

Wilms Tumor

Nephroblastoma

Developmental genetics • morphology • clinical significance

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Explain why a pediatric renal tumor can recapitulate embryonic nephrogenesis.
- Distinguish the genetic mechanisms underlying WAGR, Denys–Drash and Beckwith–Wiedemann syndromes.
- Recognize triphasic morphology, anaplasia and nephrogenic rests.
- Relate molecular and morphologic findings to clinical risk and survivorship.

Epidemiologic profile

~1 in 10,000

US children

Approximate frequency cited.

2–5 years

Peak incidence

The disease predominantly presents in early childhood.

95%

Before 10 years

Age distribution is strongly pediatric.

Wilms tumor is the most common primary renal tumor of childhood.

Place within pediatric oncology

- Wilms tumor is also called nephroblastoma.
- It is the fourth most common pediatric malignancy in the United States, as described in the source.
- It belongs to the embryonal neoplasms, which often retain features of organ development.

Pathologic implication

A primitive renal tumor may contain immature structures resembling developing kidney tissue.

Embryonal tumors differ from adult cancers

Pediatric embryonal tumors

Primitive or incompletely differentiated cells;
Morphology may mimic organogenesis; “-blastoma” nomenclature.

Typical adult epithelial cancers

Often arise from a differentiated epithelium
and show different distributions across
organs.

The distinction is a teaching framework, not an absolute diagnostic rule.

Bilateral and multicentric disease

5–10%

Both kidneys

Involvement may be synchronous or metachronous.

~10 months

Earlier onset

Median presentation of bilateral tumors is younger than unilateral tumors.

Bilateral disease raises suspicion of inherited tumor predisposition.

Two patterns of bilateral involvement

Synchronous

Wilms tumors are present in both kidneys at the same time.

Metachronous

A tumor develops in the second kidney after an initial unilateral presentation.

Both patterns motivate long-term attention to the remaining renal tissue.

Why this cancer illuminates developmental biology

Development

Renal organogenesis depends on tightly regulated differentiation.



Genetics

Predisposition genes control nephrogenesis and growth.



Neoplasia

Disrupted developmental programs permit persistent primitive cells.

The connection between organ malformation and cancer is a central theme of Wilms tumor.

How often is Wilms tumor syndromic?

$\leq 10\%$

Syndromic cases

Arise with recognizable congenital malformation syndromes.

$\sim 90\%$

Sporadic cases

Most childhood Wilms tumors have no recognized syndrome.

Rare syndromic cases revealed key molecular mechanisms.

Three major predisposition patterns

WT1-related disorders

WAGR and Denys–Drash: Different germline WT1 alterations at 11p13.

11p15.5 imprinting disorder

Beckwith–Wiedemann: Growth dysregulation affecting parent-of-origin expression.

These groups are biologically related but mechanistically distinct.

WT1: A developmental transcription factor

- WT1 encodes a DNA-binding transcription factor expressed in developing kidney and gonads.
- Normal WT1 is essential for renal and gonadal development.
- Its targets include genes involved in podocyte specialization and renal differentiation.
- WT1 acts as a tumor suppressor in Wilms tumor.

WT1 links developmental defects to tumor risk

Embryogenesis

WT1 helps orchestrate nephron and gonadal development.



Abnormal WT1

Developmental abnormalities can be clinically apparent.



Further alterations

Loss of tumor-suppressive function may contribute to Wilms tumor.

A congenital malformation syndrome does not itself imply that malignant transformation has occurred.

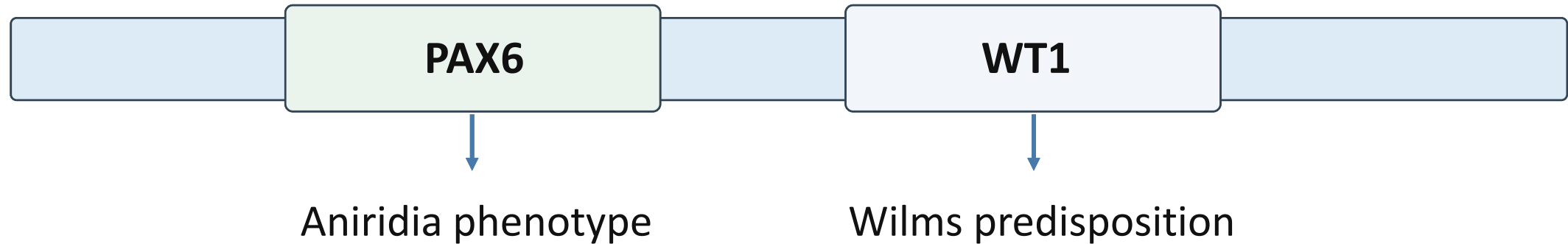
WAGR: Recognize the syndrome

- W: Wilms tumor predisposition.
- A: Aniridia (absent or markedly deficient iris).
- G: Genitourinary anomalies.
- R: Intellectual disability (historically “retardation” in the acronym).

