slight overrepresentation in pre-pubertal children.[1,2] They comprise a wide spectrum of entities that show differentiation towards cell types of the stroma and sex cord derivatives of the testis (Sertoli and Leydig cells) and ovary (granulosa cells, ovarian stromal cells), as well as others with phenotypes that are difficult to match to non-neoplastic counterparts (e.g. myoid gonadal stromal tumour, unclassified TSCST).

Currently, TSCSTs are classified based on morphology, with several tumour types being defined by their similarity to ovarian sex cord-stromal tumours. Approximately 90% of TSCSTs are clinically indolent and therefore cured by radical or testis-sparing orchiectomy, whereas the remaining 10% show metastatic potential and behave aggressively.[3–5] Aggressive TSCST are problematic for two main reasons. Firstly, the correlation between morphology and malignant potential is imperfect, and the prognostic value of adverse pathologic findings is partly dependent on tumour type; for instance, brisk mitotic activity is a predictor of aggressive potential in Leydig and Sertoli cell tumours, but not in juvenile granulosa cell tumour. Hence, malignant behaviour can be difficult to predict in a subset of primary TSCSTs. Secondly, they are almost universally resistant to systemic treatment, with complete surgical resection being the only potentially curative option for patients with clinically malignant neoplasms.[6–8]

In recent years, molecular studies have expanded our understanding of the mechanisms that underlie oncogenesis and tumour progression in TSCSTs. Moreover, meta-analyses and clinicopathologic studies have identified features that may be useful to predict malignant potential. These data provide a promising means to improve classification, risk assessment, and, ultimately, clinical management of these challenging neoplasms. However, these advances have not yet impacted TSCST classification, and there is limited awareness about them among clinical and pathology communities.

In 2023, a group of genitourinary pathologists with interest and expertise in TSCSTs (testicular sex cord-stromal tumour [TESST] group) was formed with the objective of assessing how to use this newly generated evidence to improve pathologic assessment and classification of these tumours. This initiative, which was jointly endorsed by the International Society of Urological Pathology (ISUP) and the Genitourinary Pathology Society (GUPS), included multiple activities aimed at assessing diagnostic reproducibility, agreement on classification, and optimal practices for the workup of TSCSTs based on the best available evidence. This paper summarizes the results of the consensus activities of the TESST group.

Materials and methods

The TESST group consisted of genitourinary pathologists with interest in and experience with TSCSTs

Abbreviations: FH, Fumarate hydratase; FISH, Fluorescence in-situ hybridization; IHC, immunohistochemistry; NOS, Not otherwise specified; TESST, Testicular sex cord stromal tumor expert group; TSCST, Testicular sex cord stromal tumor.

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(n = 20), a molecular pathologist expert advisor (LMS), and a rapporteur with expertise in genitourinary and molecular pathology (SS). Pre-meeting questionnaires were completed and analyzed before a live meeting held at Johns Hopkins Hospital in Baltimore (3/23/2024). At the live meeting, votes were cast by the group of genitourinary pathologists (AMA, MC, EC, KMC, AG, SG, JCC, MTI, C-SK, FM, AM, MRR, KM, MRM, SKT, TT, TMU, SRW, PG-P and DMB) to resolve issues that could not be properly resolved or addressed with the pre-meeting questionnaires. Two ISUP representatives (Glen Kristiansen and Kenneth Iczkowski) and two GUPS representatives (Rajal Shah and Rohit Mehra) were also present in the live hybrid in-person/virtual meeting as non-voting observers.

Consensus was assessed using a modified Delphi method as described elsewhere.[9] Briefly, three successive questionnaires were distributed, providing feedback on the results and a summary of the supporting evidence between each subsequent round. The initial questionnaire was created as a Google document that could be answered anonymously. However, anonymity was not maintained throughout the process because later questionnaires were submitted via email, and the last voting session was held live during the hybrid in-person/virtual meeting. Live voting was accomplished by raising hands (for in-person attendees) or using the chat of the online meeting platform. The total number of individual interpretable answers (instead of the number of participants) was used as a denominator; hence, participants who abstained from voting/answering were excluded from the denominator. A level of agreement of 70% was pre-defined as the threshold for consensus.

The recommendations presented in the results section represent a selected summary of the results of the two pre-meeting questionnaires/surveys and the live voting session.

Results

The first pre-meeting survey had 18 respondents (the first and last author of the paper excluded themselves from the voting); the second survey had 20 respondents, and the live voting session had 15 respondents. A summary of the most relevant recommendations based on the results of these activities is provided below. The questionnaires are provided as S1. A summary of the recommendations is provided in Tables 1 and 2.

RECOMMENDATIONS ON BEST PRACTICES FOR CLASSIFICATION OF TSCSTS

Leydig cell tumours/TSCSTs with underlying FH deficiency should be classified/diagnosed as 'FH-deficient Leydig cell tumour' (consensus: 14/18, 78%).

Rationale: Among TSCSTs, FH deficiency has been documented primarily in Leydig cell tumour. However, it has been noted that, in addition to neoplastic Leydig cells, some FH-deficient TSCSTs contain elements with a phenotype suggestive of sex cord differentiation.[10,11] Adding the descriptor 'FH-deficient' to the name of these tumours highlights their underlying genomic alteration, which is important for three reasons.[11] Firstly, although well-described in the literature, the association between Leydig cell tumour/TSCST and FH deficiency is not widely known.[10,12] Secondly, the presence of FH deficiency has been associated with adverse pathologic findings and aggressive clinical behaviour in Leydig cell tumour.[12] Finally, in theory, Leydig cell tumours may represent the first manifestation of a tumour predisposition syndrome caused by germline FH alterations, requiring further genetic workup.[10]

Among TSCST without nuclear beta-catenin expression, the diagnosis of Sertoli cell tumour not otherwise specified (NOS) should be restricted to neoplasms that demonstrate apparent tubular/corded architecture, with expression of markers of sex cord differentiation (e.g. WT1, SOX9) being a desirable additional feature (consensus: 18/20, 90%).

Rationale: Molecular studies have demonstrated that genomic alterations resulting in beta-catenin activation (gain-of-function *CTNNB1* variants or, rarely, loss-of-function *APC* variants) are consistently identified in clinically benign Sertoli cell tumours NOS.[12,13] This correlates with a high frequency (>90%) of diffuse nuclear beta-catenin expression in such cases.[14] Although the group acknowledges that there are rare indolent Sertoli cell tumours NOS without nuclear beta-catenin expression, the consensus opinion is that, in such a scenario, the diagnosis should be reserved for tumours with prototypical morphology.

A diagnosis of Sertoli cell tumour NOS can be favoured in primary indolent TSCSTs with unusual (e.g. microcystic/reticular, solid nested) growth patterns and diffuse nuclear beta-catenin expression (consensus: 14/15, 93%).

Rationale: Although Sertoli cell tumours NOS are characterized by the presence of tubules and/or cords, areas with different growth patterns are often identified within individual neoplasms.[3] Rarely, some neoplasms may lack overt tubular or corded architecture.

