News in the classification of WHO 2022 bladder tumors

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Review

News in the classification of WHO 2022 bladder tumors

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Summary
The fifth-edition of World Health Organization (WHO) Classification of Tumors series for urinary and male genital tract tumors has been published, six years later the fourth-edition. In these years, new treatment approaches have been implemented and new molecular data on urological cancers are known.
Morphology remains the groundwork for taxonomy of the urinary tract tumors. However, a molecular approach to classification of urothelial carcinomas and the management of selected neoplasms with new therapeutic modalities such as immunotherapy are emerging. More data are needed for the application of these advances in routine pathology practice and patient management.
The 2022 World Health Organization (WHO) Classification of Tumors of the Urinary System and Male Genital Organs represents an update in classification on urinary tract tumors. It also offers new insights with regards to the grading of heterogeneous non-invasive urothelial neoplasms, the definition of inverted neoplasms, the grading of invasive urothelial carcinomas, the diversity of morphological appearance of urothelial carcinomas, the definition of precursor lesions and the lineage of differentiation of the tumors.

Key words: bladder, urothelial tumors, grading, molecular subgroups, WHO 2022

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The grading

The grading of urotelial neoplasms is based on the level of architectural and cytological disorders. Low-grade carcinoma is characterized by lack of marked variation on nuclear size, mild loss of nuclear polarity and mild variation in nuclear size. High-grade carcinoma is characterized by marked architectural and cytologic disorders, loss of polarity, presence of irregular and pleomorphic nuclei, high number of mitoses and anaplasia.
The two-tier distinction between low-grade and high-grade carcinomas was first proposed in the 1998 WHO/ISUP consensus [1] and this has been promulgated by WHO in the third [2] and the fourth [3] edition and maintained in the fifth [4].
Low-grade and high-grade urothelial carcinomas are characterized by differences in prevalence of genetic alterations. The diagnosis of the two tumor groups (low- and high-grade) allows for correlation with cytological diagnosis using the terminology of the Paris System (TPS) [5]. The TPS, focuses on identification of high-grade tumors, is clinical

relevant and has been widely adopted. In addition, the use of low- and high-grade categories has better reproducibility and reduces the interobserver variability and is aligned with current patient management algorithms [6].

According to the 2022 classification for urinary tract neoplasia, every invasive urothelial carcinoma must be graded [7]. In a substantial percentage of cases, invasive urothelial carcinomas are characterized by high-grade cytological findings. Uncommonly, invasive urothelial carcinomas lacking marked nuclear atypia and architectural disorder – both in exophytyc and invasive components – can be encountered. It is important to distinguishing low-grade papillary tumor with lamina propria invasion among the pT1 carcinomas; in fact, literature data show that invasive pT1 low-grade tumors reveal more favorable outcome than pT1 high-grade carcinomas (Fig. 1a, 1b) [8-10]. Hence, clinical management schemes of pT1 urothelial carcinoma patients recognize different risk groups for low *vs* high-grade invasive carcinomas [11-14].

It is of note that subtypes of urothelial carcinoma and those with divergent differentiation are all considered high-grade tumors, even subtypes with a bland morphology, such as nested-type or microcystic type urothelial carcinomas [15-18].

From a pathological point of view, a critical issue is the heterogeneity of grade which occurs in one third of non-invasive papillary urothelial carcinomas, as grading is decisive for selecting the therapeutic approach. The lack of a clear cut-off for the distinguishing low- from high-grade carcinomas has led to variability in application of the criteria and sometimes poor interobserver reproducibility. Different proposals for better stratification of papillary urothelial carcinomam have been forwerded over the last years [19-21].

The Editorial Board of this fifth edition believes that there is a need to for better interobserver reproducibility for heterogeneous tumors and suggest to adopt common diagnostic criteria as a recent study has described [22]. Therefore, the WHO 2022 blue book propose reporting papillary tumors as high-grade as long as the high-grade component represents 5% or more of the tumor. Moreover, tumors with less than 5% high-grade component should be reported as low-grade with less than 5% high-grade component. This clear approach for reporting, if widely adopted, will help to achieve more interobserver reproducibility and allow for better future correlation with clinical outcomes. In the future, machine learning and artificial intelligence might help pathologists in this regard. Multidisciplinary international collaboration for this issue is suggested.

