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Review

MicroRNA Regulatory Networks in Wilms Tumor: From Molecular Pathogenesis to 3D Organoid Platforms for Biomarker Discovery

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Abstract

Wilms tumor (WT), the most common childhood kidney cancer, arises from arrested nephron progenitors, with disrupted microRNA biogenesis among its recurrent drivers. Yet the quality of the models underlying this literature has rarely been examined. We reviewed microRNA regulatory networks in WT, the models used to study them, and their biomarker and therapeutic potential, using a structured PubMed/MEDLINE search to September 2026 (1338 records screened, 176 included; 74 verified evidence entries). Mutations in *DROSHA*, *DGCR8*, *DICER1*, and *XPO5*, *SIX1*/*SIX2* alterations, and the *LIN28B*/let-7 axis converge on an arrested progenitor state. The cellular evidence is weaker than its volume suggests: of 36 studies naming a cell line, 33 used at least one line that is not an authenticated WT line (mainly G-401, SK-NEP-1), 22 presenting them as WT models, and 11 included studies have been retracted. Tissue and serum microRNA signatures are associated with histology and chemotherapy response, but independent validation is scarce. Although organoid biobanks of childhood kidney tumors exist, no microRNA profiling of a kidney tumor organoid was identified among 65 three-dimensional kidney-model records retrieved. Impaired microRNA processing is thus a well-supported pathogenic axis, whereas biomarker and therapeutic claims remain preliminary and require authenticated models, including tumor organoids.

Keywords: Wilms tumor; nephroblastoma; microRNA biogenesis; DROSHA; DGCR8; organoids; liquid biopsy; risk stratification

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1. Introduction

Wilms tumor (nephroblastoma) is the most common pediatric kidney cancer [1]. It is the classic embryonal tumor: it recapitulates the blastemal, epithelial, and stromal compartments of the developing metanephros, and its cell of origin is widely thought to

be a nephron progenitor that failed to differentiate. Overall, five-year relative survival is 92.6% in a United States population-based series [1], but clinically meaningful differences in outcome persist across risk groups. Patients with diffuse anaplasia, blastemal-predominant post-chemotherapy histology, or relapse still tend to do poorly [2], and current risk stratification cannot reliably pick them out at diagnosis.

Two things make Wilms tumor unusually attractive for microRNA research. First, unlike most solid tumors, the microRNA biogenesis apparatus is itself a direct and recurrent mutational target in this disease. Sequencing of favorable-histology tumors found mutations in the microprocessor components *DGCR8* and *DROSHA* in 15% of 534 tumors, alongside *SIX1/2* mutations in 7% [3], and the Children's Oncology Group (COG)/Therapeutically Applicable Research to Generate Effective Treatments (TARGET) landscape study confirmed *DROSHA*, *DGCR8*, *XPO5*, and *DICER1* as recurrently altered, together with *LIN28B* gain and *MIRLET7A* loss [4]. Wilms tumor is therefore not simply a tumor in which microRNAs are dysregulated downstream of other drivers: disrupted microRNA production appears to be a driver event. Second, because the tumor depends on a developmental progenitor state, microRNA families with established roles in nephrogenesis, including let-7, miR-200, and the miR-199a/214 cluster, intersect with developmental pathways relevant to Wilms tumor biology.

Against that background, the models available for functional work are limited. Wilms tumor has yielded very few authenticated cell lines, and the field's most heavily used "Wilms tumor" lines were formally shown in 2019 not to be Wilms tumor lines at all [5]. Three-dimensional patient-derived organoids have since been established for childhood kidney cancers, and they capture subtype and tissue heterogeneity that two-dimensional culture does not [6]. Whether these models can serve as a platform for microRNA discovery, however, remains an open experimental question.

The review addresses three linked questions. The first is mechanistic: which microRNA regulatory networks are established in Wilms tumor pathogenesis, and how do they connect to the progenitor state, epithelial–mesenchymal transition (EMT), and Wnt/β-catenin signaling? The second is methodological: what are the strengths and limitations of three-dimensional patient-derived kidney tumor organoids, relative to two-dimensional lines and patient-derived xenografts (PDX), specifically as a platform for microRNA profiling? The third is clinical: how far have tissue and circulating microRNAs progressed toward use in risk stratification, molecular classification, and prediction of response to neoadjuvant chemotherapy?

Much of this literature is built on non-authentic models and, as we show, a non-trivial number of the articles have been retracted. We therefore treat evidence quality as a fourth theme that runs through the whole review rather than as a limitations paragraph added at the end. Throughout, we keep separate what a study observed, what its authors interpreted, and what we ourselves synthesize across studies.

2. Evidence Base for This Review

We designed this review as a structured evidence synthesis rather than a formal systematic review or meta-analysis. The aim was not to estimate pooled effects but to map, across the literature, signals related to mechanism, model quality, clinical translation, and evidence integrity.

This review is grounded in a structured PubMed/MEDLINE search executed via the National Center for Biotechnology Information (NCBI) E-utilities from database inception to 10 September 2026. Ten predefined search tiers combined Wilms tumor/nephroblastoma population terms with one of the following sets of terms: non-coding RNA vocabulary; microRNA-processing genes (*DROSHA*, *DGCR8*, *DICER1*,

XPO5, *LIN28*, *LIN28B*); terms related to development and the epithelial–mesenchymal transition; microRNAs previously reported in Wilms tumor (tier composition in Table S1); and three-dimensional/organoid model vocabulary. Screening of the retrieved records proceeded from title, abstract, and MeSH terms against explicit inclusion criteria, any study design, in vitro through clinical, reporting a microRNA-specific measurement, mechanism, model, or clinical application in Wilms tumor with exclusion of studies whose only non-coding RNA content is a long non-coding RNA, circular RNA, piRNA, or small nucleolar RNA without an accompanying microRNA measurement. Tiers were combined as a union, so a tier can add records but cannot exclude any record retrievable by the others; a per-tier sensitivity analysis (Table S1) shows that six of the ten tiers contribute no included study uniquely, and that the microRNA-name tier contributes at most 4 of the included studies. Preprints were handled by a single rule: a preprint retrieved by the search and meeting the eligibility criteria is included and flagged as such (one of the 176); where a preprint and its peer-reviewed version were both retrieved, only the peer-reviewed version is retained in the included set and cited, and the preprint version is recorded in the screening records as a duplicate; a preprint not retrieved by the search is not cited at all. The same retrieval-based rule governs peer-reviewed context citations, so that charting status reflects what the search retrieved rather than publication venue.

Screening and charting were performed in duplicate. Two reviewers independently applied the eligibility criteria to the retrieved records and independently charted the evidence fields; disagreements were resolved by discussion between them, and a third reviewer arbitrated where consensus was not reached. Agreement was not quantified as a statistic; the record-level decisions of the final, adjudicated set are deposited in full (Table S2), so the screening can be audited independently. Every study cited in this review was obtained and read in full, and every statement made about a cited study rests on that reading rather than on its abstract; 64 of the 176 included studies are cited, together with the context literature in the reference list. The structured charting fields, by contrast, were recorded under a single rule applied to the retrieved record—title, abstract and MeSH terms—so that the same rule governed all 1338 screened records and not only the subset that met the criteria; full-text charting of 1338 records would not have been reproducible at that scale, and the 112 included studies that are not cited individually enter the counts through that rule alone. The consequence is specific and we state it rather than leave it implicit: the charted fields, and the counts derived from them, are lower bounds, while every claim this review makes about a named study rests on its full text. Where full-text reading established or corrected a charted field, as it did for cell-line attribution (Section 4.1 and Table S2), we say so at the point of use.

The search retrieved 1340 unique PubMed identifiers, 1338 of which were article records and were screened (Figure S1); of these, 172 studies met the eligibility criteria, and a documented verification search added 4 more (Section 2 and File S1), giving 176. These were charted into an evidence table recording expression direction, target gene, mechanism, specimen type, clinical association, and model-quality flags. Every charted entry was then verified against its primary source, and only entries confirmed on all five verification criteria are reported: that the identifier corresponds to the cited article, that the charted finding matches what the article reports when read against its abstract or full text, that the finding is in Wilms tumor rather than another renal tumor or glomerular disease, that the article is neither retracted nor under an expression of concern, and that any cell line used is an authenticated Wilms tumor line. Seventy-four entries from 41 studies met all five and are reported in Table S4. Seventy-three of the entries name a microRNA, covering 62 distinct microRNA names; one of these names denotes the set of

microRNAs converging on PRC1 rather than a single named microRNA, so 61 individually named microRNAs are represented. The remaining entry records two microRNA loci (MIR1469, MIR6870) at copy-number level rather than a mature microRNA, and is not counted among the named microRNAs. The structured charting fields were recorded from titles, abstracts, and MeSH terms under one rule applied to all 1338 screened records, rather than from the full texts of the included subset, and this has variable-specific consequences that we state explicitly. Cell-line identity was captured only when named in the title or abstract (36 of 176 studies); hairpin-arm designation is given for only 35 of the 74 verified entries (47%) and for 30 of the 62 microRNAs they cover; treatment status at sampling and comparator tissue were too inconsistently stated in abstracts to be charted systematically. All model-quality counts reported below are therefore lower bounds. Retraction status, by contrast, was not taken from abstracts: it was read from PubMed publication-type fields and comment/correction cross-references, and each retracted article is flagged in the screening records (Table S2). Where full texts could be retrieved, we verified the cell-line attribution classification directly against the Methods and Results sections (Section 4.1 and Table S2). Per-tier yields, record-level screening decisions, and the selection flow (Figure S1) are reported in the Supplementar y Materials (Figure S2). One entry added by the verification search (PMID 30671724) records amplification of the MIR1469 and MIR6870 loci in tumor DNA; its direction is recorded as not assessed, because the study measures copy number rather than expression, and it contributes no microRNA-target pair.

Because a single-database search is a recall risk, we measured recall against two independent indexes rather than asserting sufficiency. Translating the four main blocks into Europe PMC (14 September 2026) returned 653 unique records and re-found 149 of the 173 studies included at the time of the check; translating them into OpenAlex returned 1155 unique works and re-found 153 (88%). Neither index surfaced a MEDLINE-indexed study that a PubMed search of this shape could not reach. Fifty-five Europe PMC records were absent from PubMed altogether (39 preprints, 6 theses, 5 PMC-only records, 3 patents, 2 AGRICOLA); all were screened against the eligibility criteria, and the eligible items are either already among the included set in their published form or are cited here as context and declared in the limitations. Four of the 176 included studies are Chinese-language articles. Embase- and Scopus-exclusive content and non-deposited conference abstracts were not assessed; we therefore treat every count in this review as a lower bound and every absence as an absence in this search rather than in the literature (Table S1). Verbatim query strings had been preserved for only one of the ten tiers of the original search. We therefore re-specified the strategy from the block definitions and ran it again on 13 November 2026, under the same 10 September 2026 coverage limit, as a documented verification of the original search rather than as a replacement for it. The 11 verification tiers, with every string given in full in File S1, retrieve 996 unique records and re-find 168 of the 172 studies included in the first round; the four not re-found are kidney-organoid, renal cancer stem-cell and organotypic-culture reports that carry no Wilms tumor term and were retrieved by the original search only. The verification also surfaced 380 records not previously screened: rule-based triage carried 131 to record-level adjudication, of which 4 met the eligibility criteria and were added, taking the included set from 172 to 176. All counts in this review therefore rest on the original screening, extended by these four studies and bounded by the recall figure given above.

3. Mechanistic Criterion: microRNA Regulatory Networks in Wilms Tumor Pathogenesis

3.1. Mutation of the microRNA Biogenesis Machinery Defines a Molecular Subclass

One of the most direct mechanistic links between microRNAs and Wilms tumor is genetic rather than purely correlative. Walz and colleagues reported that the most frequent single-nucleotide substitutions and deletions in favorable-histology Wilms tumor occur in *SIX1/2* (7% of 534 tumors) and in the microRNA-processing genes *DGCR8* and *DROSHA* (15% of 534 tumors). Tumors carrying these mutations showed a pre-induction metanephric mesenchyme expression pattern and were significantly associated with perilobar nephrogenic rests and 11p15 imprinting aberrations [3]. The same study found significantly decreased mature let-7a and miR-200 family levels in these mutant tumors, a decrease associated with an undifferentiated blastemal histology [3]. The TARGET/Children's Oncology Group landscape study, combining genome-wide sequencing of 117 tumors with targeted sequencing of 651 more, independently confirmed *DROSHA*, *DGCR8*, *XPO5*, and *DICER1* among the recurrently mutated genes, and additionally picked up recurrent *LIN28B* gain and *MIRLET7A* loss at the copy-number level [4].