Underlying lesion

Constitutional contiguous-gene deletion involving chromosome 11p13.

WAGR: Contiguous deletion at 11p13



A deletion encompassing both genes produces WAGR; Isolated PAX6 loss does not confer WT1-linked tumor risk.

WAGR illustrates the two-hit model

First hit

Inherited/constitutional deletion removes one WT1 allele.



Second hit

A somatic nonsense or frameshift mutation affects the other WT1 allele.



Consequence

Biallelic WT1 inactivation favors tumor development.

The tumor-suppressor model explains why constitutional predisposition is not equivalent to cancer.

PAX6 deletion is not WT1 deletion

Isolated PAX6 loss

Produces aniridia; WT1 function is retained; Wilms tumor risk is not increased by isolated PAX6 loss.

Combined PAX6–WT1 deletion

Produces the WAGR phenotype; WT1 disruption confers Wilms tumor predisposition.

Neighboring loci can generate clinically different consequences when deleted together.

Denys–Drash: Clinical phenotype

- Gonadal dysgenesis with abnormal sexual development.
- Early-onset nephropathy that can progress to renal failure.
- Diffuse mesangial sclerosis is the characteristic glomerular lesion.
- Marked predisposition to Wilms tumor and increased risk of gonadoblastoma.

Denys–Drash: Dominant-negative WT1

Germline variant

Missense mutation in the WT1 zinc-finger DNA-binding region.



Protein effect

Mutant WT1 interferes with remaining wild-type protein function.



Tumor evolution

Wilms tumors display biallelic WT1 inactivation.

Developmental and tumor-suppressor consequences can be temporally separated.

Why Denys–Drash also causes renal disease

Developmental effect

Mutant WT1 disrupts normal nephron differentiation, affecting specialized glomerular function.

Microscopic hallmark

Diffuse mesangial sclerosis causes an early-onset nephropathy and may lead to renal failure.

The nephropathy and tumor predisposition are related to WT1 dysfunction, not identical events.

WAGR versus Denys–Drash

Characteristic	WAGR	Denys–Drash
WT1 alteration	11p13 constitutional deletion	Zinc-finger missense variant
Protein mechanism	Loss of one WT1 allele	Dominant-negative effect
Distinctive features	Aniridia; GU anomalies; intellectual disability	Gonadal dysgenesis; nephropathy
Wilms risk in source	~33% lifetime	~90%

A second WT1 inactivation event is relevant to tumor development in both conditions.

Beckwith–Wiedemann: Overgrowth phenotype

- Organomegaly and macroglossia.
- Hemihypertrophy (asymmetrical overgrowth).
- Omphalocele may be present.
- Adrenal cytomegaly is a characteristic morphologic feature.

Molecular locus

11p15.5 (historically termed the WT2 locus); Distinct from WT1 at 11p13.

Imprinting: Parent-of-origin expression

Normally active allele

Some developmental genes are transcribed primarily from one parental copy.

Imprinted allele

The other parental copy is epigenetically silenced, often through DNA methylation.

Copy number and parent of origin can both alter the effective growth-factor output.

IGF2: Normal parent-of-origin expression

Paternal IGF2 allele

Expressed → IGF2 growth-factor production

Maternal IGF2 allele

Silenced by imprinting → no normal maternal expression

Normal IGF2 expression is predominantly paternal.

IGF2 loss of imprinting

Normal

Paternal IGF2 is expressed;
Maternal allele is silent.



Imprinting loss

The normally silenced
maternal IGF2 allele is re-
expressed.



Outcome

Increased IGF2 growth-
factor expression.

This is an epigenetic route to growth deregulation in some Wilms tumors.

Paternal uniparental disomy at 11p15.5

Allele imbalance

Maternal allele is lost in tumor tissue.



Paternal duplication

Active paternal allele is represented twice.



Functional result

Increased IGF2 expression.

Different imprinting-region events can converge on the same growth-promoting output.

Predisposition mechanisms are not interchangeable

Syndrome	Genetic region	Core pathogenic concept
WAGR	11p13: WT1 + PAX6	Contiguous deletion and WT1 tumor suppressor loss
Denys–Drash	11p13: WT1	Dominant-negative WT1 and subsequent biallelic loss
Beckwith–Wiedemann	11p15.5	Altered imprinting; growth-factor dysregulation

Beckwith–Wiedemann is genetically heterogeneous; A single causative gene does not explain all cases.