Table 1. Recommendations for classification of TSCSTs

Recommendation	Justification
(1) Leydig cell tumours/TSCSTs with underlying FH deficiency should be classified/diagnosed as 'FH-deficient Leydig cell tumour' or 'FH-deficient TSCST'	The addition of this descriptor ('FH-deficient') highlights the presence of a distinct alteration that has been associated with aggressive behaviour and may require assessment of the germline status
(2) Among indolent TSCST without nuclear beta-catenin expression, the diagnosis of Sertoli cell tumour NOS should be restricted to neoplasms that demonstrate apparent tubular/corded architecture, with expression of markers of sex cord differentiation (e.g. WT1, SOX9) being a desirable additional feature	*CTNNB1* or *APC* mutations resulting in activation of Wnt signalling and nuclear beta-catenin expression are seen in >90% of clinically and pathologically indolent Sertoli cell tumours
(3) A diagnosis of Sertoli cell tumour NOS can be favoured in primary indolent TSCSTs with unusual (e.g. microcystic/reticular, solid nests) growth patterns and diffuse nuclear beta-catenin expression	Limited data suggest that these cases represent morphologic outliers
(4) Histologically aggressive and/or clinically malignant undifferentiated TSCSTs with diffuse nuclear beta-catenin expression can be considered 'undifferentiated Sertoli cell tumour NOS'	A subset of clinically and/or pathologically aggressive TSCSTs show clonal *CTNNB1* mutations with additional genomic alterations (such as chromosomal aneuploidies), suggesting that they arise as a consequence of biologic progression of Sertoli cell tumour NOS
(5) Sclerosing Sertoli cell tumour, Sertoli-stromal cell tumour and signet ring stromal tumour should be considered histologic patterns of Sertoli cell tumour NOS	These neoplasms show biologic and molecular features indistinguishable from those of Sertoli cell tumour NOS
(6) TSCSTs with *EWSR1::ATF1* should be considered a distinct entity (inflammatory and nested testicular sex cord tumour)	These tumours show unique clinicopathologic and molecular features that justify their consideration as a distinct entity
(7) A diagnostic category of 'gonadal stromal tumour' should be adopted to encompass testicular stromal neoplasms with pure spindle cell morphology	This category would encompass fibromas/thecomas and myoid gonadal stromal tumours, whose distinction can be sometimes difficult and not necessarily relevant for clinical management
(8) Juvenile-type granulosa cell tumour of the testis should be re-classified as 'benign juvenile-type granulosa cell tumour'	This designation highlights their benign nature (an important difference with ovarian counterparts, which can behave aggressively) to avoid overtreatment
(9) A diagnosis of testicular adult-type granulosa cell tumour should be made only rarely, in neoplasms showing prototypical morphology (akin to ovarian counterparts). *FOXL2* p.C134W could be assessed to support the diagnosis, if available	Limited data suggests that this diagnostic category may have been used as a diagnosis of exclusion for tumours that cannot be categorized into one of the well-recognized TSCST subtypes. In the ovary, >95% of adult-type granulosa cell tumours are driven by *FOXL2* p.C134W
(10) 'Mixed sex cord-stromal tumours' should be kept a category that encompasses testicular tumours with sex cord and stromal neoplastic components not classifiable into other specific subtypes	Combining these tumours with monophasic unclassified sex cord-stromal tumour may result in a high degree of heterogeneity within the category
(11) Testicular Sertoli-Leydig cell tumour should be considered a distinct, albeit exceedingly rare, entity	Rare testicular sex cord-stromal tumour with known or presumed underlying *DICER1* alterations have been documented, including a case with Sertoli-Leydig phenotype

NOS, not otherwise specified, TSCST, testicular sex cord-stromal tumour.

Genomic methylation analyses of a small number of such neoplasms with diffuse nuclear beta-catenin expression (>90% of tumour cell nuclei) demonstrated marked similarities to typical Sertoli cell tumour NOS, suggesting that they represent morphologic outliers of this entity (Figure 1).[15]

Histologically aggressive and/or clinically malignant poorly differentiated TSCSTs with diffuse nuclear beta-catenin expression can be considered 'poorly differentiated Sertoli cell tumour NOS' (consensus: 13/14, 93%).

Rationale: Genomic assessment of Sertoli cell tumour NOS has shown that a subset of clinically malignant TSCSTs with sex cord phenotype (including expression of 'sex cord-stromal tumour markers') harbour gain-of-function *CTNNB1* variants.[12,13,15]

Table 2. Recommendations for workup of TSCSTs

(1) IHC should be performed on most TSCSTs, especially by pathologists who do not have significant expertise with these neoplasms	TSCSTs are uncommon and, therefore, difficult to diagnose by pathologist who see them only rarely
(2) Subclassification of TSCSTs is important for clinical management and therefore desirable	Risk of malignancy is in part dependent on histologic subtype. Some subtypes are associated with germline alterations/ syndromes
(3) Assignation of risk of recurrence or metastasis is at least in part dependent on the histologic subtype	Some TSCSTs types are invariably benign, whereas others include a subset of cases with aggressive behaviour or are almost invariably aggressive ('inflammatory and nested testicular sex cord tumour')
(4) In the absence of metastatic disease, TSCSTs affecting post-pubertal patients should be classified as of 'low risk' or 'high risk' of malignant behaviour rather than as 'malignant' or 'benign'	The correlation between clinicopathologic findings and clinical behaviour is imperfect. The only definite indicator of clinically malignant disease in sex cord-stromal tumours is the presence of metastases (exception: 'inflammatory and nested testicular sex cord tumour')
(5) The size threshold that is considered a 'risk factor' should be specific for each tumour type	Different size cut-offs have been proposed for different histologic subtypes in the literature
(6) Age should be considered a potential risk factor for malignant behaviour in TSCSTs that show worrisome histopathologic findings	The overwhelming majority of malignant TSCSTs occur in post-pubertal patients, mostly in adult patients (>3rd–4th decade)
(7) The pathologic Tumour Node and Metastasis (pTNM) system used to stage germ cell tumours should not be used for TSCSTs	Most TSCSTs are clinically indolent (never metastasize). Some of the parameters that determine stage in the pTNM cannot be easily extrapolated to TSCSTs
(8) Fumarate Hydratase (FH) and MDM2 IHC [or *MDM2* fluorescence in-situ hybridization (FISH)] is recommended/desirable in primary Leydig cell tumours with worrisome histopathologic findings to assess risk of malignant clinical behaviour	FH deficiency and *MDM2* amplification have been identified in subsets of pathologically and clinically aggressive Leydig cell tumours
(9) FH immunohistochemistry is desirable in all metastasizing Leydig cell tumours	Although not relevant for treatment, FH deficiency in clinically malignant Leydig cell tumours may indicate the need for genetic counselling/germline testing
(10) TSCSTs with nested architecture and inflammatory infiltrates ('resembling seminoma') should be assessed for *EWSR1* rearrangements or *EWSR1::ATF1*	These neoplasms are typically driven by *EWSR1::ATF1*
(11) Molecular assessment of multifocal or bilateral Sertoli cell tumour NOS is desirable, and genetic counselling of these patients could be considered	Rare Sertoli cell tumours NOS are driven by biallelic inactivation of *APC* in the context of a germline variant
(12) Loss of PRKAR1A expression demonstrated by IHC or detection of pathogenic *PRKAR1A* variants by DNA sequencing are desirable (albeit not necessary) to support a diagnosis of large cell calcifying Sertoli cell tumour	These alterations are found at very high frequency (>90%) in large cell calcifying Sertoli cell tumour, but not in other subtypes.