Three later lines of work build on this. The first is functional: a multiomic analysis sorted Wilms tumor mutations into four transcriptional subclasses (microRNA processing, MYCN activation, chromatin remodeling, and kidney developmental factors) and found that *DROSHA* mutations were correlated with derepression of microRNA–target genes that regulate differentiation and proliferation, and with a self-renewing mesenchymal state [7]. These findings provide functional evidence that DROSHA mutation is associated with derepression of microRNA-regulated progenitor programs; loss of these microRNAs may therefore permit persistence of progenitor-associated transcriptional programs. The second is germline predisposition. Pathogenic germline *DROSHA* variants have now been linked to a pineoblastoma and Wilms tumor predisposition phenotype in nine children from eight families (eight with pineoblastoma and one with Wilms tumor), which extends to *DROSHA* the tumor-predisposition role already established for *DGCR8* and *DICER1* [8]. The third is clinical stratification by *DICER1*: a 2026 case series described *DICER1*-mutated renal neoplasia spanning cystic nephroma, Wilms tumor, and anaplastic sarcoma of the kidney, suggesting that these renal neoplasms may represent a DICER1-associated disease spectrum rather than entirely independent entities [9].

The role of this pathway in relapse is less clear. A study of 19 paired primary and recurrent tumors, plus 10 primary tumors from patients who later relapsed, was designed specifically to test whether *SIX1* and *DROSHA* mutations drive recurrence. It found a *SIX1* mutation in only one case, but microRNA-processing-gene mutations in seven; in the recurrent tumors, these mutations were homogeneously present and appeared positively selected, and their association with relapse was borderline ($p = 0.05$) [10]. The evidence therefore supports a role for microRNA-processing-gene mutations in progression to recurrence more than for *SIX1*, and it remains limited by sample size. We highlight it because the *SIX1*/microRNA-processing axis is often cited in the context of relapse without this caveat.

In summary, the microRNA-processing-gene subclass of Wilms tumor is supported by convergent genetic, expression, and functional evidence linking alterations in the microRNA machinery with altered mature microRNA abundance, derepression of progenitor-associated targets, and impaired differentiation. This component of the literature also depends less on the cellular model limitations discussed in Section 4 than do many indi-

vidual microRNA-target studies.

3.2. Lin28/let-7 and the Nephron Progenitor State

The Lin28/let-7 axis is the developmental counterpart of the processing-gene story. LIN28B gain and MIRLET7A loss were recurrent copy-number events in the TARGET cohort [4], and reduced levels of mature let-7a accompany microprocessor mutation [3]. These alterations converge on overlapping developmental programs characterized by persistence of nephron-progenitor features and reduced let-7 activity. MYCN offers a third way into the same node. Transcriptomic profiling of anaplastic Wilms tumor cell lines found that MYCN positively regulates LIN28B itself, alongside the methylome components PRMT1, PRMT5, and WDR77 [11]. Because that study measures no mature microRNA, it did not meet our eligibility criteria, and we cite it here as mechanistic context rather than charting it in Table S4.

Germline variation at the same node has also been linked to disease risk. A four-center case–control study genotyped 355 Wilms tumor patients and 1070 controls in China and found that two *LIN28A* polymorphisms (rs3811463 T>C, rs34787247 G>A) were associated with adjusted odds ratios of 1.58 and 1.56, respectively, according to the genotype categories reported by the authors, with an eQTL signal linking the rs3811463 C allele to higher *LIN28A* transcript levels [12]. This is a genetic association in a single national cohort, not a functional demonstration, and the authors' inference of increased predisposition still requires replication in an independent population.

DIS3L2, the 3′–5′ exonuclease once proposed to degrade uridylated pre-let-7, is a partial exception to this convergence rather than a fourth confirmation of it. Loss of *Dis3l2* in mice partially phenocopies the Perlman overgrowth phenotype and upregulates *Igf2* in nephron progenitors, but the same study found no effect of Dis3l2 loss on mature let-7 levels. These findings argue against altered mature let-7 abundance as the mechanism in that experimental model, and the authors instead propose that DIS3L2 restrains Igf2 through a let-7-independent route [13]. We flag this because the DIS3L2–let-7–IGF2 chain is repeated in secondary literature as though it were established. The primary data support a DIS3L2–IGF2 link, not a DIS3L2–let-7–IGF2 one, and the human counterpart of either link has not been shown directly.

A circular RNA route to LIN28B stabilization through *N*6-methyladenosine biology has also been proposed, but the single Wilms tumor report of it charts no microRNA and has since been retracted, so it falls outside the scope defined in Section 2 and is not carried into the evidence table. In practice, the LIN28B competing-endogenous-RNA hypothesis in Wilms tumor currently rests on withdrawn evidence.

Normal nephrogenesis provides the reference condition here. The miR-199a/214 cluster was shown to control nephrogenesis and vascularization in a human embryonic stem cell–derived kidney model [14], and an in situ hybridization protocol has been published for detecting microRNAs in human embryonic kidney and human pluripotent stem cell–derived kidney organoids [15]. Within the literature identified here, these were the only studies we found that localized microRNAs within three-dimensional human kidney tissue, and neither involved tumor (Section 4.4).

3.3. SIX1/SIX2, WT1 and Wnt/β-Catenin

SIX1 and *SIX2* mark the self-renewing cap mesenchyme, and their mutation co-segregates with microRNA-processing-gene mutation in the same favorable-histology subclass [3]. *WT1* itself has been modeled in three dimensions. Deleting *WT1* during human kidney organoid development caused progenitor cells to overgrow at the expense of differentiating glomeruli and tubules, halting progenitor progression at a pre-epithelialized

state and recapitulating the transcriptional changes seen in a subgroup of Wilms tumor patients with ectopic myogenesis [16]. A second organoid study used *WT1* mutation to map regulatory paths in podocyte development [17]. Both are organoid experiments relevant to WT1 biology, and neither measured microRNAs, a point we return to in Section 4.4.

A separate, non-organoid line of work proposes that *WT1* has a second, non-transcriptional role in this pathway. Work circulated in preprint form, which we do not cite here because it is not indexed in PubMed and was not retrieved by our search, reports that WT1 interacts with let-7 microRNAs and with the microRNA-processing machinery. If that holds up, it will put WT1, which we have otherwise treated only as a transcription factor, mechanistically inside the same let-7 node as the *DROSHA*/*DGCR8*/*LIN28B* machinery from Sections 3.1 and 3.2, rather than upstream or parallel to it. Two caveats are worth flagging here. Neither the 2019 nor the 2025 version of this work has, as far as we know, been published in a peer-reviewed journal in the seven years since the first preprint. Both versions were also missed by our search strategy because they are framed around kidney mesenchyme in general, without an explicit Wilms tumor term in the title or abstract. Because these preprints were not retrieved by our search blocks, they fall under the context-citation rule stated in Section 2 and are not charted in Table S4; this is a documented search miss (limitations), not a decision about preprints as a publication class.

The clearest place where microRNA processing and Wnt signaling converge on a clinically relevant readout is a report that PD-L1 expression in Wilms tumor is mediated jointly by microRNA processing, Wnt/β-catenin signaling, and chemotherapy [18]. The same study is also indexed in PubMed as a preprint (PMID 39677784); we count the two as one study and cite only the peer-reviewed version. The corpus also contains one further preprint, on convergence of Wilms tumor mutational subclasses [19], which we likewise flag as not peer-reviewed.

3.4. Epithelial–Mesenchymal Transition and the Mesenchymal Program

EMT-related biology in Wilms tumor differs conceptually from canonical EMT in carcinoma. Wilms tumor arises within a developmental context characterized by persistence of nephrogenic progenitor states and incomplete differentiation, so changes in EMT-associated microRNAs may reflect developmental arrest as well as acquired cellular plasticity. Both the miR-200 family reduction in microprocessor-mutant tumors [3] and the *DROSHA*-associated mesenchymal expression program [7] fit that developmental reading.

At the level of individual microRNAs, the charted evidence links several molecules to EMT or metastasis phenotypes: miR-572 targeting *CDH1* to promote metastasis [20]; miR-194-5p, reported to inhibit metastasis and EMT via *Crk* in an article that has since been retracted (PMID 31889432 [21]; Section 6.2 and Table S2) ; miR-195-5p, released from DLX6-AS1 sponging and acting on *KIF23* [22]; and miR-483-3p, promoting proliferation, migration, and invasion through *PTEN*, with EMT and chemoresistance components [23]. Only the miR-194-5p report is retracted. The other three rest on studies with neither a retraction nor exclusive reliance on non-authentic lines. Two further Wilms tumor EMT reports, HOXA11-AS downstream of HIF-1α and C/EBPβ, and EMX2OS acting through IGF2BP1, chart no microRNA and fall outside the scope of this review.

3.5. Competing Endogenous RNA Networks: microRNAs as the Charted Unit

Sponge studies, in which a long non-coding RNA or circular RNA is proposed to sequester a microRNA as a competing endogenous RNA (ceRNA), make up a large share

of the recent Wilms tumor microRNA literature. We chart these at the level of the microRNA and its target, not the sponge itself: a study only enters the evidence table when the microRNA is measured. Representative recent examples include DLX6-AS1 sponging miR-195-5p to upregulate *KIF23* [22], LINC01339 acting through a miR-135b-3p/*ADH1C* axis [24], SNHG6 acting through miR-429/*FRS2* [25], lncRNA FTX acting through miR-215-5p [26], where the effect of miR-215-5p itself on PI3K/AKT was not assessed, KCNQ1OT1 acting through miR-21/*PTEN* [27], and XIST acting through miR-193a-5p [28]. Sponge studies that do not report a microRNA measurement, including the Wilms tumor MEG3 and circMARK2 reports, fall outside our scope and are not charted.

Three structural weaknesses run through this body of work, and we quantify them in Sections 6 and 4.1. Replication is almost nonexistent: of the 62 distinct microRNAs in the verified evidence table (Table S4), 52 are reported by a single study. A large share of the functional experiments was done in cell lines that are not Wilms tumor lines. In addition, retractions cluster in this part of the literature. We therefore treat individual ceRNA axes as hypotheses requiring confirmation in authentic material rather than as established Wilms tumor mechanisms; this judgment applies to the specific claims examined here, not to the ceRNA concept itself.

3.6. Status of Previously Reported microRNA–Target Pairs

We re-examined a set of microRNA–target pairs previously highlighted by our group against the primary Wilms tumor literature retrieved in this search. Seven were previously described as supported by a primary Wilms tumor study, and miR-190b and miR-21 were discussed alongside them. Of these nine, only two survive verification against the primary source at the level of the specific pair: miR-572/CDH1 [20] and miR-21/PTEN [27]. Of the remainder, miR-155-5p/IGF2 [29], miR-1180/p73 (the 5p arm appears only in the title and keywords) [30], miR-143-3p/KRAS [31], miR-215-5p via lncRNA FTX [26] and miR-190b [32] rest on studies whose cellular evidence comes from G-401 or SK-NEP-1, and miR-22-3p/AKT3 [33] and miR-590-3p/DKK1 [34] are not stated in the terms charted. For miR-21, one expression study found only weak involvement [35]. This is the clearest illustration of the point made throughout this review: a pair that is repeatedly cited is not thereby verified, and the distinction only becomes visible when each pair is read back against its source. Figure 1 maps onto their signaling pathways only the individually reported pairs that pass this verification (Table S4).

Two points require clarification. First, miR-193a/WT1 is not a Wilms tumor finding and is therefore not charted as such. The miR-193a/WT1 literature retrieved by this search concerns podocyte trans-differentiation, focal segmental glomerulosclerosis, membranous nephropathy, breast cancer, and acute myeloid leukemia. The only Wilms tumor study involving miR-193a in this corpus reports XIST-mediated modulation of miR-193a-5p in tumor cell migration [28], which is a different claim. Second, the five pairs whose cellular evidence comes from G-401 or SK-NEP-1 are not drawn in Figure 1 and are not treated as validated here, and one further study supporting miR-155-5p has been retracted (PMID 30779069 [36]; Table S2).