Non-invasive urothelial lesions

Regarding non invasive papillary neoplasms, the WHO 2022 maintains the papillary urothelial neoplasia of low malignant potential (PUNLMP) which has lower rates of recurrence and progression than pTa LG carcinoma [23,24] as a clinically relevant category, as well as the low-grade, and the high-grade papillary carcinoma categories.

It is important to recognize the inverted pattern of growth and to differentiate it from the invasive lesions.

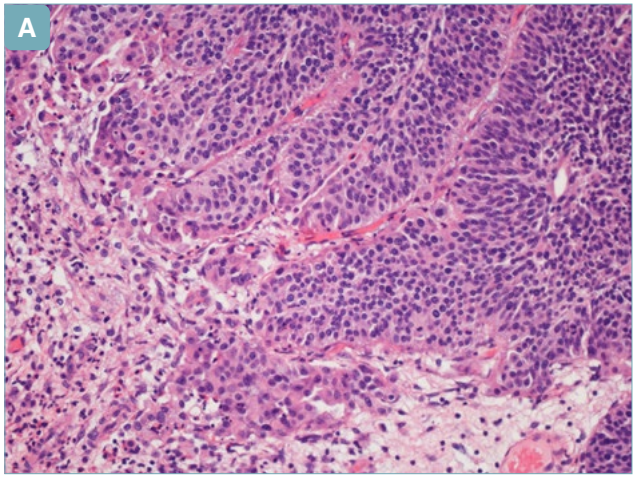

Figure 1a. Papillary urothelial carcinoma, low grade, with a focus of low-grade urothelial carcinoma invading lamina propria.

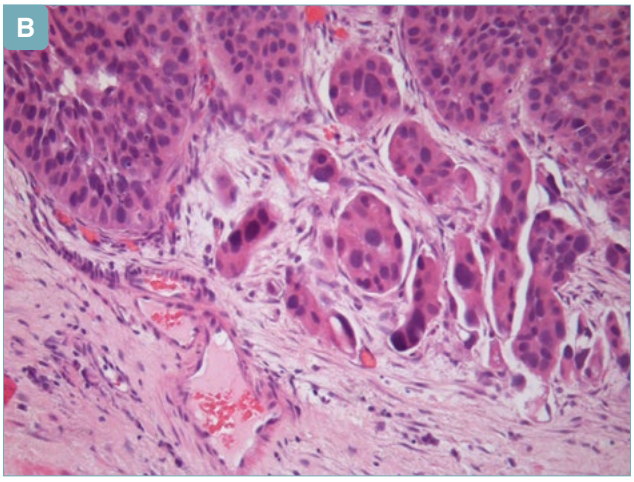

Figure 1b. Papillary urothelial carcinoma, high grade, invading lamina propria.

The reporting of presence of inverted pattern of growth also allows for better correlation with cystoscopic findings. Clarifications criteria for the differential diagnosis for tumors with inverted histology have been itemized. This includes the non-invasive papillary urothelial carcinoma, papillary urothelial neoplasm of low malignant potential and urothelial papilloma groups. While dedicated sections are reserved for uncommon benign lesions such as urothelial papilloma and inverted urothelial papilloma, other inverted lesions (eg. Inverted PUNLMP and inverted low-grade and high-grade non-invasive carcinomas) are included in the sections dedicated to the more common exophytic counterparts [25-28].

Subtype of urothelial carcinoma

The terminology of histologic "subtypes" has replaced "variants" throughout the fifth series. Invasive urothelial carcinoma presents with a diversity of morphologic appearances (Figs. 2-9). The different subtypes of urothelial carcinoma can occur in pure forms or more commonly admixed with conventional urothelial carcinoma. There are new subtypes of urothelial carcinoma, such as the tubular urothelial carcinoma, which in pure fashion is caracterized by bland cells, arranged in tubular structures, and the large nested urothelial carcinoma [29-30] that has been distinguished from the nested type.

In addition there are refinements of the name *clear cell urothelial carcinoma* with the addition of the term *glycogen rich* [31-32] to clearly discriminate it from clear cell adenocarcinoma with Mullerian differentiation; and the term *signet ring/diffuse* has been dropped from the plasmacytoid subtype.