IHC, immunohistochemistry, NOS, not otherwise specified, TSCST, testicular sex cord-stromal tumour.

Unlike clinically benign tumours, these show additional genomic alterations likely associated with progression, such as multiple chromosomal aneuploidies, amplification of oncogenes and homozygous deletion of tumour suppressors.[12,15] These malignant neoplasms display aggressive histopathologic features and may lack overt tubular or corded architecture.[15] In these neoplasms, the loss of prototypical morphologic findings is probably due to biological progression and, therefore, they likely represent poorly differentiated examples of Sertoli cell tumour NOS.

Sclerosing Sertoli cell tumour and signet ring stromal tumour should be considered histologic patterns of Sertoli cell tumour NOS (consensus for sclerosing Sertoli cell tumour: 19/20, 95%; consensus for signet ring stromal tumour: 18/20, 90%).

Rationale: Sertoli cell tumours NOS may contain foci with hyalinized/sclerotic stroma and neoplastic

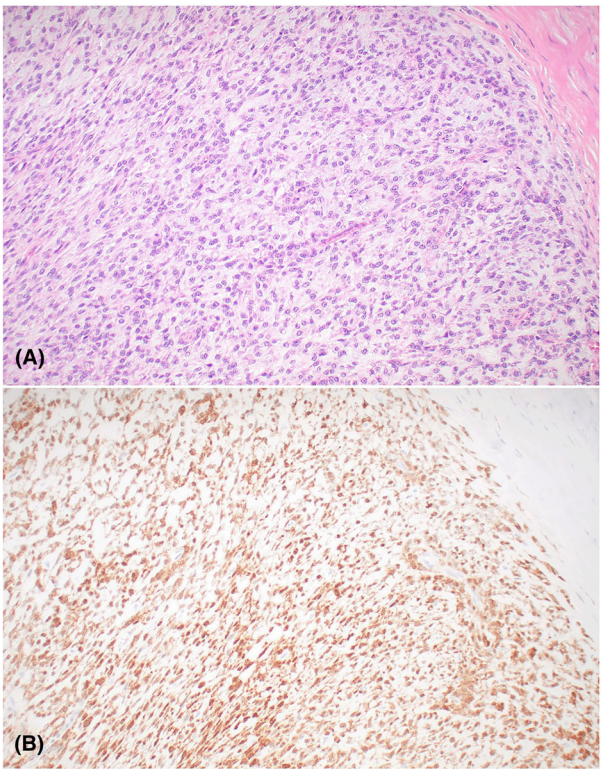

Figure 1. Testicular sex cord-stromal tumour without overt tubular or corded architecture (**A**). This tumour shows nuclear beta-catenin expression (**B**). Recent data suggest that these neoplasms may represent morphologic outliers of Sertoli cell tumour not otherwise specified.

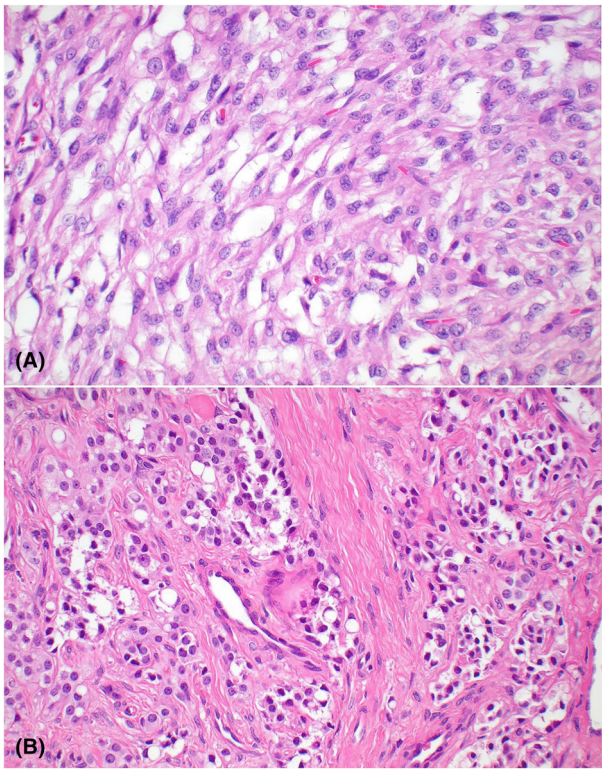

Figure 2. Areas with subtle spindle cell morphology (**A**) and univacuolated ('signet ring'-like) cells (**B**) in otherwise typical Sertoli cell tumour not otherwise specified.

cells with vacuolated cytoplasm (signet ring) or spindled morphology (Figure 2).[3] Tumours in which these features become dominant or exclusive have been described in the literature as sclerosing Sertoli cell tumour, signet ring cell stromal tumour, and Sertoli-stromal cell tumour.[16–20] Nuclear beta-catenin expression and underlying *CTNNB1* mutations are identified in most of these neoplasms, at a frequency similar to that of Sertoli cell tumour NOS in sclerosing Sertoli cell tumour and signet ring cell stromal tumour, and at a somewhat lower frequency in Sertoli-stromal cell tumour.[17,19–22] Currently, there is insufficient evidence to support that these neoplasms represent distinct entities, with the available data suggesting that they are most likely morphologic variations of Sertoli cell tumour NOS. Therefore, the group recommends that they be considered patterns of Sertoli cell tumour NOS. Of note, biphasic neoplasms containing sex cord (i.e. Sertoli cell) and stromal (i.e. spindle cell) components are probably best considered mixed sex cord-stromal tumors.[20,22]

Testicular sex cord tumours with nested architecture and mixed inflammatory infiltrates (ideally with demonstrable *EWSR1::ATF1* or *EWSR1* rearrangements) should be considered a distinct entity: inflammatory and nested testicular sex cord tumour (consensus 15/18, 83%).

Rationale: More than 20 years ago, Henley *et al.* described a subset of clinically malignant Sertoli cell tumours with solid architecture and inflammatory infiltrates that contained abundant lymphocytes, mimicking seminoma.[23] In fact, a substantial subset of these cases was originally received in consultation with a diagnosis of seminoma. However, unlike seminoma, these neoplasms lack expression of germ cell tumour markers and express sex cord markers instead.[23] They typically show solid nested architecture, including small and intermediate-sized nests (Figure 3), some of which exhibit internal discohesion resulting in 'pseudo-papillary' or 'pseudo-tubular' morphology.[23–25] Variably prominent mixed inflammatory infiltrates, including abundant lymphocytes and plasma cells, are typically present.[23–25] These clinically malignant neoplasms were initially thought