3.7. Why These Families: Network Context for the Recurrently Reported microRNAs

The microRNAs that recur in this corpus are not a random sample of the miRNome. Four families account for most of the molecules repeatedly examined in this literature, and they share a property that explains their recurrence: each one is a node in a network that controls a developmental transition the kidney must complete, rather than a generic proliferative pathway. Read that way, the fragmented pair-level literature summarized in Section 3.6 resolves into four control points—exit from the nephron progenitor state,

mesenchymal-to-epithelial transition, tubular epithelial differentiation, and IGF2 dosage at 11p15—all of which lie downstream of one of the two lesions that define the disease genetically: mutation of the microRNA-processing machinery and loss of imprinting at 11p15. Table 1 summarizes the networks; this section explains the logic, and we flag throughout which parts are established in Wilms tumor and which are extrapolated from other tissues.

3.7.1. let-7: The Timer on Progenitor Self-Renewal

The let-7 family is the clearest case of a microRNA network whose failure produces an arrested developmental state rather than unrestrained growth. LIN28A and LIN28B bind the terminal loop of pre-let-7 and recruit the terminal uridylyl transferases TUT4/TUT7; the uridylated precursor is degraded by DIS3L2, so mature let-7 is depleted without any change in transcription of its host genes [37–39]. The mature family then acts on a coherent self-renewal module: *HMGA2* [40], the IGF2 mRNA-binding proteins IGF2BP1-3, *MYC/MYCN*, *KRAS/NRAS* [41], *CCND1*, and *LIN28B* itself, which closes a double-negative feedback loop. The practical consequence is bistability: a cell is either in the LIN28-high/let-7-low progenitor state or in the let-7-high differentiated state, and the switch between them is a developmental timer.

In the kidney that timer sets the window during which SIX2-positive cap mesenchyme can self-renew. Forced Lin28b expression in murine nephron progenitors extends the window and produces Wilms-like tumors, and the phenotype is let-7-dependent [42]; Lin28/let-7 also governs the timing of cessation of nephrogenesis [43]. The human disease hits this node in two independent ways: LIN28B copy gain with MIRLET7A loss in the TARGET cohort [4], and microprocessor mutation, which lowers mature let-7a and is associated with undifferentiated blastemal histology [3]. Mechanistic work in Wilms tumor material shows that DROSHA and DICER1 mutations impair biogenesis through distinct routes, which is why they produce overlapping but non-identical mature-microRNA deficits [44].

The tumor phenotype that follows is therefore best read as failure to exit the progenitor state. Blastemal-predominant histology, the persistence of nephrogenic rests, and the DROSHA-associated self-renewing mesenchymal program [7] are all expressions of the same arrest, and this is the mechanistic reason the processing-gene subclass tracks with high-risk disease rather than simply with proliferation rate.

3.7.2. The miR-200 Family: The Mesenchymal-to-Epithelial Switch

Nephron formation requires a mesenchymal-to-epithelial transition: cap mesenchyme condenses into the renal vesicle and then into the comma- and S-shaped bodies. The miR-200 family (miR-200a, -200b, -200c, -141, -429) is the canonical controller of that transition. Its members target *ZEB1* and *ZEB2*, which in turn repress the miR-200 promoters, a double-negative loop that behaves as a switch between the mesenchymal and epithelial states and sets *CDH1* expression as its readout [45,46].

In Wilms tumor the switch is reported as stuck on the mesenchymal side. miR-200 family levels are reduced in microprocessor-mutant tumors [3], the family is downregulated in renal childhood neoplasms together with miR-192/194/215 [47], and the DROSHA-associated expression program is mesenchymal and self-renewing [7]. Family members were also identified as discriminating cancer-initiating from non-initiating cells in Wilms tumor xenografts [48]. The verified target-level work is narrower than the volume of reports suggests: miR-200b and miR-429 acting on IKK-beta in a stemness context (Table S4). Other reported targets of the family, among them AKT/GLUT1, EP300, FRS2, CCNE2 and CDC7, come from entries that did not pass verification against

their source and are not counted as evidence here (Section 2). This is the family-level counterpart of the individual EMT reports in Section 3.4, with the important qualification that in an embryonal tumor arising from retained nephrogenic tissue, a mesenchymal signature plausibly reflects a transition that never occurred rather than one that was reversed.

3.7.3. miR-192/194/215: The Tubular Differentiation Module

miR-194 is encoded twice in the genome, clustered with miR-215 at 1q41 and with miR-192 at 11q13.1, and the clusters are expressed in differentiating renal tubular epithelium. Functionally they reinforce the miR-200 switch, since miR-192 and miR-215 also act on ZEB2, so the two families are better treated as one differentiation module than as independent findings.

The Wilms-tumor-specific evidence is a single study, and it is the one that links the two families: miR-192, miR-194, miR-215, miR-200c and miR-141 are all downregulated in renal childhood neoplasms, and their common target *ACVR2B*, *a TGF-beta superfamily type II receptor, is strongly expressed* [47]. *The pairing is not only predicted: in that study each of the five microRNAs repressed ACVR2B 3′-UTR reporter constructs in the authenticated Wilms tumor line WT-CLS1 and lowered ACVR2B protein in HEK293 cells, while in tumor tissue the downregulation of miR-141 and miR-200c was significant in blastemal-type and mixed-type tumors but not in epithelial-type tumors* [47]. A shared target for five co-downregulated microRNAs is a network-level observation of a kind this literature rarely produces, and it provides the mechanistic rationale: coordinated loss of the module de-represses TGF-beta/activin receptor signaling in a tissue whose differentiation depends on it. Beyond that study, the verified miR-194-5p evidence is thin: it is reported by two studies sharing a first author, one of which states downregulation (Table S4), but the one Wilms tumor study assigning it a target (*CRK*, EMT and metastasis) has been retracted (PMID 31889432 [21]; Section 6.2) , and no other verified study assigns miR-194-5p a target. We therefore present this module as a well-motivated hypothesis with one supporting Wilms tumor study, not as an established axis.

3.7.4. miR-483: The 11p15 Locus Read Out as a microRNA

miR-483 is processed from intron 2 of *IGF2* at 11p15.5, the imprinted locus whose loss of imprinting or paternal uniparental disomy is the commonest epigenetic lesion in Wilms tumor. Its expression is therefore coupled to the same dosage event that drives IGF2 overexpression, which is why it behaves unlike a conventional oncomiR: it is not independently dysregulated, it is a reporter of the locus. miR-483-3p was reported overexpressed in 100% of the Wilms tumors examined in the original description of the locus, where it targets *BBC3*/PUMA and blocks apoptosis [49]; in Wilms tumor cells, it also targets *PTEN*, feeding PI3K/AKT and chemoresistance [23]. The 5p arm has a different target set, including *MKNK1* [50].

This family is also the sharpest illustration of why the arm-designation recommendation in Section 6.1 is a mechanistic requirement and not a bibliographic nicety. The two arms derive from one hairpin at one locus, yet they are reported with opposite directions and act on different networks; pooling them manufactures a contradiction and resolving them dissolves it. Any therapeutic proposal built on “miR-483” that does not specify the arm is, in network terms, under-specified.

3.7.5. miR-21 and the General-Purpose Amplifiers

A fifth group is best characterized by what it does not explain. miR-21 is the single microRNA most often examined in this literature, acting on *PTEN* [27,51,52] and through

PI3K/AKT. But miR-21 up-regulation is close to universal across tumor types, its targets (*PTEN*, *PDCD4*, *SPRY1/2*, *TIMP3*) are general survival and motility regulators, and the Wilms tumor evidence for it is weaker than the count implies: one study found overexpression in only 4 of 24 tumors, with borderline expression in three more and no difference in the remaining 17 with no in situ hybridization signal [35], and two of the tissue reports share an identical author list (Section 5.1). We therefore distinguish, in Table 1, families whose network has a developmental rationale in this disease from amplifiers whose dysregulation is real but not disease-specific, a distinction that matters directly for biomarker specificity.

3.7.6. What the Four Networks Have in Common

The convergence is the point. Loss of let-7 sustains the progenitor state; loss of miR-200 prevents the mesenchymal-to-epithelial transition; loss of miR-192/194/215 removes a tubular differentiation brake; and gain of miR-483 amplifies the IGF2 axis and blocks apoptosis. These are four sequential control points in a single developmental program, and three of the four are directly downstream of microprocessor function, which is why a mutation in DROSHA or DGCR8 does not produce a random microRNA deficit but a coherent arrest at the nephron progenitor stage. The fourth, miR-483, is downstream of the other defining lesion of the disease, 11p15 loss of imprinting. Wilms tumor microRNA biology is therefore better described as a developmental timing defect with two genetic entry points than as a collection of independent oncomiR and tumor-suppressor pairs.

Two caveats follow from this review's own standards. For every family except miR-483, the target networks summarized here were established principally in non-renal tissue, and their Wilms-tumor-specific validation is thin; Table 1 separates these columns explicitly. And a substantial part of the pair-level evidence that appears to support them was generated in cell lines that are not Wilms tumor lines (Section 4.1). The network logic is strong; the Wilms-tumor-specific experimental support for it is exactly what the organoid program proposed in Sections 10 and 4.5 is designed to supply.

Table 1. MicroRNA families recurrently reported in Wilms tumor: networks and phenotypic consequences. Columns 2–4 summarize network biology established principally in non-renal tissue; the final column states what this review's evidence base supports in Wilms tumor specifically. Retracted sources are marked and are not treated as evidence (Section 6.2).

Family	Locus/Upstream Control	Core Validated Targets	Developmental Control Point	Consequence of Dysregulation	Wilms Tumor-Specific Evidence in This Review
let-7 (let-7a, let-7 family)	Multiple loci; MIRLET7A at 9q22. Post-transcriptionally blocked by LIN28A/B and TUT4/7, then DIS3L2 degradation [37–39]	HMGA2 [40], IGF2BP1-3, MYC/MYCN, KRAS/NRAS [41], CCND1, LIN28B (feedback)	Timing of nephron progenitor (SIX2+ cap mesenchyme) self-renewal vs. differentiation	Progenitor state persists; blastemal-predominant histology; nephrogenic rests	Strong. LIN28B gain + MIRLET7A loss [4]; reduced mature let-7a in microprocessor-mutant tumors [3]; Lin28b overexpression induces Wilms-like tumors in mice, let-7-dependent [42]; distinct biogenesis defects for DROSHA vs. DICER1 mutants [44]
miR-200 family (miR-200a/b/c, -141, -429)	Two clusters, 1p36 and 12p13; ZEB1/ZEB2 repress their promoters (double-negative loop)	ZEB1, ZEB2 [45,46]; in Wilms tumor: ACVR2B [47]; IKK-beta (miR-200b, miR-429; Table S4)	Mesenchymal-to-epithelial transition of cap mesenchyme into renal vesicle	MET switch fails; mesenchymal/blastemal program retained; CDH1 low	Moderate. Family reduced in microprocessor-mutant tumors [3]; downregulated in renal childhood neoplasms [47]; discriminates cancer-initiating cells in WT xenografts [48]; other reported target axes did not pass verification against their source (Section 3.7)
miR-192/194/215	miR-194-1/miR-215 at 1q41; miR-192/miR-194-2 at 11q13.1; expressed in differentiating tubular epithelium	ZEB2; in Wilms tumor: ACVR2B [47]; CRK (retracted article, PMID 31889432 [21])	Tubular epithelial differentiation; reinforcement of the miR-200 switch	Derepression of TGF-beta/activin receptor signaling; differentiation brake lost	Limited. One study links the whole module through a common target [47]; miR-194-5p is reported by two verified studies sharing a first author, one of which states downregulation (Table S4); the only WT target study is retracted (PMID 3188932).
miR-483 (-5p, -3p)	Intron 2 of IGF2, 11p15.5; expression coupled to the imprinted locus	miR-483-3p: BBC3/PUMA [49], PTEN [23]; miR-483-5p: MKNK1 [50]	IGF2 dosage; apoptotic threshold in an IGF2-driven embryonal tumor	Apoptosis blocked; PI3K/AKT amplified; chemoresistance	Moderate, but arm-dependent. 3p overexpressed in 100% of tumors in the locus description [49]; the two arms are reported with opposite directions (Section 6.1), which pooling conceals
miR-21 and general amplifiers	17q23, intronic to VMP1; stimulus-responsive (NF-kB, STAT3)	PTEN [27,51,52], PDCD4, SPRY1/2, TIMP3	None specific to nephrogenesis	PI3K/AKT amplification; survival and motility, not disease-specific	Weak relative to its citation frequency. 4 of 24 tumors positive by qPCR with no ISH signal in one study [35]; two tissue reports share an author list (Section 5.1)