The knowledge of diversity in appearance of urothelial carcinoma with its specific subtypes is important for the recognition of the deceptively benign appearance of some subtypes such as microcystic, tubular, nested and large nested types when in pure form and for the differential diagnosis with non-urothelial tumor with morphological similarities.

Urothelial carcinoma can present areas of divergent differentiation that include glandular, squamous [33], trophoblastic [34], Mullerian [35] and even neuroendocrine lineages. The fifth edition underlines the need to report the presence and percentage(s) of the different subtypes and divergent differentiations in urothelial carcinomas which can be useful for patient management [36-38].

Precursor lesions

Urothelial dysplasia

The term dysplasia is controversial, not the least as a result of being based on the absence of criteria for a definite diagnosis of carcinoma in situ (CIS). Dysplasia in the urinary tract does not equate with CIS. The diagnosis of dysplasia consists of a preneoplastic lesion that "*cytologically fall short of the diagnosis of carcinoma in situ*" [39]. The diagnostic term *dysplasia* is maintained in the fifth edition. However, instead of having its own entire chapter, like in the fourth-edition, it turns into a short description in the Urothelial Carcinoma in Situ chapter.

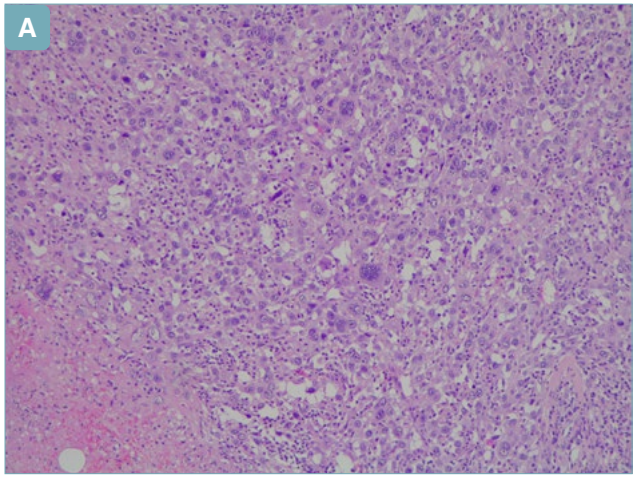

Figure 2a. Urothelial carcinoma with trophoblastic differentiation. Tumor with syncytiotrophoblasytic cells.

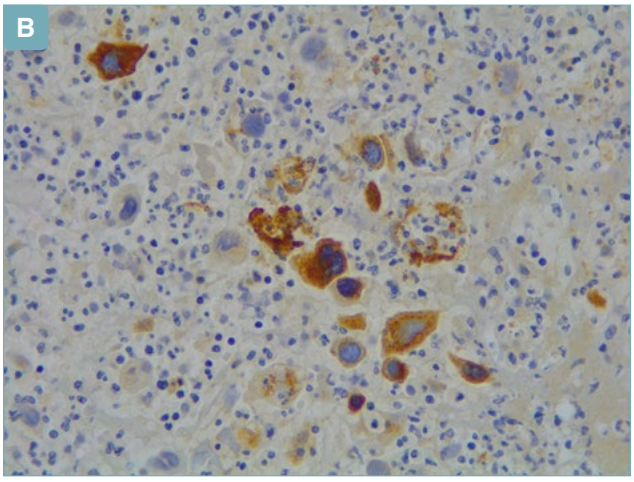

Figure 2b. Urothelial carcinoma with trophoblastic differentiation. Beta-hCG stain positive in syncytiotrophoblasytic cells.

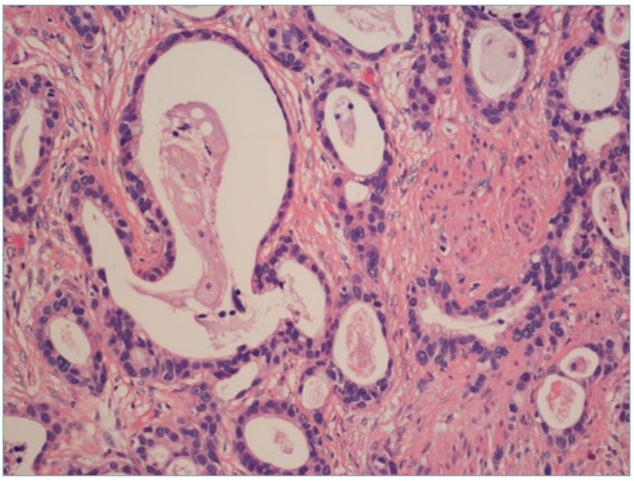

Figure 3. Microcystic urothelial carcinoma. Presence of cystic structures infiltrating a non-reactive stroma.