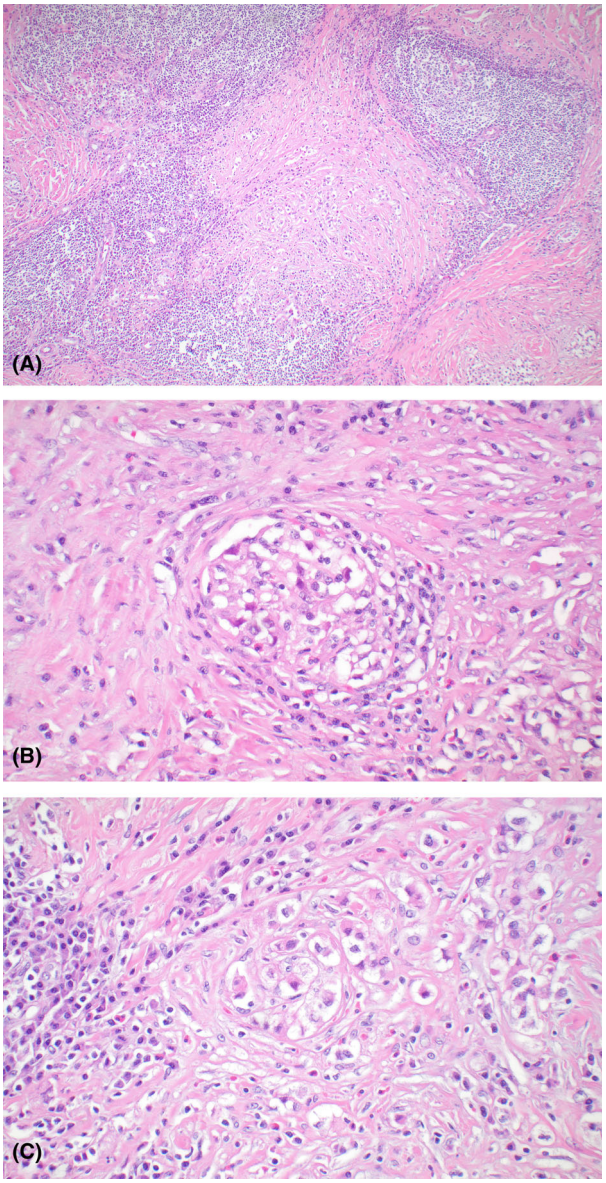

Figure 3. Inflammatory and nested testicular sex cord tumour with prominent inflammatory infiltrates appreciated at low magnification (**A**). Micrographs at higher magnification highlight nests of epithelioid neoplastic cells with eosinophilic to clear vacuolated cytoplasm (**B**, **C**).

to represent a morphologic variant of Sertoli cell tumour NOS. Recent molecular analyses have demonstrated that most of them harbour *EWSR1::ATF1* or *EWSR1* rearrangements and lack nuclear beta-catenin by IHC.[24,25] Given their unique clinical, histopathologic, and molecular features, the group recommends that they be considered a distinct entity: inflammatory and nested testicular sex cord tumour. Unlike Sertoli cell tumour NOS, these neoplasms seem to be invariably aggressive (i.e. clinically malignant), metastasizing to retroperitoneal lymph nodes, viscera, and bone. The group also recommends that TSCSTs (either primary or metastatic) with nested architecture and inflammatory infiltrates be tested for *EWSR1::ATF1* (RNA sequencing or fluorescence in-situ hybridization) or *EWSR1* rearrangements (fluorescence in-situ hybridization), if these studies are available. However, we believe that this diagnosis can still be rendered or favoured in the absence of ancillary molecular studies based on the unique morphologic and immunophenotypic features of this entity, which include a nested architecture, a dense and often hyalinized collagenous stroma, mixed inflammatory infiltrates, and a unique immunoprofile characterized by co-expression of inhibin, SF1, EMA and CD30 (~80%), with absence of nuclear positivity for beta-catenin.

A diagnostic category of 'gonadal stromal tumour' should be adopted to encompass testicular stromal neoplasms with pure spindle cell morphology (consensus: 16/20, 80%). Diagnostic reports of these tumours (including those that can be classified as myoid gonadal stromal tumour and fibroma/thecoma) should include a comment that, according to the cases documented in the literature, they can be considered clinically indolent.

Rationale: Currently, pure spindle cell neoplasms of purported testicular stromal origin comprise tumours classified mostly as myoid gonadal stromal tumour, fibroma/thecoma, and sex cord-stromal tumour NOS.[15,26–28] Myoid gonadal stromal tumour is a pure spindle cell neoplasm thought to originate in peritubular myoid cells which, by definition, co-expresses actin and S100 protein.[26,27] Fibromas/thecomas are defined based on their resemblance to ovarian counterparts and are often associated with/attached to the tunica albuginea.[28] Of note, actin and S100 protein lack specificity and can be expressed by multiple TSCST types. The genomes of testicular neoplasms with pure or predominant spindle cell morphology exhibit recurrent widespread chromosome level or chromosome-arm level copy number gains, but specific alterations that can distinguish between the different types have not been found yet.[15,22,29,30] Importantly, these neoplasms appear to be invariably benign, with no malignant example reported to date, to the best of our knowledge. Considering the clinicopathologic and molecular overlap that exists between these tumour types, their distinction is often subjective and may lead to excessive and futile workups. Consequently, the group recommends that an umbrella 'gonadal stromal tumour' category be

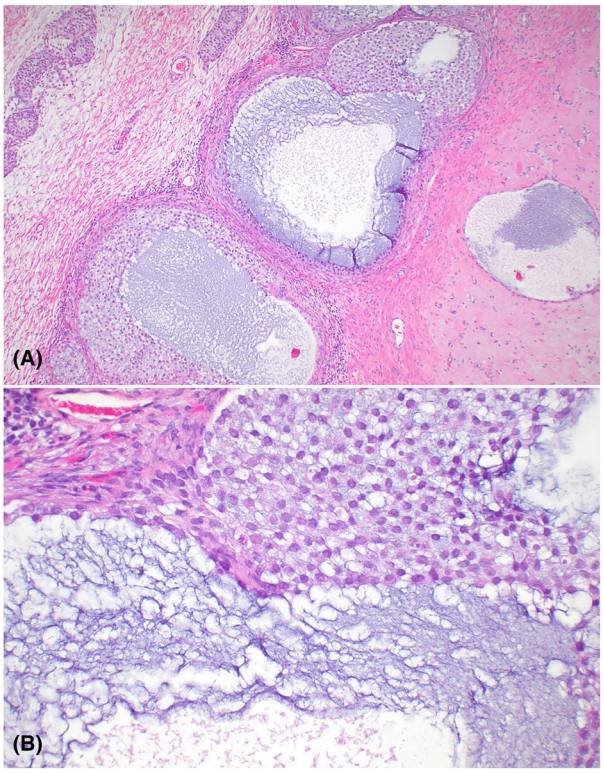

Figure 4. Juvenile granulosa cell tumour of the testis. This tumour shows striking morphologic resemblance to ovarian counterparts, with microfollicles containing thin basophilic mucinous secretion, separated by prominent fibrous septae (**A**). Tumour cells are small, with an ovoid to stellate shape, and have small irregular nuclei, often lacking noticeable nucleoli (**B**).

implemented to encompass pure spindle cell stromal tumours of the testis currently classified as different entities. This category can be used as a diagnosis ('gonadal stromal tumour NOS') when a definite/objective distinction between specific types is not feasible.

Juvenile granulosa cell tumour of the testis should be renamed 'benign juvenile granulosa cell tumour' (consensus on the need to rename: 12/15, 80%; consensus on the name 'benign juvenile granulosa cell tumor': 15/15, 100%).