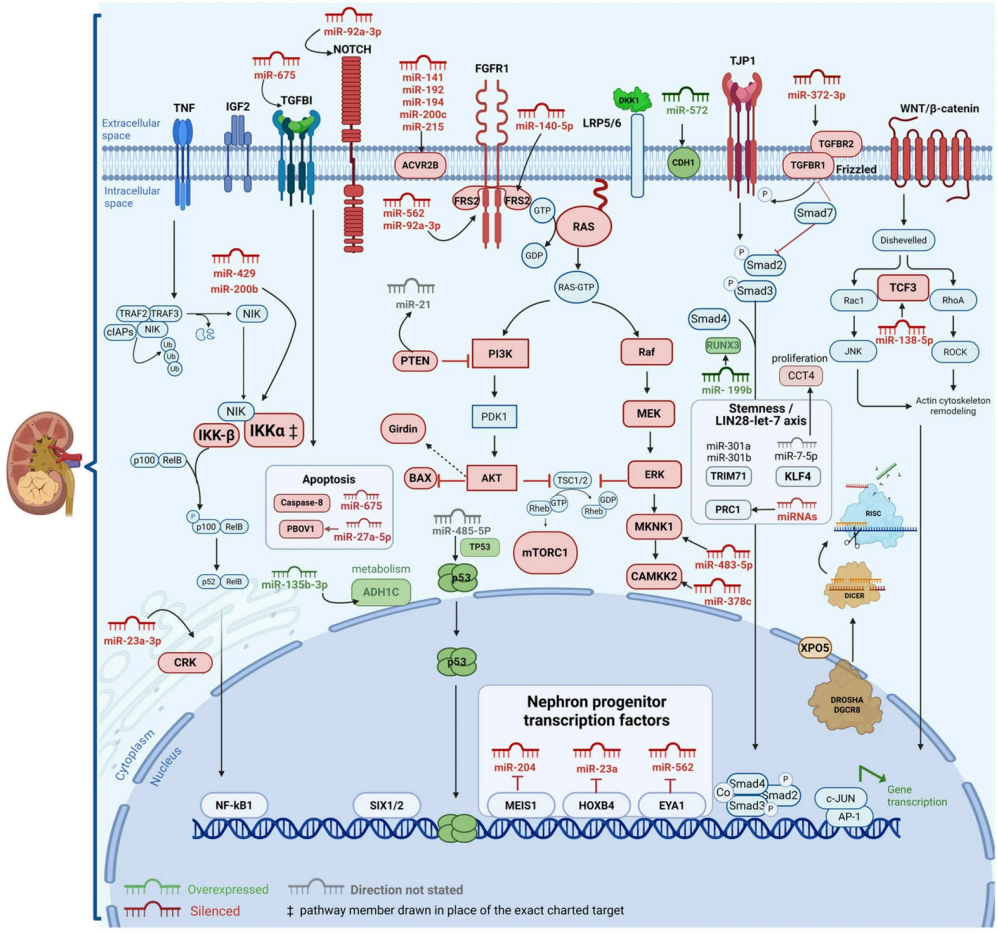


Figure 1. Verified microRNA–target relationships in Wilms tumor. All 31 microRNA–target relationships in the verified evidence table (Table S4) are drawn, involving 28 microRNAs from 24 studies. They are grouped by the process on which they act: nephron progenitor transcription factors (MEIS1, HOXB4, EYA1), the LIN28/let-7 stemness axis (TRIM71, KLF4, PRC1), and the canonical signaling pathways RAS/MAPK, NF-κB, TGF-β/Smad, Wnt/β-catenin, PI3K/AKT/mTOR and p53. Hairpin color gives the direction reported by the primary source: green, reported overexpressed; red, reported silenced; gray, direction not stated in the source. Arrows indicate the direction of signal flow or an activating relationship, and bar-headed lines indicate repression; a hairpin joinde to a molecule denotes a reported microRNA-target relationship. Only pairs that passed verification against their primary source are drawn. Pairs resting on a retracted study, on a non-authentic cell line, or on a finding not stated in the source are excluded from the figure, , which is why the earlier evidence-quality symbols are no longer required here; the integrity analysis itself is reported in Figure 2 and Section 6.2. Where the molecule drawn is the pathway member rather than the exact charted target (IKKα drawn for IKK-β), this is marked with a double dagger. The hairpin reaching PRC1 is labeled generically because its source reports downregulated PRC1-targeting microRNAs without naming them [53]; the gray miR-7-5p hairpin reaching CCT4 is a second, independent relationship of that microRNA [54]. Receptors and pathway components that carry no microRNA are drawn as architectural context and do not derive from the verified evidence table. The microRNA biogenesis module (DROSHA/DGCR8, XPO5, DICER, RISC) rests on studies of genetic lesions in the processing machinery rather than on charted microRNA–target rows. One relationship, miR-675 with TGFBI and caspase-8, rests on HFWT, a cell line for which no independent STR re-authentication is on record (Table S3). No miR-193a/WNT relationship is shown, because no study in the evidence base supports it in Wilms tumor. Created in BioRender. Martinez, N.L. (2026) https://BioRender.com/y4lt4c6. .

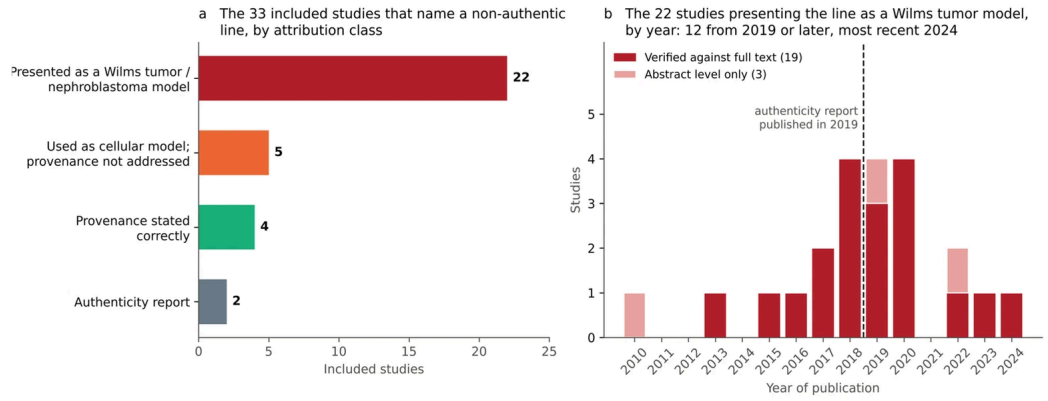


Figure 2. Cell line authenticity in the Wilms tumor microRNA literature. (**a**) The 33 included studies that name a non-authentic line, by attribution class (22 present it as a Wilms tumor model, 5 use it without addressing provenance, 4 state the provenance correctly, and 2 are the authenticity reports). (**b**) The 22 studies that present such a line as a Wilms tumor model, by publication year, distinguishing those verified against the full text from those classified at abstract level; the dashed line marks the year of the 2019 authenticity report. Classification was confirmed against full texts in 19 of the 22 studies in the "presented as a Wilms tumor model" class, and all 19 were confirmed; the verbatim Methods or Results sentence for each is given in Table S2, where every study contributing to this figure is itemized with its PMID, DOI, year and journal, so each classification can be traced to its source, and 5 of the 22 are cited in the reference list; the other 17 are documented in Table S2 only. None of these 22 studies contributes an entry to the verified evidence table (Table S4): every evidence row that rested on a non-authentic line was excluded at verification. Detection is at the title/abstract level, so counts are lower bounds. One further study (PMID 41157796) names G-401 and states its correct rhabdoid-tumor provenance in the Methods while still treating it as a Wilms tumor model in the Results and Discussion; it is classified here as stating provenance correctly, with that qualification recorded in Table S2. Four studies added by the verification search are included in these counts and are itemized in Table S2 alongside the original records; the screening record for the 380 records that search surfaced is given in Table S2b.

4. Methodological Criterion: What the Models Can and Cannot Support

4.1. The Cellular Evidence Base Rests Substantially on Non-Wilms Cell Lines

Any assessment of organoids as a platform must start with what they would replace. In 2019, Pritchard-Jones and Perotti published a formal warning that G-401 and SK-NEP-1, the two most widely used "Wilms tumor" cell lines, are not Wilms tumor lines at all. G-401 is a malignant rhabdoid tumor of the kidney, and SK-NEP-1, long considered an anaplastic Wilms tumor line, is related to Ewing sarcoma [5]. An earlier report had already shown this for SK-NEP-1 and the related line Rh1 by identifying the EWS-FLI1 fusion [55].

We quantified how far this problem extends into the microRNA literature. Among the 176 studies reviewed here, 36 name a cell line in the title or abstract. Of these, 33 name a line that is not a Wilms tumor line—31 use it as a model and 2 are the authenticity reports themselves, and 28 name no authentic Wilms tumor line at all. Only 8 name an authentic line. Across the full 1338-record corpus, G-401 appears in 67 records (23 included studies) and SK-NEP-1 in 41 records (17 included studies), against just 25 records for the authenticated line WiT49 (5 included studies) and 8 for WT-CLS1 (3 included studies). Because cell lines are frequently described only in the Methods sections, this title/abstract-based count is expected to underestimate the frequency of non-authenticated or misclassified lines; the full-text verification reported below bears this out for the studies it covers, but the magnitude of the underestimation across the whole corpus can-

not be determined from the charted fields.

Reading the actual line-naming sentence of each flagged study splits them into four groups (Figure 2). Twenty-two of the 31 studies that use such a line present it explicitly as a Wilms tumor or nephroblastoma model. Five use such a line as their only cellular model without stating any provenance at all. Four state the provenance correctly, describing the lines by their true tumor types or as formerly classified Wilms lines, which is a legitimate use of the lines for the diseases they actually model. The remaining two records are the authenticity reports themselves.

The most telling observation here is temporal. Within this corpus, misattribution did not stop when the warning was published: of the 22 studies that present a non-authentic line as a Wilms tumor model, 12 appeared in 2019 or later, and the most recent is from 2024. Because this classification was taken from the charted fields, which are abstract-level, we verified it against the full texts for 19 of the 22 studies; in all 19 the Methods or Results explicitly designate G-401, SK-NEP-1 or another non-authentic line as a Wilms tumor or nephroblastoma line, 10 of them published in 2019 or later, and 2 of the 19 have themselves since been retracted (Table S2). The remaining three (PMIDs 20979833, 31194576 and 35144475) could be read only at abstract level, where each names the line and presents it as a nephroblastoma model; their classification rests on the quoted abstract sentence recorded in Table S2, and the counts are reported as lower bounds accordingly. *This is our own synthesis, not a claim made by any individual study*, but it has a direct implication for this review: a substantial fraction of the mechanistic microRNA–target literature summarized in Section 3.5 effectively describes the biology of rhabdoid and Ewing family tumors while labeling it Wilms tumor.

A second, softer flag applies to HFWT, which shows up in 16 corpus records (6 included studies). HFWT is reported as a Wilms tumor line, and we have not classified it as non-authentic. We note only that we could not find an independent short tandem repeat (STR) re-authentication anywhere in this corpus, and that such confirmation would be advisable before the line is used as the sole model for a mechanistic claim.

4.2. Authentic Two-Dimensional Lines and Patient-Derived Xenografts

WiT49, derived from an anaplastic Wilms tumor lung metastasis, is the best-characterized authentic line, and it appears in recent functional work: for example, miR-138-5p inhibiting WiT49 growth by downregulating *TCF3*, with in vivo confirmation [56]. WT-CLS1 is a second authenticated option, named in the title or abstract of three of the included studies and used for the reporter assays of at least one more [47]. Both, however, share the inherent limitations of monolayer culture in a tumor defined by triphasic histology. A single line cannot represent blastemal, epithelial, and stromal compartments all at once, and adaptation to plastic culture tends to select against the very progenitor state that defines the disease.