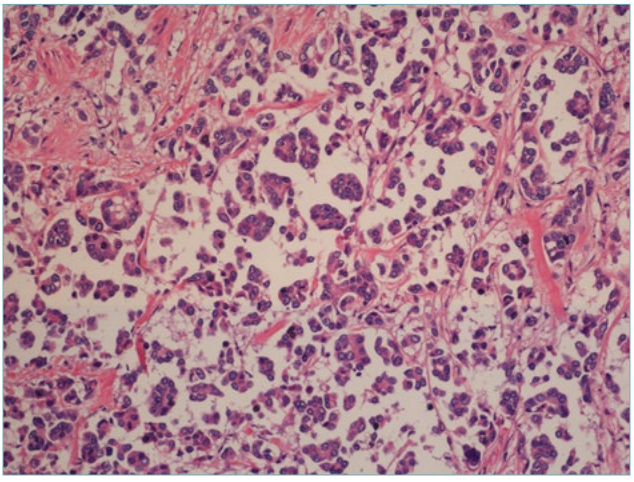

Figure 4. Micropapillary urothelial carcinoma. Tumor with micropapillary architecture.

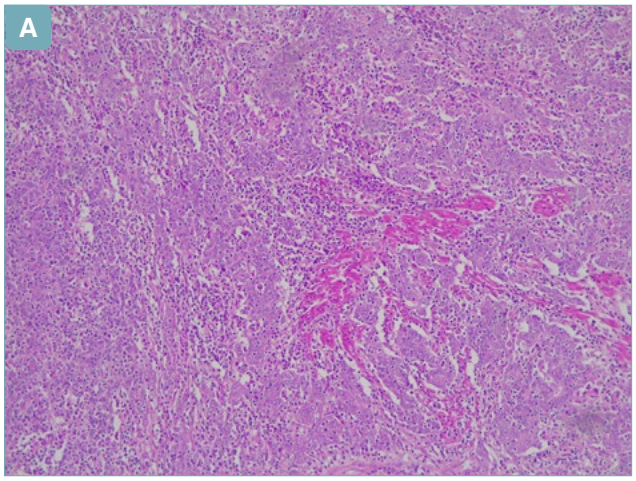

Figure 5a. Lymphoepithelioma-like urothelial carcinoma.

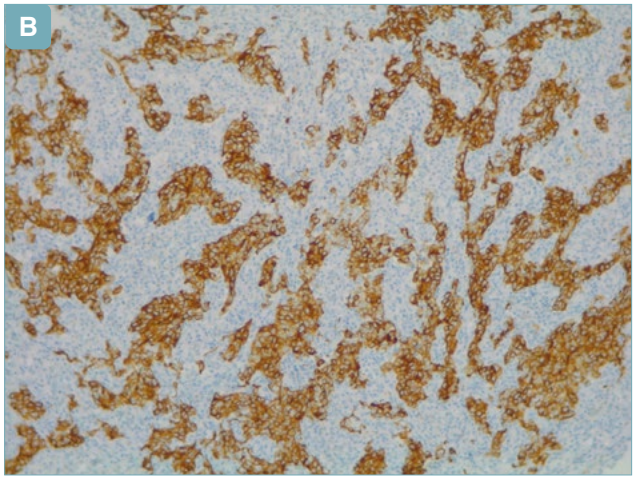

Figure 5b. Lymphoepithelioma-like urothelial carcinoma. Sheet of CK7 positive cells with a syncytial feature.

Urothelial papillary proliferation of undetermined malignant potential

In the 2016 edition of the classification for urinary tract neoplasia, undulating urothelial proliferations that were considered like precursors of non-invasive low-grade papillary urothelial carcinoma were termed "urothelial proliferation with undetermined malignant potential". For such lesions, the term atypical urothelial proliferation (AUP) with tented and flat patterns has also been proposed [40]; hovewer, in the 2022 edition, these lesions are no longer recognized as a stand-alone entity and are considered either early noninvasive low-grade papillary carcinomas or extensions of the edge of such tumors.