Rationale: Juvenile granulosa cell tumour of the testis was originally defined as such based on its morphologic resemblance to ovarian homonyms (Figure 4).[31] However, testicular and ovarian juvenile granulosa cell tumours show marked clinicopathologic and molecular differences.[31–38] In the ovary, juvenile granulosa cell tumours affect mostly paediatric patients (median age: ~8 years), but a subset may affect post-pubertal children and adults, including cases that present during pregnancy.[32,33,35,36,39] These tumours characteristically produce steroid sex hormones, and a subset of ~10% behaves aggressively, with local recurrences within the abdomen/pelvis or metastases to distant sites.[32,33,35,36] From a genomic perspective, ovarian neoplasms harbour well-known pathogenic alterations including (but not restricted to) internal tandem duplications within the pleckstrin homology domain of *AKT1* and hotspot gain-of-function *GNAS* variants.[34,37] Despite their morphologic similarities to ovarian counterparts, testicular juvenile granulosa cell tumours are a largely infantile entity, with >90% of cases occurring within the first year of life.[31] They are mostly hormonally inactive, and a subset may arise in dysgenetic gonads. Importantly, juvenile granulosa cell tumours of the testis appear to lack malignant potential, and a genomic study of a limited number of cases has shown that they do not harbour the pathogenic alterations identified in the ovarian homonyms.[31,38,40]

In light of the important differences between ovarian and testicular juvenile granulosa cell tumours, we believe that the current terminology can be confusing for treating clinicians. More specifically, by considering testicular juvenile granulosa cell tumors analogous to ovarian counterparts, they may interpret that they have malignant potential, resulting in unnecessary workups or overtreatment. Therefore, the group recommends that these TSCSTs be renamed as 'benign juvenile granulosa cell tumours'. Moreover, adding a comment explaining that these tumours show significant clinical and molecular differences with juvenile granulosa cell tumours of the ovary is encouraged.

A diagnosis of testicular adult granulosa cell tumour should be made only sparingly, in neoplasms showing prototypical morphology. Additionally, the demonstration of *FOXL2* p.C134W, albeit not necessary, can be used to support this diagnosis (consensus: 16/20, 80%).

Rationale: Adult granulosa cell tumours of the testis were originally defined based on their resemblance to ovarian counterparts. Studies have shown that the morphologic spectrum of neoplasms classified as adult granulosa cell tumour is wide, making this a heterogeneous category.[41] *FOXL2* p.C134W, the hotspot mutation seen in the overwhelming majority of adult granulosa cell tumours of the ovary (>90–95% in most series), is only present in a relatively small subset of testicular homonyms. Tumours classified as adult granulosa cell tumours in the testis show marked genomic heterogeneity.[42–46] Hence, the morphologic and molecular diversity of testicular adult granulosa cell tumours suggests that this category

has been used as a 'diagnosis of exclusion' for TSCSTs that cannot be easily recognized as one of the other well-defined entities. Although adult granulosa cell tumours analogous to those arising in the ovary do exist in the testis, they seem to be exceedingly rare. Therefore, the group recommends using this diagnosis only for neoplasms with prototypical morphologic features (i.e. akin to those seen in the ovary). Additionally, detection of *FOXL2* p.C134W could be considered to support the diagnosis, if available.

'Mixed sex cord-stromal tumours' should be kept a category that encompasses testicular tumours with sex cord and stromal components not classifiable into other specific types (consensus: 14/14, 100%).

Rationale: The latest WHO classification includes a category of 'mixed sex cord-stromal tumours' for mixed neoplasms that cannot be classified into one of the other specific types.[47] This category is separate from 'unclassified sex cord-stromal tumours' (which do not contain a mixture of sex cord and stromal components), but the degree of morphologic, clinical and molecular overlap between these groups remains uncertain. Therefore, it was proposed that combining both categories into a single one designated 'unclassified sex cord-stromal tumour' or 'sex cord-stromal-tumour NOS' could be reasonable. However, it is the opinion of the group that both categories should be kept separate until more data is generated to avoid creating excessive internal heterogeneity within a single catergory.

Testicular Sertoli-Leydig cell tumour should be considered a distinct, albeit exceedingly rare, entity (consenus: 15/15, 100%).

Rationale: In the ovary, Sertoli-Leydig cell tumours are characteristically associated with mutations in the RNAse IIIb domain of *DICER1*.[48,49] By contrast, in the testis, most testicular tumours with combinations of Sertoli and Leydig cell components are thought to represent Sertoli cell tumours NOS with entrapped non-neoplastic Leydig cells, especially if they harbour *CTNNB1* mutations or exhibit nuclear beta-catenin expression restricted to Sertoli cells.[15] Both Sertoli cell tumour NOS and Leydig cell tumour have been reported in children with *DICER1* syndrome.[50] Moreover, a TSCST with Sertoli and Leydig cell neoplastic components, including cells with 'intermediate' phenotype, closely resembling ovarian counterparts and harbouring a hotspot RNAse IIIb *DICER1* mutation, has been recently documented.[22] Considering the limited existing evidence, the group believes that testicular Sertoli-Leydig cell tumour, albeit exceedingly rare, does exist. This diagnosis requires exclusion of Sertoli cell tumour NOS with entrapped non-neoplastic Leydig cells by demonstrating absence of *CTNNB1* mutations and/or nuclear beta-catenin expression in the Sertoli cell component and, ideally, demonstration of *DICER1* alterations.

RECOMMENDATIONS ON BEST PRACTICES FOR CLINICOPATHOLOGIC AND MOLECULAR ASSESSMENT OF TSCSTS

Immunohistochemistry (IHC) should be performed on most TSCSTs, especially by pathologists who do not have significant experience with these neoplasms (consensus: 16/20; 80%).

Rationale: TSCSTs are rare, and most pathologists see a limited number of cases yearly. Moreover, there is significant morphological overlap between TSCST types (e.g. between large cell calcifying Sertoli cell tumour and Leydig cell tumour), as well as between TSCSTs and germ cell tumours, soft tissue neoplasms, and metastatic carcinoma. In this scenario, IHC is often useful to support a diagnosis of TSCST and, in some instances, may aid in classification. A minimal workup to determine sex cord-stromal differentiation is suggested, with additional stains tailored to the differential diagnoses being considered and the recommendations for each TSCST type (see below). Overall, the most sensitive markers to establish sex cord-stromal differentiation are SF1 and inhibin, although the latter demonstrates limited sensitivity for Sertoli cell tumours.[51] SOX9, FOXL2, calretinin and WT1 may also be circumstantially helpful. Performing at least two markers of sex cord-stromal differentiation, in addition to those catered to entities included in the differential diagnosis, represents a reasonable approach (Table 3). Please see below for recommendations on FH/MDM2, beta-catenin, and PRKAR1A immunohistochemistry in Leydig cell tumour, Sertoli cell tumour NOS, and large cell calcifying Sertoli cell tumour, respectively.

Classification of TSCSTs is important for clinical management and therefore desirable (consensus: 18/20, 90%).