Patient-derived xenografts partially address that heterogeneity problem and have been used for therapeutically oriented work: for instance, characterizing sensitivity to vincristine, irinotecan, and telomerase-targeted therapy in diffuse anaplastic Wilms tumor using cell lines, spheroids, and four patient-derived xenografts [57]. PDX models preserve tumor architecture and inter-patient variation, but they are slow and costly, do not allow high-throughput perturbation, and place human tumor cells in a murine stroma within an immune-deficient host, which is a specific problem for microRNA work, where the tumor microenvironment and extracellular-vesicle traffic matter.

4.3. Kidney Tumor Organoids: What Has Been Established

The pediatric kidney cancer organoid biobank reported by Calandrini and col-

leagues contains tumor and matching normal kidney organoids from more than 50 children, across Wilms tumor, malignant rhabdoid tumor, renal cell carcinoma, and congenital mesoblastic nephroma. The authors showed that these organoids retain key properties of the native tumors and reveal patient-specific drug sensitivities [6]. This is the field's reference point: it establishes that pediatric renal tumors can be propagated in three dimensions while keeping their genomic and transcriptomic identity, and that matched normal tissue is obtainable from the same patient, a control that neither cell lines nor PDX can offer.

Later work has refined what the different three-dimensional formats actually capture. A 2025 study set up long-term Wilms tumor cultures through three different routes and found that adherent cultures end up dominated by stromal cells, three-dimensional spheroids model blastema, and patient-derived organoid cultures of tumor and healthy kidney preferentially grow epithelial cells [58]. This is methodologically important and, in our view, under-appreciated: the culture format selects the compartment. A microRNA profile generated from a Wilms tumor organoid is not a profile of "the tumor" but a profile of whichever compartment the chosen format happens to enrich, which for organoid culture appears to be epithelial, a compartment not typically associated with the poor outcomes of blastemal-predominant disease. A second, independent approach targets the blastemal compartment directly rather than working around its loss in standard culture. Applying niche conditions originally developed for normal nephron progenitor cells to primary Wilms tumor material maintained the progenitor/cancer-stem-cell markers *SIX2*, *NCAM*, *YAP1*, and *ALDH1* through multiple passages in five patient tumors, yielding new multi-passage Wilms tumor cell lines biased toward the blastemal lineage [59]. This study was not retrieved by our search strategy, which represents a genuine gap in coverage rather than a borderline exclusion. It reports no microRNA data and is therefore not charted in Table S4; it was missed because it describes "niche conditions" and "cell culture" rather than "organoid", "spheroid", or "3D," the terms on which our three-dimensional model search block was built. To our knowledge, it is the only published culture system designed specifically to enrich, rather than dilute, the blastemal compartment, and it would pair naturally with compartment-resolved microRNA profiling (Section 4.5).

Organoids have also been used for tumor-relevant genetic modeling rather than propagation. *WT1* deletion during kidney organoid development produced progenitor overgrowth at the expense of differentiation and recapitulated transcriptional changes seen in a patient subgroup [16], and *WT1*-mutant organoids have been used to map podocyte developmental regulation [17]. Safety-oriented work established that induced pluripotent stem cell–derived kidney organoids can form tumors, though not teratomas, on long-term implantation [60], and nephron progenitor expansion systems now allow organoid maturation and disease modeling [61]. Other groups have added immune components through organoid-on-chip approaches [62].

4.4. No Study Profiling microRNAs in a Kidney Tumor Organoid Was Identified in This Search

We tested this gap empirically rather than assuming it. Within the 1338-record corpus, 65 records use a genuine three-dimensional kidney model (organoid, tumoroid, spheroid, or organotypic culture; we excluded Matrigel invasion and Transwell assays, which are two-dimensional; Table S2). Of these, 46 concern a kidney tumor model and report no microRNA data, 7 measure microRNAs but in normal or developmental kidney organoids, and 10 are normal-kidney three-dimensional studies with no microRNA data; the remaining two records are discussed below. None of the records identified in this search measures microRNAs in a kidney tumor organoid (Figure 3). The three-di-

mensional model block was re-run in both recall checks (Table S1) and neither returned such a study; nonetheless, one three-dimensional Wilms tumor culture system was missed by this block on vocabulary grounds [59], so this is an absence in the present search rather than a demonstrated absence in the literature. Two records appeared, on automated screening, to combine a kidney tumor model with microRNA data, but we excluded them on reading: an adult clear cell renal cell carcinoma extracellular-vesicle study that mentions kidney organoids only as a speculative future source of therapeutic vesicles [63], and a narrative review of renal regenerative medicine [64].

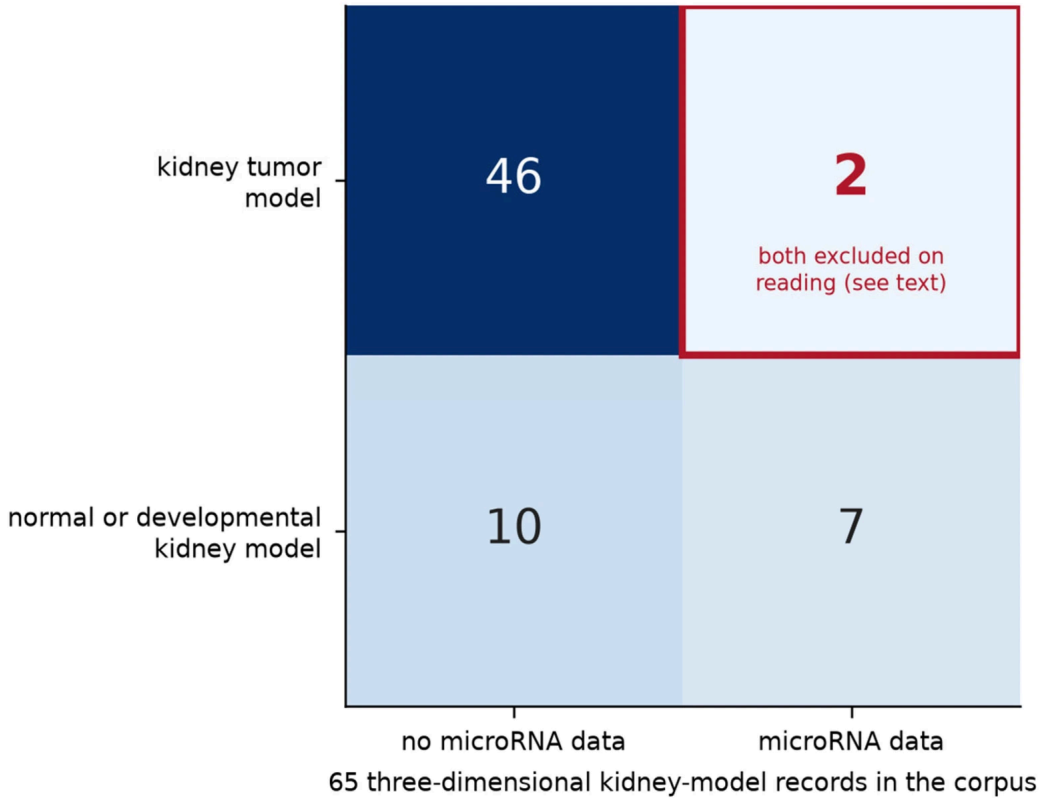


Figure 3. The organoid–microRNA gap. The 65 records identified in this search that use a genuine three-dimensional kidney model, cross-classified by whether the model is a kidney tumor model and whether microRNA data are reported. The two records falling in the tumor × microRNA cell were excluded on closer reading (Section 4.4), leaving it empty.

The gap is therefore not one of capability. The organoid models exist [6,58], microRNA in situ detection chemistry has already been demonstrated in human kidney organoids [15], and functional microRNA work in three-dimensional kidney tissue has been published in the developmental setting [14]. These two literatures have simply not yet been combined.

4.5. Design Considerations for microRNA Profiling in Wilms Tumor Organoids

From the foregoing, we derive four requirements that we believe a first study should satisfy, offered as this review's synthesis rather than as established practice.

1. Compartment must be reported, not assumed. Given that culture format selects compartment [58], microRNA profiles should be accompanied by compartment markers and, ideally, generated from more than one format (organoid and spheroid) from the same tumor.
2. Matched normal kidney organoids should serve as the comparator. The biobank de-

sign already provides them [6], and doing so avoids the adjacent-normal-tissue problem that complicates interpretation of tissue-based expression direction (Section 6).

3. Small RNA sequencing rather than targeted panels, with isomiR-level resolution. Recent Wilms tumor work shows that isomiR diversity carries biological signal that panel assays cannot see: higher diversity and abundance of miR-455-5p isoforms were associated with a suppressive role, with key findings validated in an independent cohort of 63 surgical samples (55 tumors and 8 normal controls), in which SP100 expression and its co-localization with miR-455-5p were validated [65]. Arm-level reporting is equally essential (Section 6).
4. Genotype the organoids for microRNA-processing-gene mutations. Since *DROSHA*/*DGCR8* status defines a distinct microRNA output state [3,7], an unstratified organoid panel risks averaging across two mechanistically different diseases.

5. Clinical and Translational Criterion: microRNAs as Biomarkers

5.1. Tissue microRNAs, Histology and Risk Stratification

The most clinically direct application proposed for Wilms tumor microRNAs is stratification at the pre-treatment biopsy stage. Watson and colleagues generated genome-wide microRNA profiles of blastemal cells from tumors treated on the International Society of Pediatric Oncology (SIOP) protocol and found that unsupervised hierarchical clustering separates intermediate-risk from high-risk tumors, proposing the profile as a predictor of chemoresponsiveness [66]. More than a decade later, this is still one of the few studies in this literature built around a defined clinical decision point rather than a molecular mechanism.

More recent work has pushed toward higher resolution. An isomiR-level analysis of TARGET data found that greater diversity and abundance of miR-455-5p isoforms are associated with a suppressive role in Wilms tumor, with validation of key findings by immunohistochemistry and multiplex immunofluorescence combined with in situ hybridization in an independent cohort of 63 surgical samples (55 tumors and 8 normal controls) [65]. To our knowledge, this is the only Wilms tumor microRNA study in this corpus that reports isomiR-level resolution together with validation of key findings in an independent cohort. Elsewhere, miR-204 and miR-483-5p have been examined against clinicopathological parameters [67], and microRNA alterations have been characterized in diffuse hyperplastic perilobar nephroblastomatosis (DHPLN), the precursor lesion whose relationship to overt tumor is central to the progenitor-arrest model in Section 3.

A nine-microRNA panel there (let-7, miR-135, miR-146a-5p, miR-182-5p, miR-183-5p, miR-20b-3p, miR-29b-3p, miR-195-5p, miR-17-5p) showed potential to distinguish DHPLN from WT in a four-case FFPE study compared against public data, and the authors note that further validation is needed [68]. The same group later applied the same panel approach to a different clinical question, comparing primary and metastatic WT directly rather than WT and its precursor lesion, and found five microRNAs (miR-17-3p, miR-34b-3p, miR-34c-5p, miR-375-3p, miR-616-3p) differentially expressed between the two. The miR-34 family finding stands out because these microRNAs are usually tumor-suppressive and downregulated in most other cancers, but here they were elevated in metastatic tissue [69].