Organization of the fifth edition

Each tumor type is described listing benign and malignant entities. Urinary tract neoplasms are now listed in chapters that are mainly organized by tumor lineages of differentiation: urothelial, squamous and glandular tumors. Therefore, there are no longer dedicated organ-based chapters for urothelial tumors of prostate, urethra and upper urinary tract. Exceptions are made for histological findings useful for the diagnosis of rare tumors, such as urachal, diverticular and urethral accessory glands tumors that are described in specific sections.

Neuroendocrine neoplasms are described in a ded-

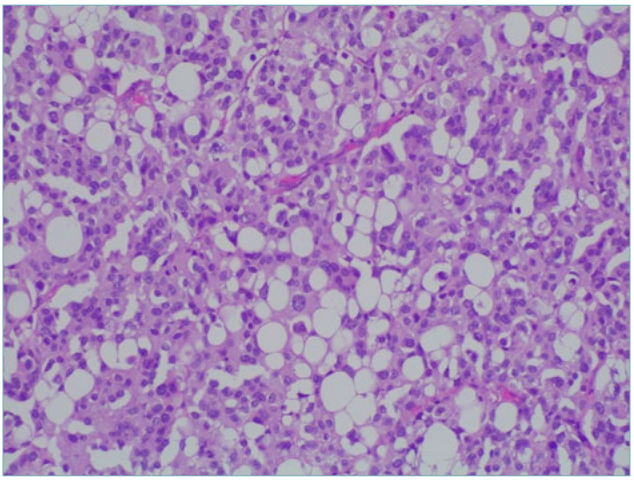

Figure 6. Lipid-rich urothelial carcinoma. Tumor cells with a lipoblast-like appearance.

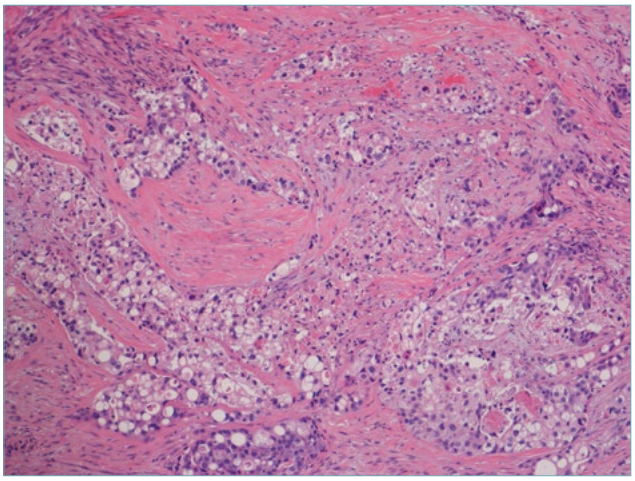

Figure 8. Clear cell (glycogen-rich) urothelial carcinoma. Sheet of cells with clear cytoplasm invading the muscle.

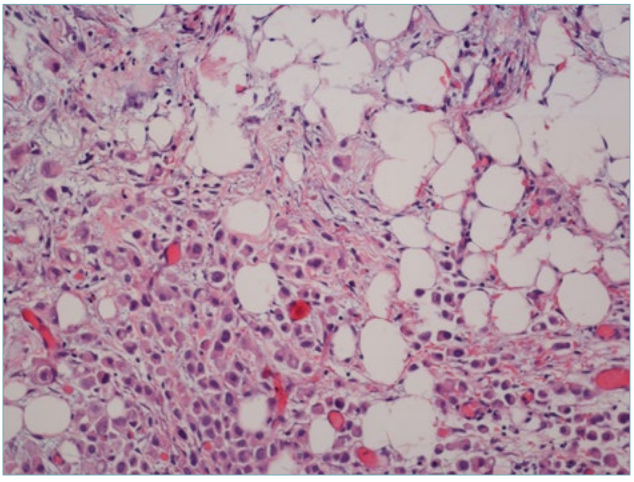

Figure 7. Plasmacytoid urothelial carcinoma. Dyscoesive and plasmacytoid-appearance tumor cells invading the perivesical fat.