Rationale: Although not always achievable, classification can be helpful to guide clinical management because clinical behaviour is in part correlated with the histologic type. For instance, sex cord-stromal tumours with underlying *EWSR1::ATF1* fusions appear to be invariably aggressive, whereas only 10% of Sertoli cell tumours are clinically malignant, and myoid gonadal stromal tumour, fibromas, and juvenile granulosa cell tumours are invariably indolent.[3,24,26,27,31] Additionally, histologic types such as large cell calcifying Sertoli cell tumour and

Table 3. Immunophenotypic features of the most common TSCST types

Immunohistochemistry	Leydig cell tumour	Sertoli cell tumour NOS	LCCSCT	INTSCT
Diagnostically useful typically positive (≥40%) results	SF1	SF1	SF1	SF1
	Inhibin	SOX9	SOX9	Inhibin
	Calretinin	WT1	Inhibin	EMA
		FOXL2	Calretinin	CD30
		Calretinin	Loss of PRKAR1A expression	
		B-catenin (nuclear, diffuse)		
Diagnostically useful unique IHC features	FH deficiency in a small subset	—	—	—
	MDM2 overexpression in a subset	—	—	—
Diagnostically useful typically negative (<40%) results	WT1	PRKAR1A expression is retained	B-catenin (membranous/ cytoplasmic staining)	B-catenin (membranous/ cytoplasmic staining)
	SOX9			
	FOXL2			
	B-catenin (membranous or focal/ multifocal nuclear, typically in <50% of the cells)			
	Keratin			
	PRKAR1A expression is retained			
Diagnostically useful always negative results	SALL4	SALL4	SALL4	SALL4
	OCT4	OCT4	OCT4	OCT4
	PLAP	PLAP	PLAP	PLAP
	NANOG	NANOG	NANOG	NANOG

IHC, immunohistochemistry, INTSCT, inflammatory and nested testicular sex cord tumour, LCCSCT, large cell calcifying Sertoli cell tumour, NOS, not otherwise specified, TSCST, testicular sex cord-stromal tumour.

intratubular large cell hyalinizing Sertoli cell tumour show an association with inherited cancer predisposition syndromes, sometimes requiring consideration of genetic counselling and/or germline testing in selected patients.[4,52]

Assignation of risk of recurrence or metastasis is at least in part dependent on the histologic type (consensus: 19/20, 95%).

Rationale: Risk of malignant behaviour seems to be correlated with the histologic type. For instance, metastatic disease develops in ~10% of Leydig cell tumour, Sertoli cell tumour NOS and large cell calcifying Sertoli cell tumour, whereas myoid gonadal stromal tumours, juvenile granulosa cell tumour, fibroma/thecoma and intratubular large cell hyalinizing Sertoli cell tumour appear to be invariably indolent.[27,31,53,54] In contrast, documented cases of TSCSTs 'resembling seminoma', most with *EWSR1::ATF1* or *EWSR1* rearrangements and now classified as 'inflammatory and nested testicular sex cord tumor', have shown aggressive clinical behaviour.[24,25]

In the absence of metastatic disease, TSCSTs affecting post-pubertal patients should be classified as having 'low risk' or 'high risk' of malignant behaviour rather than as 'benign' or 'malignant' (consensus: 13/13, 100%).

Rationale: The correlation between the histopathologic characteristics of primary TSCSTs and metastatic potential is incompletely understood. More specifically, there are rare clinically aggressive tumours that lack (or exhibit only 1) aggressive histopathologic features, whereas some TSCSTs with worrisome histopathologic findings do not metastasize.[4,7,31,55,56] As mentioned above, malignant potential is in part dependent on tumour type, with some types such as myoid gonadal stromal tumour, juvenile granulosa cell tumour, testicular 'tumours' of the androgenital syndrome, and fibroma/thecoma being invariably benign, according to published data. On the other end of the spectrum, TSCSTs with *EWSR1::ATF1* seem to be invariably aggressive, regardless of their histological appearance.[24,25] The group recognizes that definitive (i.e. clinically validated) methods to evaluate risk of malignancy in TSCSTs are currently lacking. However, multi-parametric assessment of histopathologic features such as mitotic index, tumour size, tumour necrosis, lymphovascular invasion and infiltrative growth pattern (among others) is recommended, using proposed systems/criteria for each tumour type that have been published in the literature [see references 3, 4, 53, 57 for further details]. Clinicopathologic findings associated with aggressive behaviour have been described for Leydig cell tumour, Sertoli cell tumour NOS, large cell calcifying Sertoli cell tumour, and adult granulosa cell tumour.[3,4,40,41,57] The overall message that the group is trying to convey is that, because many TSCST types such as Leydig and Sertoli cell tumour NOS can behave unpredictably, the only definitive criterion of malignancy is the development of metastases (somewhat like in adrenal cortical neoplasms). Therefore, in the absence of metastatic disease, primary tumours are best considered of low risk or high risk of malignancy based on their morphologic and immunophenotypic/molecular characteristics (when applicable). We acknowledge that some tumours may fall in between low and high risk categories; in such scenario, we suggest that these neoplasms be regarded as of ' uncertain/indeterminate risk of malignancy', likely requiring clinical follow up.

The size threshold that is considered a 'risk factor' should be specific for each tumour type (consensus: 17/20, 85%).

Rationale: Different size cutoffs associated with risk of aggressive clinical behaviour have been proposed for different types of TSCST.[3,4,41,53,54,56,57] However, the optimal cutoffs for each of these entities remain to be defined, underscoring the need for further studies in this area. In general, it seems reasonable to consider that most TSCSTs larger than ~3 cm are worrisome, especially if they show 1 or more additional aggressive histologic features (e.g. high mitotic activity). However, the precise cutoff likely varies slightly between tumour types (e.g. cutoffs of 2.4 and 3–5 cm have been proposed for Leydig and Sertoli cell tumour, respectively), and TSCST with *EWSR1::ATF1*, should be considered malignant regardless of their size.[5,53,54,58]

Age should be considered a potential risk factor for malignant behaviour in TSCSTs that show worrisome histopathologic findings (consensus: 10/14, 70%).

Rationale: Prior studies have shown that the overwhelming majority of metastatic Leydig cell tumours, Sertoli cell tumours NOS, large cell calcifying Sertoli cell tumours, and adult-type granulosa cell tumours affect post-pubertal patients.[4,40,53,54,56] In fact, clinically malignant (i.e. metastatic) Leydig cell tumours have not been previously documented in children, to the best of our knowledge.[53] Moreover, several studies have shown that metastatic TSCSTs tend to affect patients in an older age group, although the specific age threshold seems to vary according to tumour type.[4,40,53,56] In light of these findings, the group believes that age should be considered a potential additional risk factor in tumours that display worrisome histopathologic features. In general, TSCSTs with worrisome histopathologic features affecting patients older than 40 years of age should be considered 'high-risk', with risk likely being higher in middle-aged (4th–5th decade) and elderly men. However, as it is the case for tumour size, the specific age cutoff that represents a risk factor may vary between tumour types and requires further investigation.[53,54] This consideration excludes tumours that are invariably indolent (e.g. myoid gonadal stromal tumour), which affect adult patients or are invariably aggressive (e.g. TSCST with *EWSR1::ATF1*).

The pathologic Tumour Node and Metastasis (pTNM) system used to stage germ cell tumours should not be used for TSCSTs (consensus: 14/15, 93%).