Archival formalin-fixed, paraffin-embedded (FFPE) specimens have also been profiled: a pilot study of eight regressive Wilms tumors reported underexpression of miR-184, miR-194-5p, and miR-203a and showed that most FFPE samples up to 9 years old yielded microRNA of sufficient quantity and quality for quantitative real-time PCR [70]. miR-21 is among the tissue microRNAs most often examined in this literature, although

only one report is retained in the verified evidence table (Table S4). Overexpression relative to para-tumoral tissue, with reciprocal PTEN reduction, has been reported in relation to clinicopathological parameters and prognosis [51], in tumors with aggressive behavior [52]. A further study, however, found overexpression by quantitative PCR in only 4 of 24 tumors and no in situ hybridization signal, and concluded that the involvement of miR-21 may be weak [35]. A lncRNA-mediated mechanism through KCNQ1OT1 has also been proposed [27]. Part of the functional work on miR-21/PTEN was done in non-authentic cell lines (Section 4.1). The tissue-level association is supported by patient material, but it is less well replicated than its citation frequency suggests: two of the tissue reports [51,52] share an identical author list and year. Their full texts report different patient series, accrued in non-overlapping periods at the same institution (89 tumors collected 2007–2010 and 41 collected 2013–2016, Shandong Provincial Hospital), so the cohorts do not overlap but they are not independent either: one group, one institution, one referral population. We therefore treat miR-21 as repeatedly reported but not independently replicated at the tissue level. A second pair in this corpus has the same structure. PMID 31907159 (2019, Chinese) and reference [29] (2020) report miR-155-5p in Wilms tumor under an identical ten-author list in the same order, in different journals and one month apart (issue dates December 2019 and May 2020; PubMed entry January and February 2020), too close together for either to be read as revising the other. They are not a duplicate publication: the later paper adds a microRNA microarray, RNA sequencing, a re-analysis of public cohorts, chemotherapy stratification and the IGF2/PI3K mechanism that the earlier one does not contain. But the earlier paper reports a 40-patient tissue cohort and the later one does not state the provenance of its specimens, so the two tissue observations cannot be assumed independent. The pair is also instructive for Section 4.1: the 2019 paper calls G401 a “Wilms tumor cell line” while the 2020 paper from the same authors describes it correctly as “a rhabdoid cell line” alongside “Ewing sarcoma cell line (SK-NEP-1)”, which is why the two sit in different attribution classes in Table S2.

A distinct and fast-growing category is the in silico prognostic signature built from public data, for example cuproptosis-related lncRNA signatures [71]. These studies typically derive risk scores through least absolute shrinkage and selection operator (LASSO)-Cox regression on data from The Cancer Genome Atlas (TCGA), TARGET, and the Gene Expression Omnibus (GEO). Two limitations apply to the whole class rather than any single paper here. The same small number of public Wilms tumor cohorts keeps getting reused, so what looks like independent replication across signatures may not actually be independent. And external validation in a prospectively collected cohort has not, in this corpus, been shown for any of them.

Germline variation in microRNA genes has also been examined: the miR-196a2 rs11614913 C allele was associated with increased Wilms tumor susceptibility in 416 Chinese Han patients versus 936 matched controls [72]. This is a single-population case–control result, and it requires replication in other ancestries before it can be treated as a susceptibility locus for the disease more broadly.

5.2. Circulating microRNAs and Liquid Biopsy

Serum and plasma microRNAs are appealing in a tumor where biopsy carries a tumor-spillage risk, and where SIOP protocols commit patients to preoperative chemotherapy without histological confirmation. Next-generation sequencing of the serum microRNAome in an Egyptian pediatric cohort identified miR-1180-3p as a candidate biomarker for anaplastic (unfavorable-histology) disease, with 92% sensitivity and 85% specificity in that cohort [73]. This is a considerably more concrete diagnostic perfor-

mance figure than most of this literature offers, although it comes from a single, unreplicated cohort. Tissue-level work reaches a related but distinct conclusion about a different pair of microRNAs: miR-29a and miR-200b distinguished metastatic Wilms tumor from controls in an independent cohort, although the difference against non-metastatic tumors was not significant; the authors framed this around Hippo-pathway involvement in the five microRNAs they examined [74]. Other classes of circulating non-coding RNA, serum piRNAs and exosomal long non-coding RNAs, have been proposed in Wilms tumor too, but they report no microRNA measurement and fall outside what we chart here.

In our assessment, this area is promising but still immature. The studies are small, single-center, and single-cohort. Pre-analytical variables known to dominate circulating microRNA measurements (hemolysis, normalization strategy, platelet contamination) are reported inconsistently at best. Moreover, no circulating Wilms tumor microRNA in this corpus has been validated across two independent cohorts. We found no study reporting serial circulating microRNA measurement across the neoadjuvant chemotherapy window, which is exactly the measurement needed to support the response-monitoring application most often proposed for these markers.

5.3. Response to Neoadjuvant Chemotherapy and Chemoresistance

Direct evidence on chemotherapy response is limited in this corpus: one study related the microRNA profiles of blastemal cells from SIOP-treated tumors to chemoresponsiveness [66], and one reported that miR-483-3p promotes chemoresistance in Wilms tumor cells in vitro [23]. The persistent difficulty is that post-chemotherapy specimens are the norm under SIOP protocols, while pre-chemotherapy specimens are the norm under COG protocols, so expression measured in one setting is not directly comparable to the other. Several of the contradictions cataloged in Section 6 plausibly arise from exactly this difference, and we recommend that Wilms tumor microRNA studies treat treatment status at sampling as a mandatory reporting item.

6. Cross-Cutting: Evidence Quality, Contradictions and Integrity

6.1. Directional Contradictions

Charting expression direction systematically brings up disagreements that narrative reviews tend to overlook. After separating hairpin arms and comparing specimen compartments, disagreements between studies remain. We describe them narratively below rather than tabulating them, because a directional contradiction can only be asserted where both sides have been verified against their sources. miR-483-5p is reported as upregulated in post-chemotherapy high-risk blastemal tissue relative to the epithelial and stromal components of intermediate-risk tumors, with no significant difference in pretreatment biopsies (corrected $p = 0.193$) [66] and in tumor tissue relative to normal tissue [67], but as downregulated in tumor tissue relative to adjacent normal tissue in another study [50]; only the last two studies use the same contrast, and they disagree. miR-143-3p is reported as elevated in serum in the initial set of one study (6.9-fold) but lower in patients than in controls in that study's own independent validation set, where the retained signature kept only miR-100-5p and miR-130b-3p [75], and as reduced in tumor tissue in two other studies [31,76], one of which showed tumor-suppressive function in a non-authentic line [31] and one of which did not state the arm and compared Wilms tumor with neuroblastoma [76]; the serum and tissue findings concern different compartments and are not strictly contradictory. miR-145-5p gets opposite roles from two 2021 studies that disagree only in the inferred direction of a competing-endogenous-RNA axis [77,78]; neither abstract name a cell line, but the full texts show that both rely on SK-

NEP-1 and G401 for their functional work. Here the conflict concerns interpretation rather than the expression actually measured.

An instructive near-contradiction concerns miR-483. Reports of opposite direction for "miR-483" disappear once you keep the arms separate: miR-483-5p and miR-483-3p are distinct molecules with distinct reported behavior, and collapsing them together, which is common practice in this literature, creates a conflict that does not really exist. The opposite error also occurs: several papers use the arm suffix inconsistently. We recommend that arm designation become mandatory nomenclature in this field. This recommendation is our own synthesis and follows directly from the charting exercise.

A second kind of apparent conflict comes from comparator choice. Studies comparing tumor with adjacent "para-tumoral" or "adjacent normal" kidney do not measure the same contrast as studies comparing tumor with fetal or developing kidney, and in an embryonal tumor that arises from retained nephrogenic tissue, that difference matters. Where direction disagrees between studies using different comparators, we record both rather than picking one.

We also screened and rejected two further candidate conflicts that arose from automated text classification: for miR-21, a tumor-suppressor gene named in the same sentence as the microRNA was misread as a statement about the microRNA; for miR-140-5p, two different microRNAs described in a single sentence were merged. These rejected candidates are retained in the register with their reason for rejection, so that the adjudication is auditable rather than invisible.

6.2. Retracted Publications

Screening publication types and correction cross-references in the retrieved PubMed records turned up 24 retracted articles within the corpus, of which 11 fall inside the included set (Figure 4 and Table S2). Four of these are also flagged for non-authentic cell line use. The retracted set clusters in the competing-endogenous-RNA literature described in Section 3.5, and at least one microRNA–target pair discussed in Section 3.6 (miR-155-5p) is also supported by a retracted study [36].

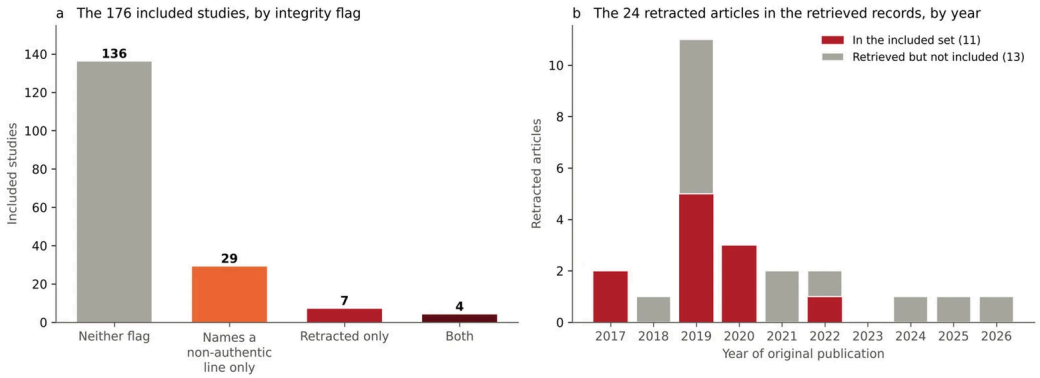


Figure 4. Evidence integrity. (**a**) The 176 studies reviewed here, by integrity flag: retracted only (7), naming a non-authentic line only (29), both (4), or neither (136). (**b**) Year of original publication of the 24 retracted articles identified in this literature, split by whether they fall inside the included set.

Three points are worth making here. Retraction status has to be checked at the point of citation, not inherited from earlier reviews, since retraction notices are often published after the reviews that cite the original paper. A retracted article is not evidence, but neither is it evidence of the opposite: the underlying hypothesis simply returns to being untested rather than disproved. And the fact that retraction and non-authentic model

use cluster together in the same subliterature is, in our view, the clearest signal we have that the Wilms tumor ceRNA field needs independent confirmation in authentic material before any of its individual axes move into clinical or preclinical development.

6.3. Replication

Of the 62 distinct microRNAs in the verified evidence table (Table S4), 52 are reported by a single study (this and all other counts in this section keep 5p/3p arms separate, consistent with the arm-designation recommendation in Section 10; collapsing to 57 precursor-level loci, treating both arms of the same hairpin as one entity, leaves 43 of 57 reported once and does not materially change this picture). Only 10 microRNAs are reported by 2 or more studies, and for 3 of these (miR-184, miR-194-5p, and miR-203a), both reports share a first author. Only miR-483-5p is reported three times, and its direction differs between studies (Section 6.1). These counts are sensitive to arm reporting: the one study that reports miR-194 and miR-215 without an arm designation [47] is kept separate from the miR-194-5p and miR-215-5p entries, and if the same mature species was measured, miR-194-5p would have three reports and miR-215-5p two. Molecules that dominate the wider literature, such as miR-21, the miR-200 family, miR-140 and the let-7 family, are not among the replicated entries: most of the reports on them rest on non-authentic cell lines, on retracted articles, or on findings that could not be confirmed against the source, and were therefore excluded at verification (Sections 2, 4.1 and 6.2). The field's usable evidence is thus a short list of replicated observations plus a long unreplicated tail. Figure 5 shows the distribution. This is not unusual for a rare tumor, but it affects how this literature should be read: single-study findings are hypotheses, and the value of a review such as this one lies in identifying which of them are worth testing in authentic models.

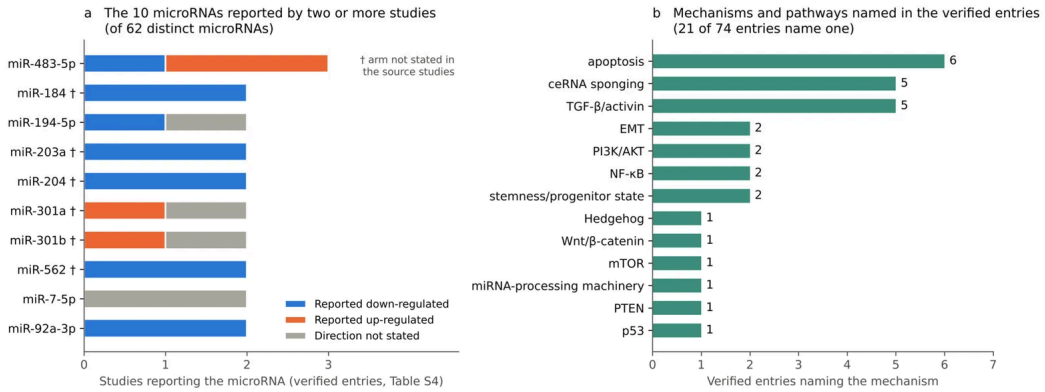


Figure 5. The Wilms tumor microRNA landscape. (**a**) The ten microRNAs in the verified evidence table (Table S4) reported by two or more studies, of 62 distinct microRNAs, with 5p and 3p arms kept separate and broken down by the expression direction each study reports. Entries marked † are those for which the source studies give no arm designation (6 of the 10; across the whole table, 39 of the 74 entries, 53%, carry no arm designation), the reporting deficit that motivates the arm-designation recommendation in Section 6.1. The unit is studies, not independent research groups; for miR-184, miR-194-5p and miR-203a the two contributing studies share a first author. (**b**) Mechanisms and signaling pathways named in the verified entries; 21 of the 74 entries name one.