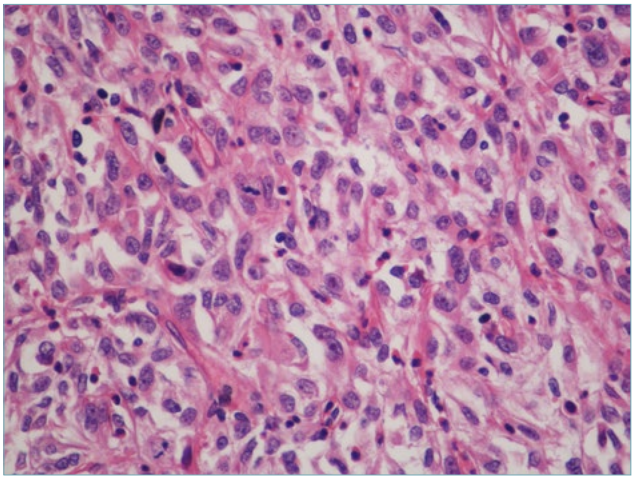

Figure 9. Sarcomatoid urothelial carcinoma. Spindle tumor cells with high grade atypia.

icated section. The classification which had been developed at the 2017 International Agency for Research on Cancer (IARC) neuroendocrine neoplasms consensus conference [41] is adopted for genitourinary tract organs as well as for all fifth-edition of World Health Organization (WHO) Classification of tumor series.

Mesenchymal, hematolymphoid, melanocitic and metastatic tumor are also reported in specific chapters. Genetic syndromes relevant for urinary tract tumors are described in the chapter on Genetic tumor syndromes of the urinary and male genital tract.

Unsolved matters

There remains some unsolved matters in bladder and urinary tract pathology in fifth-edition, such as the substaging for pT1 tumors and the molecular classification for urothelial carcinoma.

Substaging for pT1 tumors

Bladder cancer is staged using the TNM system [42-45]. The depth of tumor invasion into bladder wall and adjacent structures defines the pT categories. Tumor stage represents one of the most important factors for prognosis and management in bladder cancer pa-

tients. An unresolved matter is the substaging for pT1 HG urothelial carcinoma although there is agreement on the prognostic value of the depth of lamina propria invasion [46-47]. The fragmented nature of transurethral resection specimens and lack of orientation cause difficulties in the assessment of depth of lamina propria invasion. Histoanatomical and micrometric based systems have been proposed for substaging [48-56]. Using a histoanatomical approach, the pT1 substage is evaluated according to tumor invasion within or beyond the muscularis mucosae or the large vessels of the lamina propria. The micrometric approach is based on the actual measurement of the invasive component. For the latter approach, different cut-offs have been proposed for substaging of invasion in the lamina propria. Despite the variability in the cut-off of micrometric approach and/or the type of approach to be used, the fifth edition strongly suggests to quantify tumor invasion in lamina propria with any of the proposed systems.

Molecular findings

Recent studies on muscle-invasive bladder carcinoma have revealed six molecular subgroups with different prognosis [57-61]. Luminal-papillary subgroups are identified in 24% of muscle-invasive tumors, luminal non-specified in 8%; luminal-unstable in 15%, stromal-rich in 15%, basal-squamous in 35% and neuroendocrine-like in 3% of muscle-invasive bladder carcinoma.

The various gene expression based subgroups are enriched for some histologic features, immune microenvironments and gene signatures. For example, *FGFR3* mutations are more frequent in luminal-papillary subtype, while *TP53* mutations are more likely in neuroendocrine-like, basal-squamous and luminal-unstable.

From a therapeutic point of view, alterations in ERCC2 and other DNA damage repair genes are have been associated with better response to cisplatin-based chemotherapy [62-63]. Mutation, amplification, and fusion of FGFR3 can be associated with anti-FGFR agents [64-65].

Athough at the current time it is not possible to go towards a molecular classification of urinary tract tumors, the 2022 blue book highlights the great potential impact of the novel molecular advances for diagnosis and management of urinary tract tumors [66-68].

Conflicts of interest

The authors declare no conflict of interest.

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Authors' contributions

Writing-original draft preparation, MRR; writing-review and editing, MRR, EMC, ALB, RM, AC, TT, GJN. All authors have read and agreed to the published version of the manuscript.

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