Rationale: Unlike germ cell neoplasia in situ-derived gem cell tumours, which are malignant by definition, most (~90%) TSCSTs are clinically indolent and, therefore, do not require staging. As highlighted above, the risk of malignancy in TSCSTs seems to be correlated in part with the tumour type. Extrapolating the pTNM system used for germ cell tumours to TSCST types with metastatic potential seems inadequate, since there is no evidence to support that the parameters that predict clinical outcomes in germ cell

tumours are also relevant for TSCSTs. For instance, Leydig cell tumours without aggressive histopathologic features and testicular 'tumours' of the androgenital syndrome may arise in the hilum and involve hilar fat; in this context, however, this finding likely does not reflect a high risk of malignancy.[59,60] Similarly, the involvement of the rete testis by myoid gonadal stromal tumour is common and unassociated with aggressive behaviour.[26,27,29] Although the group acknowledges that the pTNM system is suboptimal for TSCSTs, it also recognizes the need to provide clinicians with information that is useful for patient management. For TSCST types with malignant potential, the group recommends the use of descriptive reports that include histologic type, size, disease extent (confined to the testis versus extending into extra-testicular tissues), presence of worrisome/adverse histopathologic findings (partly dependent on tumour type, but typically including at least: number of mitoses per 2 mm^2, necrosis, and lymphovascular invasion), surgical margin status and a comment about the risk of malignant behaviour.

The group recognizes that a systematic reporting system would be beneficial for clinical management. Therefore, once the factors that determine outcomes are better understood, the creation of a TSCST-specific staging system should be considered, at least for the subset of tumours deemed to have malignant potential.

Fumarate Hydratase (FH) and MDM2 IHC [or MDM2 fluorescence in-situ hybridization (FISH)] are recommended/desirable in primary Leydig cell tumours with worrisome histopathologic findings to assess the risk of malignant clinical behaviour (consensus: 20/20, 100%).

Rationale: Rare cases of Leydig cell tumour harbour *FH* variants that lead to functional inactivation of the gene, including some presenting in patients with known germline *FH* alterations (hereditary leiomyomatosis and renal cell carcinoma).[10,61] Recently, it has been shown that FH deficiency is enriched among Leydig cell tumours that exhibit malignant clinical behaviour or aggressive histopathologic features, whereas it appears to be rare among neoplasms that are clinically benign or lack worrisome histopathologic findings.[10,61] Additionally, genomic studies have identified recurrent *MDM2* amplification in up to 30%–50% of clinically malignant (i.e. metastasizing) Leydig cell tumours, and this event has also been detected in at least one primary neoplasm with aggressive histopathologic features.[57,61,62] Protein expression assessed by IHC represents a reasonable surrogate marker of *MDM2* amplification and homozygous inactivation of *FH*, with the caveat that MDM2 antibodies show limited sensitivity for identifying amplifications that are otherwise evident on FISH.[63] Therefore, *MDM2* FISH could be considered if MDM2 IHC is negative, or to confirm a seemingly positive IHC result. Also, immunostaining for S-(2-succino)cysteine (2SC) can be performed to complement FH IHC if the antibody is available in house. Of note, some members of the group have seen FH-deficient primary Leydig cell tumours that lacked aggressive histopathologic features and yet exhibited malignant clinical behaviour, with FH deficiency being demonstrated after the patient developed metastases (Figure 5).

In light of the data mentioned above, overexpression of MDM2, *MDM2* amplification, and loss of FH expression can be considered additional indicators of malignant potential in primary (i.e. testicular) Leydig cell tumours with worrisome histopathologic findings. Such results should be communicated to the

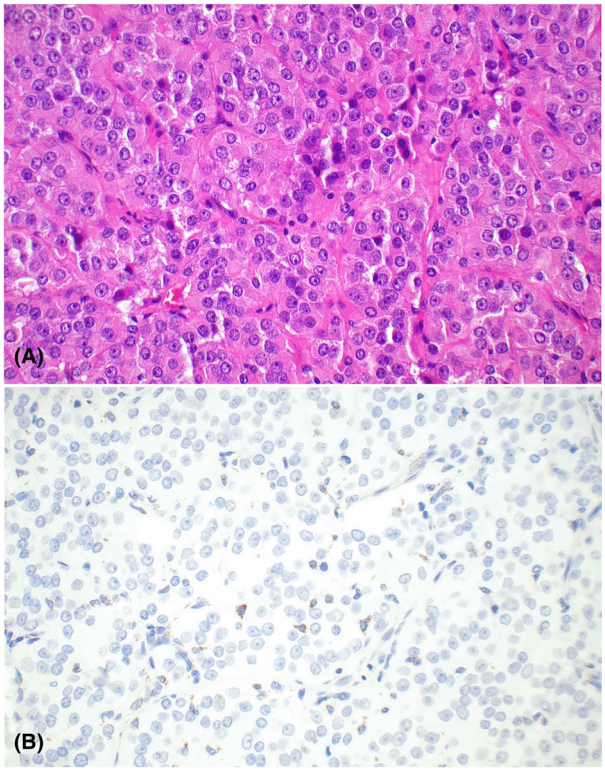

Figure 5. Fumarate hydratase (FH)-deficient Leydig cell tumour (**A**). Immunohistochemistry demonstrates loss of FH expression in tumour cells, with retained expression in infiltrating inflammatory cells (**B**). Of note, the primary tumour did not show aggressive histopathologic features and nonetheless metastasized many years after the original diagnosis (the images correspond to the metastasis). Case courtesy of Dr. Maurizio Colecchia.

clinicians, so that they can discuss options for further management with their patients. Of note, it is currently uncertain to what degree (if any) these IHC/FISH findings represent independent predictors of malignant behaviour.

FH immunohistochemistry is desirable in all metastasizing Leydig cell tumours (consensus: 20/20, 100%).

Rationale: As mentioned above, FH deficiency is enriched among clinically malignant Leydig cell tumours.[61] Additionally, some *FH* variants identified in these neoplasms are of germline origin and associated with hereditary leiomyomatosis and renal cell carcinoma.[10] Although the identification of FH deficiency has no impact on the treatment of clinically malignant Leydig cell tumours, it may raise the possibility of a germline alteration that needs further investigation.

Assessment of *EWSR1* rearrangements or *EWSR1::ATF1* is recommended for TSCSTs with nested architecture and inflammatory infiltrates ('resembling seminoma') (see recommendations on classification of these tumours above).

Rationale: This recommendation is derived from the group's interpretation that these tumours represent a distinct entity with recurrent *EWSR1::ATF1* and/or *EWSR1* rearrangements.

Molecular assessment of multifocal or bilateral Sertoli cell tumour NOS is desirable, and genetic counselling of these patients could be considered (consensus: 15/15, 100%).

Rationale: The overwhelming majority of Sertoli cell tumours NOS are unifocal, unilateral and driven by gain-of-function *CTNNB1* variants.[3,12,13] Rare examples of Sertoli cell tumour NOS have been associated with biallelic inactivation of *APC*, including some occurring in the context of germline *APC* variants and/or a known history of familial adenomatous polyposis.[64,65] A subset of them was associated with the presence of bilateral tumours or multifocal Sertoli cell lesions.[64,65] Hence, the group recommends considering genomic assessment of bilateral or multifocal Sertoli cell tumours NOS when there is no pre-existing diagnosis of familial adenomatous polyposis coli. If *APC* alterations are identified, the possibility of genetic counselling or germline testing should be discussed with the clinician.

Loss of PRKAR1A expression demonstrated by IHC or detection of pathogenic *PRKAR1A* variants by DNA sequencing is desirable (albeit not necessary) to support a diagnosis of large cell calcifying Sertoli cell tumour (consensus: 15/15, 100%).