7. Recent Literature, 2024–2026

Thirty of the included studies were published from 2024 onward (13 in 2024, 12 in 2025, 5 in 2026 up to the search date); and they are identifiable in the screening records (Table S2), and those whose findings passed verification appear in Table S4.

Four developments in this window change the picture rather than merely adding to it. The functional characterization of *DROSHA*-driven mesenchymal gene expression [7] turns the processing-gene subclass from a genomic association into a mechanism. Germline *DROSHA* variants were established as a pineoblastoma/Wilms tumor predisposition phenotype [8], and the *DICER1*-associated renal neoplasia spectrum was described [9], extending the microRNA-machinery story into cancer predisposition. The finding that culture format selects tumor compartment in Wilms tumor cultures [58] gives us the key design constraint for any future organoid-based profiling study. And isomiR-level analysis with validation of key findings in an independent cohort [65] shows that resolution below the mature-microRNA level carries signal in this disease.

Two of these thirty carry a non-authentic cell line flag at the abstract level, one published in 2024 and the other in 2026 [79] (Table S2). This shows that the model-authenticity problem remains current rather than merely historical, even though its abstract-level prevalence in the most recent window appears low.

8. Summary of the Evidence

This section condenses what the preceding sections establish, separating three things that are easy to conflate: results that have been observed, interpretations that the original authors placed on them, and the synthesis this review adds. Table 2 summarizes the position by criterion.

Across the three criteria the evidence is not uniformly strong, and its strength does not track the volume of publication. The mechanistic criterion is the best supported. Recurrent mutation of *DROSHA*, *DGCR8*, *DICER1,* and *XPO5*, *SIX1*/*SIX2* alteration, *LIN28B* gain with *MIRLET7A* loss, and the resulting shift toward an arrested metanephric mesenchyme state are observations from large, independently assembled human cohorts [3,4,7,10], and the functional work that followed [7] turns the genomic association into a mechanism. This part of the field would survive the removal of any single study.

The methodological and clinical criteria are not in that position. Most individual microRNA–target axes in our evidence table rest on a single study: 52 of the 62 microRNAs in the verified evidence table are reported once (Section 6.3 and Table S4). A large share of the cellular work rests on material that is not Wilms tumor: of 36 studies naming a cell line in the title or abstract, 33 named at least one non-authenticated line, and 22 presented such a line as a Wilms tumor or nephroblastoma model (Section 4.1 and Figure 2). Eleven of the included studies have been retracted (Section 6.2 and Figure 4). On the clinical side, tissue and circulating signatures are reported in association with histology, nephrogenic rests and chemotherapy response, but almost none has been re-measured in an independent cohort under a stated normalization strategy (Section 5).

The third element of Table 2 is an absence rather than a weakness. Patient-derived organoid biobanks of childhood kidney tumors exist and recapitulate the genomic and transcriptomic heterogeneity of the source tumors [6], but across 65 three-dimensional kidney-model records the tumor-model × microRNA cell of the matrix is empty (Section 4.4 and Figure 3). The platform the field would need in order to re-test its own weakest claims has been built, and has not yet been used for this purpose.

Table 2. Summary of the evidence by review criterion. "Established" denotes findings reported consistently in more than one independent human cohort or functionally validated; "uncertain" denotes findings resting on single studies, contradictory reports, or non-authenticated models; "absent" denotes questions for which this review identified no eligible evidence.

Criterion	Established	Uncertain	Absent
Mechanistic (Section 3)	Recurrent *DROSHA*/*DGCR8*/*DICER1*/*XPO5* mutation defines a molecular subclass [3,4]; *DROSHA* mutation derepresses microRNA–target genes and drives a mesenchymal, self-renewing program [7]; *LIN28B* gain/*MIRLET7A* loss and convergence with *SIX1*/*SIX2* on arrested metanephric mesenchyme [4,10]; germline *DROSHA* and *DICER1* variants as predisposition [8,9]	Most single microRNA–target axes (Section 3.6); directional disagreements that persist after hairpin-arm separation and comparator matching (Section 6.1); 52 of the 62 microRNAs in the verified evidence table reported by a single study (Table S4); ceRNA/sponge architectures, frequently reported in retracted work	Whether restoring mature microRNA output in a processing-gene-mutant tumor reverses the progenitor phenotype
Methodological (Section 4)	Organoid biobanks of childhood kidney tumors capture donor genomic and transcriptomic heterogeneity [6]; culture format selects tumor compartment—adherent/stroma, spheroid/blastema, organoid/epithelium [58]	Transferability of findings obtained in G-401 and SK-NEP-1 to Wilms tumor biology; the small number of authenticated lines (WiT49, WT-CLS1) and their representativeness	microRNA profiling in a kidney tumor organoid: 0 of 65 three-dimensional kidney-model records (Section 4.4)
Clinical (Section 5)	Tissue and serum microRNA levels differ between Wilms tumor and control tissue in multiple independent cohorts; feasibility of serum microRNA measurement in children with nephroblastoma [75]	Risk-stratification and chemotherapy-response signatures: largely single-cohort, with variable normalization and inconsistent statement of treatment status at sampling	Prospective serial sampling across the SIOP neoadjuvant window; any prospectively validated microRNA biomarker with a defined decision threshold
Therapeutic (Section 9)	LIN28/let-7 is a chemically addressable node [80–82]; microRNA-directed agents are technically deliverable to human tumors and modulate target genes in patients [83,84]	Whether any Wilms tumor microRNA axis is a tractable target: in vivo work exists, but only 9 of the 41 studies in the verified evidence table used xenografts (Table S4); xenograft work resting on a non-authentic line was excluded at verification	No microRNA-directed agent has been evaluated clinically in Wilms tumor; no registered interventional trial identified

9. Future Perspectives: Therapeutic Implications

The preceding sections were deliberately conservative about therapy, because the evidence base does not yet support therapeutic claims. The question of what would have to happen for microRNA-directed therapy to become realistic in this disease is nonetheless worth stating precisely, and it follows directly from the mechanistic section.

9.1. Why Wilms Tumor Is, in Principle, a Favorable Setting

Three features distinguish Wilms tumor from most solid tumors in which microRNA therapeutics have been attempted. First, the lesion in the microRNA machinery is predominantly loss of function: *DROSHA* E1147K acts in a dominant-negative manner and *DGCR8* E518K impairs processing, so the downstream consequence is depletion of specific mature microRNAs rather than their overproduction [3,4]. A deficiency state is, conceptually, a replacement target—the therapeutic logic of a mimic—whereas gain-of-function microRNA states require inhibition, which has proved the easier of the two to deliver but the harder to make selective. Second, the pathway converges on a developmental node, *LIN28B*/let-7, for which chemical matter already exists: small-molecule inhibitors of the LIN28–let-7 interaction have been reported from both fluorescence-polarization and FRET-based screens [80,81], and in neuroblastoma, another *LIN28B*-driven embryonal tumor, disruption of the *LIN28B*/let-7 interaction reduced aggressiveness in preclinical models [82]. Third, at least one Wilms tumor oncomiR is unusually pervasive: miR-483-3p, encoded within intron 2 of *IGF2*, was reported as overexpressed in 100% of the Wilms tumors examined in the original description of the locus, and an anti-miR oligonucleotide against it suppressed tumorigenicity—although in a hepatoma line, not in Wilms tumor material [49]. We note that the same hairpin's 5p arm is reported with opposite directions in different Wilms tumor cohorts (Section 6.1), so arm-resolved measurement is a precondition for treating this locus as a target rather than a hypothesis.

9.2. What the Clinical Experience with microRNA Therapeutics Actually Shows

The field's clinical record is short and should be read carefully. MRX34, a liposomal miR-34a mimic, was the first microRNA-based cancer therapy to reach first-in-human testing [83]. In the full Phase 1 report, 85 patients were enrolled; the authors reported delivery of miR-34a to tumors and dose-dependent modulation of target gene expression in white blood cells, with three partial responses and 16 patients with stable disease lasting at least four cycles, but the trial was closed early because of serious immune-mediated adverse events, with four patient deaths [84]. The authors' interpretation was that the pharmacodynamic data provide proof of concept for microRNA-based cancer therapy; our reading is that the trial establishes two things simultaneously—that systemic delivery of a microRNA mimic can engage its targets in patients, and that the innate-immune consequences of delivering a double-stranded oligonucleotide are the rate-limiting safety problem. Inhibitor-side chemistry has been explored in local or hematologic settings: cobomarsen, a locked nucleic acid inhibitor of miR-155, de-repressed direct targets and reduced proliferation in cutaneous T-cell lymphoma cell lines, and a first-in-human trial was under way at the time of that report [85], and remlarsen, a miR-29 mimic, repressed extracellular-matrix expression in human skin after intradermal administration [86]. No microRNA-directed agent has yet reached regulatory approval in oncology; recent reviews converge on delivery, off-target breadth, and immune activation as the recurrent obstacles [87–89].

9.3. Delivery, and the Specific Constraints of a Pediatric Renal Tumor

Delivery to the kidney is the practical bottleneck. Systemic lipid nanoparticles distribute overwhelmingly to liver, and extrahepatic targeting is a recent and still preclinical capability: selective organ targeting (SORT) formulations achieved up to 60–80% knockdown of tissue-enriched endogenous targets in kidney, lung, and spleen in mice, although in an unbiased reporter model the reduction was only 15% in kidney, against 58% in lung and 45% in spleen [90]. Whether this extends to a heterogeneous, chemotherapy-exposed embryonal tumor in a child is untested.

Three disease-specific constraints shape any realistic development path, and we state them as our synthesis rather than as findings. First, the therapeutic window is narrow and already occupied: under SIOP protocols patients receive preoperative chemotherapy before nephrectomy [91], so a systemic investigational agent has to be either added to that window or deployed at relapse. Second, the efficacy bar is high. Outcomes are excellent for most patients (five-year relative survival of 92.6% in a United States population-based series [1]), and the populations with genuine unmet need—high-risk blastemal-type, diffuse anaplastic, and relapsed or refractory disease [2]—are the populations in which a role for the microRNA-processing subclass is most plausible, because microRNA-processing-gene mutations are associated with undifferentiated blastemal histology and, in combination with *SIX1/2* mutations, with higher rates of relapse and death [3]; the cohort studied there, however, comprised favorable-histology tumors, and diffuse anaplastic disease was not examined. This is an argument for genotype-selected rather than unselected development. Third, toxicity has a developmental dimension that is absent in adult oncology: let-7 and the miR-200 family act in normal nephrogenesis, the contralateral kidney may carry nephrogenic rests, and the patient is still growing. A let-7-restoring or LIN28-inhibiting agent would therefore need a therapeutic index defined against developing kidney, not only against normal adult tissue.

9.4. Organoids as the Preclinical Filter This Proposal Requires

The organoid gap documented in Section 4.4 is also the main obstacle to therapeutic development, because the platform that would qualify a target is the one the field has not yet applied to microRNAs. Pediatric kidney tumor organoid biobanks already support patient-specific drug sensitivity testing [6], and the approach has produced actionable results in a neighboring entity: metabolic profiling of pediatric tumor organoids identified de novo nucleotide synthesis as a vulnerability of malignant rhabdoid tumor and validated it pharmacologically in the same material [92]. The equivalent experiment for microRNAs—transfect or transduce a mimic or inhibitor into genotyped, authenticated Wilms tumor organoids and matched normal kidney organoids, and read out target derepression, compartment marker shift and viability—is feasible with existing material and reagents.