Rationale: Large cell calcifying Sertoli cell tumour has been associated with the Carney complex in ~20% of patients overall, being overrepresented in young patients with bilateral and/or multifocal tumours.[4,56] Genomic studies have shown that *PRKAR1A* variants are consistently present both in syndromic and sporadic tumours.[66–69] Correspondingly, immunohistochemistry has demonstrated loss of PRKAR1A expression in >90% of large cell calcifying Sertoli cell tumours.[66] Demonstration of loss of PRKAR1A expression (or presence of pathogenic *PRKAR1A* variants) can be useful to distinguish between large cell calcifying Sertoli cell tumour and Leydig cell tumour, especially considering that a subset of the former may lack typical features (abundant calcifications, abundant myxoid stroma) and the latter may occasionally show microscopic calcifications. Given that functional inactivation of *PRKAR1A* seems to be almost invariably present in large cell calcifying Sertoli cell tumour but not in other TSCST types, demonstration of loss of PRKAR1A expression by IHC or the presence of a pathogenic *PRKAR1A* variant by sequencing is desirable to support the diagnosis when these techniques are available.

SELECTED RELEVANT AREAS IN WHICH CONSENSUS WAS NOT REACHED

Although a majority of the TESST members (12/20, 60%) thought that myoid gonadal stromal tumour represents a distinct entity, the pre-defined threshold for consensus was not reached. The current WHO classification of urinary and male genital tumours incorporates myoid gonadal stromal tumour as a specific TSCST type defined by pure spindle cell histology and co-expression of actin and S100.[47] The main problem of such definition is that it relies on non-specific markers that can be expressed by multiple other TSCST types. Moreover, molecular analyses of a limited number of myoid gonadal stromal tumours have failed to identify alterations that distinguish them from other TSCST with prominent spindle cell components.[15,22,29,30]

No agreement was reached on whether primary Leydig cell tumours without worrisome histopathologic features should be assessed with FH immunohistochemistry (in favour: 12/20, 60%). As mentioned above, an example of a clinically malignant FH-deficient Leydig cell tumour without aggressive histopathologic findings has been encountered by members of the group, and no specific mention of adverse pathologic findings was made in the description of

the first two FH-deficient Leydig cell tumours documented in the literature.[10] However, FH deficiency seems to be enriched in pathologically or clinically aggressive tumours, being exceedingly rare in unselected cases. Further investigations are needed to identify features (if any) that may indicate underlying FH deficiency in primary tumours without aggressive histopathologic findings.

Most experts in the group have seen TSCSTs that include a germ cell component; however, there was no consensus on whether the classification of these neoplasms should include a category of mixed germ cell/sex cord-stromal tumour (separate from gonadoblastoma; in favour: 13/20, 65%). Gonadoblastoma is now considered a pre-neoplastic entity in the 5th edition of the WHO classification and is known to contain neoplastic germ cells that can progress to dysgerminoma/seminoma.[47] Otherwise, the germ cells present in other TSCSTs have been proposed to represent an entrapped non-neoplastic component by some authors.[20] By contrast, others have suggested that these germ cells are indeed neoplastic, showing similarities to spermatocytic tumour.[70,71] Further studies are needed to define the nature of the germ cells present in these mixed tumours.

Finally, no agreement was reached on whether Ki-67 should be used to assess the risk of aggressive behaviour in TSCSTs (in favour: 9/18, 50%). Some studies have shown that clinically malignant TSCSTs show higher proliferation rates measured with this immunostain; however, the group believes that there is still limited evidence and, importantly, useful cut-off values have not been properly defined and validated.[5] Moreover, it is uncertain if the assessment of the proliferative rate using Ki-67 would add to the mitotic count that is part of the proposed multi-parametric scores. More data are certainly needed to define the prognostic value of this widely available tool.

Discussion and Conclusion

The incorporation of molecular data in surgical pathology has led to significant improvements in classification, prognostication, and clinical management of oncologic patients across subspecialties. In the field of genitourinary pathology, TSCSTs represent a group of neoplasms that are currently classified based almost entirely on morphology, including several entities that are defined by their resemblance to sex cord-stromal tumours of the ovary. The most important drawback of such classification is that it results in significant overlap between entities with distinct biologic features and likely shows poor reproducibility for uncommon types, especially among pathologists that see these tumours only rarely. Another problem associated with the routine pathologic evaluation of TSCSTs is that their clinical behaviour may not be always easy to predict based on the morphologic features of the primary tumour.

Molecular alterations that underlie oncogenesis and progression in TSCSTs have been described in recent years; however, they have not yet impacted their classification and clinical management. This was the catalyst for gathering a group of expert genitourinary pathologists tasked with assessing diagnostic reproducibility and issuing recommendations on the management and classification of TSCSTs based on the best available evidence. This article summarizes the most salient recommendations issued by the group, acknowledging that evidence in many areas is limited mostly due to the rarity of TSCSTs. However, it is now clear that some of the new developments behoove reconsideration of old concepts about classification and clinical management. A good example is represented by TSCSTs 'resembling seminoma', which have been historically considered to belong to the spectrum of Sertoli cell tumour NOS.[23] Recent studies have identified that these neoplasms harbour *EWSR1::ATF1*, appear to be invariably aggressive and may require proactive clinical management (including the possibility of upfront retroperitoneal lymph node dissection); hence, their reclassification seems justified.[24,25] Similar considerations justify a reappraisal of the diagnostic terminology used for Leydig cell tumours with underlying FH deficiency.[11]

Undoubtedly, significant work still needs to be done to refine risk assessment and determine the need for molecular analyses (such as germline interrogation) in patients with TSCSTs. The identification of better predictors of malignant potential would be particularly beneficial for patients with Leydig cell tumour, Sertoli cell tumour NOS, large cell calcifying Sertoli cell tumour, and adult-type granulosa cell tumour because, while most (~90%) are benign, aggressive behaviour can be difficult to predict in a subset. This undertaking will likely require multi-institutional collaborations, ideally with the establishment of clinically annotated international repositories.

Despite the constraints imposed by the rarity of these tumours and the limited nature of the available evidence, we believe that the recommendations presented herein represent a useful guide for practicing pathologists and clinicians facing patients with TSCSTs. We understand that some of the recommended ancillary testing may not be readily available

in many practices, precluding confirmation of certain diagnoses, such as FH-deficient Leydig cell tumour. In these cases, the possibility of sending the material in consultation or performing the suggested ancillary workup as 'send-out' tests should be considered, using the best clinical judgement (i.e., considering the implications of the diagnosis). Otherwise, a differential diagnosis can be provided, or a specific entity can be favoured based on morphologic and immunophenotypic findings. We also acknowledge that the diagnosis of the rarer tumour types often requires review by genitourinary pathologists; therefore, in such scenarios, general pathologists are encouraged to seek expert consultation. Future endeavours of the group will address remaining knowledge gaps and hopefully result in further refinement of the recommendations summarized herein.

Author Contributions

Concept and coordination and manuscript draft: AMA and DMB. All authors involved in the manuscript editing and consensus activities.

Conflicts of interest

The authors declare that they do not have intellectual or financial conflicts of interest pertaining to the contents of this manuscript.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1.
Data S2.
Data S3.