One caveat from Section 4.2 applies with particular force here. Because culture format selects compartment, with organoids preferentially expanding epithelium and spheroids modeling blastema [58], a therapeutic effect measured only in an organoid is an effect on the epithelial compartment, which is the compartment least associated with adverse outcome. Preclinical qualification of a microRNA-directed agent for high-risk disease therefore requires a blastema-containing format alongside the organoid, not instead of it.

9.5. What Would Have to Be True

We propose five go/no-go criteria for any Wilms tumor microRNA-directed pro-

gram, in order: (1) the target axis is reproduced in authenticated material (WiT49, WT-CLS1, or patient-derived organoids) with arm-resolved measurement; (2) the direction of effect is consistent across at least two independent cohorts, with the contradictions in Section 6.1 checked first; (3) the agent produces measurable derepression or repression of the intended target transcripts in the tumor compartment of interest, not only a viability signal; (4) a therapeutic index is demonstrated against matched normal kidney organoids and, for let-7/LIN28-directed agents, against nephrogenic-rest-like tissue; and (5) development is genotype-selected toward the microRNA-processing subclass and high-risk histology, where need and mechanistic rationale coincide.

At present none of the axes reviewed in Section 3.6 has cleared criterion (1). A search of ClinicalTrials.gov (Wilms OR nephroblastoma, combined with microRNA OR miRNA; accessed 5 October 2026) returned no interventional study of a microRNA-directed agent in this disease; the retrieved records were observational tissue-banking and *DICER1* predisposition studies. The honest summary is that microRNA-directed therapy in Wilms tumor is at the target-validation stage, and the instrument needed to complete that stage already exists.

10. Conclusions and Research Agenda

Wilms tumor occupies an unusual position within microRNA oncology. The biogenesis machinery is a recurrent driver, the disease arises from a developmental progenitor state whose let-7 and miR-200 family biology is already well defined, and three-dimensional patient-derived models exist for both the tumor and its matched normal tissue. The mechanistic core is well supported by large human cohorts: *DROSHA*/*DGCR8*/*XPO5*/*DICER1* mutation, *LIN28B* gain and *MIRLET7A* loss, and convergence with *SIX1*/*SIX2* on an arrested metanephric mesenchyme state. This part is robust.

The periphery is not. Most individual microRNA–target axes rest on a single study; a substantial share of the cellular work uses lines that are not Wilms tumor lines, and misattribution has continued after the 2019 correction, as recently as 2024; retracted articles are concentrated in the fastest-growing part of the literature. In our view the gap between these two tiers is the central problem for the field, and better models are what can close it. The same gap is why the therapeutic discussion in Section 9 remains a perspective rather than a pipeline: a target cannot be qualified in material that is not the disease.

We propose five priorities.

1. Profile small RNAs in kidney tumor organoids. No such study was identified in this search. The biobank material, the three-dimensional formats and the detection chemistry are all established; what is missing is the experiment. It should be compartment-aware, use matched normal kidney organoids as a comparator, resolve isomiRs, and stratify by microRNA-processing-gene genotype.
2. Re-test the major microRNA–target axes in authenticated material. The axes summarized in Section 3.6 are plausible and clinically interesting, but several are supported only by work in rhabdoid or Ewing family lines. Re-testing them in WiT49, WT-CLS1 or patient-derived organoids would either establish them or retire them.
3. **Adopt reporting standards specific to this disease.** That means mandatory arm designation, mandatory statement of treatment status at sampling (pre- versus post-neoadjuvant), mandatory statement of comparator tissue (adjacent normal versus fetal kidney), and cell line provenance with an authentication method. Given that misattribution has continued for at least five years after the 2019 warning (Section 4.1 and Figure 2b), we would go further than a reporting norm: journals publishing Wilms tumor cell-line work should require short tandem repeat (STR) profiling doc-

umentation at submission. A voluntary standard has not been sufficient in this field.

4. Validate circulating microRNA candidates serially across the neoadjuvant window. This has the clearest clinical rationale of any application discussed here, in a SIOP-protocol setting, and no such data currently exist. In practice it means adding blood draws at time points already built into SIOP preoperative care—at diagnosis, at the mid-neoadjuvant assessment, and at nephrectomy—rather than introducing new visits, so that pre-analytical variability (hemolysis, normalization strategy, platelet contamination; Section 5.2) is standardized prospectively instead of reconciled retrospectively across incompatible single-cohort studies.
5. Treat therapeutic development as target validation, not yet as a delivery problem. The clinical record of microRNA therapeutics shows that engagement of targets in patients is achievable, and that immune-mediated toxicity and off-target breadth are the limiting risks [84,87–89]. For Wilms tumor the limiting step is earlier: no axis has been validated in authenticated material. The five go/no-go criteria in Section 9.5 are intended as a minimum standard before a mimic or inhibitor is proposed for this disease, and the first three of them can be met with organoid experiments that are feasible today.

Taken together, the mechanistic case that impaired microRNA processing contributes to Wilms tumor pathogenesis is strong and independently replicated; the biomarker and therapeutic cases are preliminary, and they are preliminary for a reason that is fixable. The models now exist. What the field needs next is not more single-cohort association studies but a smaller number of experiments done in material that is genuinely Wilms tumor.

Limitations of This Review

Every study cited in this review was read in full, but the structured charting fields for the included set as a whole were recorded from titles, abstracts, and MeSH terms under one rule applied to all 1338 screened records. Cell lines, cohort sizes and reagents reported only in the Methods sections were therefore not captured in the charted fields, and all model-quality and authenticity estimates derived from those fields should be considered lower bounds. Where the full texts were used to verify a charted field, as for cell-line attribution, the result is reported separately (Section 4.1). The search was limited to PubMed/MEDLINE, so conference abstracts, theses, non-indexed regional journals, and studies without an English abstract may be under-represented.

We also compared our search with Europe PMC and OpenAlex using translations of the main PubMed search blocks. Europe PMC retrieved 149 of the 173 studies included at the time of the check, and OpenAlex retrieved 153. These checks were run once, on the included set as it stood at the time, and their record-level outputs are not deposited. Neither identified an additional MEDLINE-indexed study that was clearly missed by our PubMed search. The few apparently new records were either retracted publications with inconsistent indexing or preprints whose published versions were already included. However, these checks do not establish search completeness, and Embase- or Scopus-exclusive studies remain unassessed. Two PubMed-indexed articles cited as mechanistic or methodological context were not retrieved by our search blocks [12,59], and a third, [11], was retrieved but excluded because it reports no microRNA data. Apart from the one preprint retrieved by the search and included under the rule stated in Section 2 [19], material circulating only as preprints is not cited in this review.

Expression direction was initially assigned by automated sentence parsing, followed by manual adjudication of ambiguous cases. Although this approach was reproducible, it cannot fully substitute for systematic full-text assessment. During revision,

every charted entry was therefore re-verified against its primary source on the five criteria stated in Section 2, and entries whose finding could not be confirmed were removed; where the finding was confirmed but individual charted fields did not match the article, those fields were corrected against the source and are listed in Table S4. Only the 74 entries that passed are reported (Table S4). Exclusion was applied to the whole entry: unless its fields were corrected against the source as noted in Table S4, an entry with any field that did not match the article was removed, even when its central finding was stated in the source. Table S4 is therefore a conservative subset of the evidence rather than a complete one, and a study may be cited in the text for what its full text reports while contributing no entry to Table S4; 15 of the 64 individually cited included studies contribute one. This verification was made against the full text where it could be obtained and against the abstract otherwise, so it remains bounded by access.

No formal risk-of-bias or quality-appraisal instrument was applied to the included studies. This review maps evidence rather than estimating pooled effects, so instruments designed for that purpose (for example QUADAS-2 or ROBINS-I) do not fit the heterogeneous mix of in vitro, animal, genomic and clinical designs charted here. In their place we assessed three integrity dimensions systematically and report them for every included study: cell-line authenticity, retraction status, and replication across independent studies (Sections 4.1, 6.2 and 6.3). These flags are not a substitute for a validated appraisal tool, and findings in this review are therefore not weighted by study quality beyond them.

Finally, our inclusion criteria were broader than those in a previous protocol framework developed by this group, which required a three-dimensional model. We report this as a protocol deviation. Importantly, applying the narrower three-dimensional criterion produced no qualifying studies, consistent with the organoid evidence gap described in Section 4.4.

The therapeutic perspective in Section 9 also cites work outside the Wilms tumor search blocks—clinical and preclinical studies of microRNA mimics and inhibitors in other diseases, LIN28/let-7 chemical probes, nucleic acid delivery, and organoid pharmacology [49,80–92]. These are context citations: they were not retrieved by our search, were not charted, and are not counted in any of the tallies reported in this review.

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Informed Consent Statement: Not applicable. This review analyzed only previously published literature.

Data Availability Statement: No new primary experimental data were generated for this study. All data extracted and generated during the review—the search log, the screening records, the cell-line registry and the verified evidence table—are contained within the article and its Supplem entary Materials. Entries in the evidence table are reported only where the finding could be confirmed against the primary source; the verification criteria are stated in the footnote to Table S4.

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Abbreviations

The following abbreviations are used in this manuscript:

ADH1C	Alcohol dehydrogenase 1C
APC	Adenomatous polyposis coli
ceRNA	Competing endogenous RNA
CDH1	Cadherin 1 (E-cadherin)
COG	Children's Oncology Group
DDX5	DEAD-box helicase 5
DGCR8	DiGeorge syndrome critical region gene 8
DHPLN	Diffuse hyperplastic perilobar nephroblastomatosis
DIS3L2	DIS3-like 3′-5′ exoribonuclease 2
DKK1	Dickkopf WNT signaling pathway inhibitor 1
DLX6-AS1	DLX6 antisense RNA 1
DOI	Digital object identifier
EMT	Epithelial-to-mesenchymal transition
ERK	Extracellular signal-regulated kinase
FFPE	Formalin-fixed, paraffin-embedded
FRS2	Fibroblast growth factor receptor substrate 2
FTX	FTX transcript, XIST regulator (long non-coding RNA)
GEO	Gene Expression Omnibus
HOXA11-AS	HOXA11 antisense RNA
IGF1R	Insulin-like growth factor 1 receptor
IGF2	Insulin-like growth factor 2
IGF2BP1	Insulin-like growth factor 2 mRNA-binding protein 1
IKKα/IKKβ	Inhibitor of nuclear factor kappa-B kinase subunit alpha/beta
isomiR	MicroRNA sequence variant (isoform of a mature microRNA)
JAG1	Jagged canonical Notch ligand 1
KCNQ1OT1	KCNQ1 opposite strand/antisense transcript 1 (long non-coding RNA)
KIF23	Kinesin family member 23
KRAS	Kirsten rat sarcoma viral oncogene homolog
LASSO	Least absolute shrinkage and selection operator (regression)
LIN28A/B	Lin-28 homolog A/B
LINC01339	Long intergenic non-protein-coding RNA 1339

MAPK	Mitogen-activated protein kinase
MEG3	Maternally expressed gene 3 (long non-coding RNA)
MEK	Mitogen-activated protein kinase
MeSH	Medical Subject Headings
MIRLET7A	MicroRNA let-7a gene
MKNK1	MAP kinase-interacting serine/threonine kinase 1
MYCN	MYCN proto-oncogene, N-Myc
NCAM	Neural cell adhesion molecule
NCBI	National Center for Biotechnology Information
NF-κB1	Nuclear factor kappa B subunit 1
PD-L1	Programmed death-ligand 1
PDX	Patient-derived xenograft
PI3K/AKT/mTOR	Phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin
PMID	PubMed identifier
PRMT1/PRMT5	Protein arginine methyltransferase 1/5
PTEN	Phosphatase and tensin homolog
SIOP	International Society of Pediatric Oncology
SIX1/SIX2	SIX homeobox 1/2
SNHG6	Small nucleolar RNA host gene 6
STR	Short tandem repeat
TARGET	Therapeutically Applicable Research to Generate Effective Treatments
TCF3	Transcription factor 3
TCGA	The Cancer Genome Atlas
TGF-β	Transforming growth factor beta
WDR77	WD repeat domain 77
WT	Wilms tumor
WT1	Wilms tumor 1 (gene/protein, distinct from the disease abbreviation WT)
XIST	X-inactive specific transcript
XPO5	Exportin 5
YAP1	Yes-associated protein 1

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