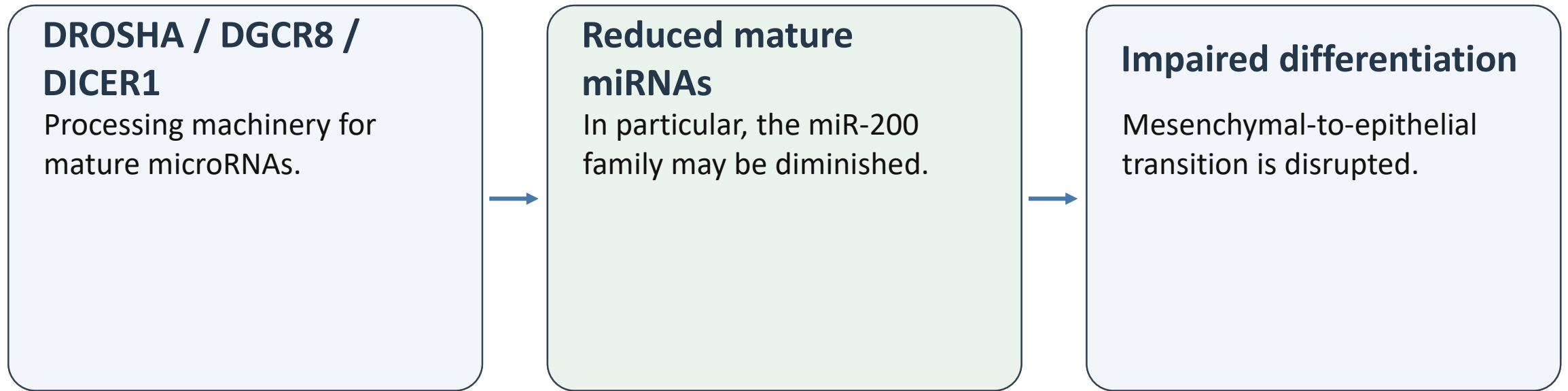
Sporadic Wilms tumors are genetically diverse

- Approximately 90% of Wilms tumors are nonsyndromic.
- Approximately 10% of sporadic cases show WT1 mutations; A similar proportion have activating β -catenin mutations.
- Other recurrent changes affect microRNA maturation and DNA-damage responses.
- Some molecular changes correlate with specific histologic patterns.

MicroRNA-processing genes in Wilms tumor

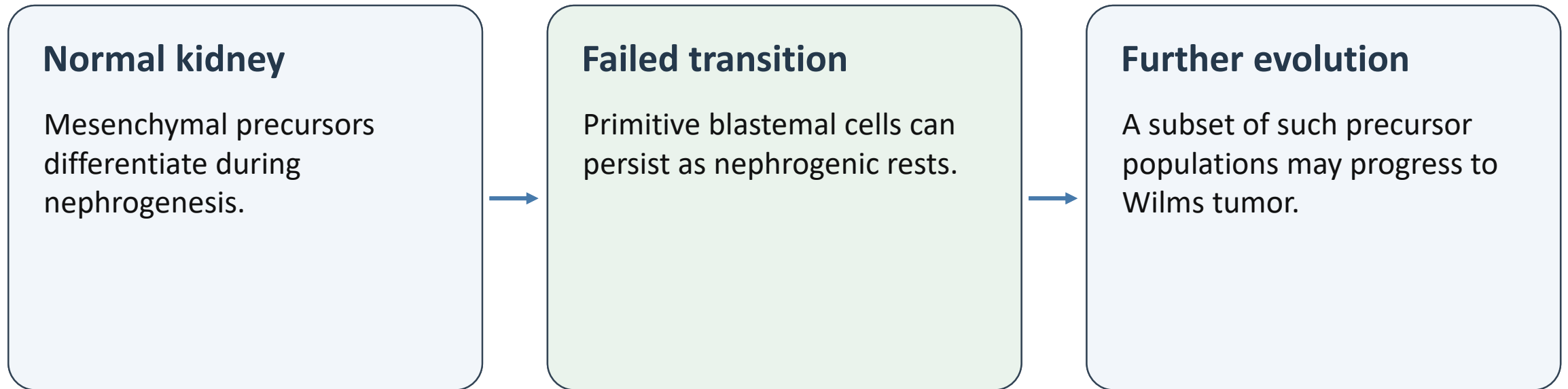
- Recurrent alterations involve DROSHA, DGCR8 and DICER1.
- These genes participate in processing microRNAs into their mature forms.
- Alterations are reported in 15–20% of tumors with predominantly blastemal histology.
- The histologic association is informative but not a stand-alone diagnostic criterion.

MicroRNA maturation and epithelial differentiation



The pathway provides a plausible developmental link to blastemal persistence.

From persistent blastema to tumor



This is a pathogenetic model, not proof that every tumor arises through the same sequence.

Tumor genes have distinct roles

Development and differentiation

WT1, β -catenin pathway and microRNA machinery influence nephrogenesis and cell identity.

Cell survival under damage

TP53 loss is associated with anaplasia and resistance to cytotoxic therapy.

The model separates developmental disruption from treatment-response biology.

TP53 and anaplastic tumor biology

- TP53 mutations are associated with anaplastic Wilms tumors.
- P53 normally helps initiate apoptosis in cells with DNA damage.
- Loss of p53 can diminish the response to cytotoxic chemotherapy.
- Anaplastic morphology predicts a distinctly less favorable course.

Molecular changes: What they tell us

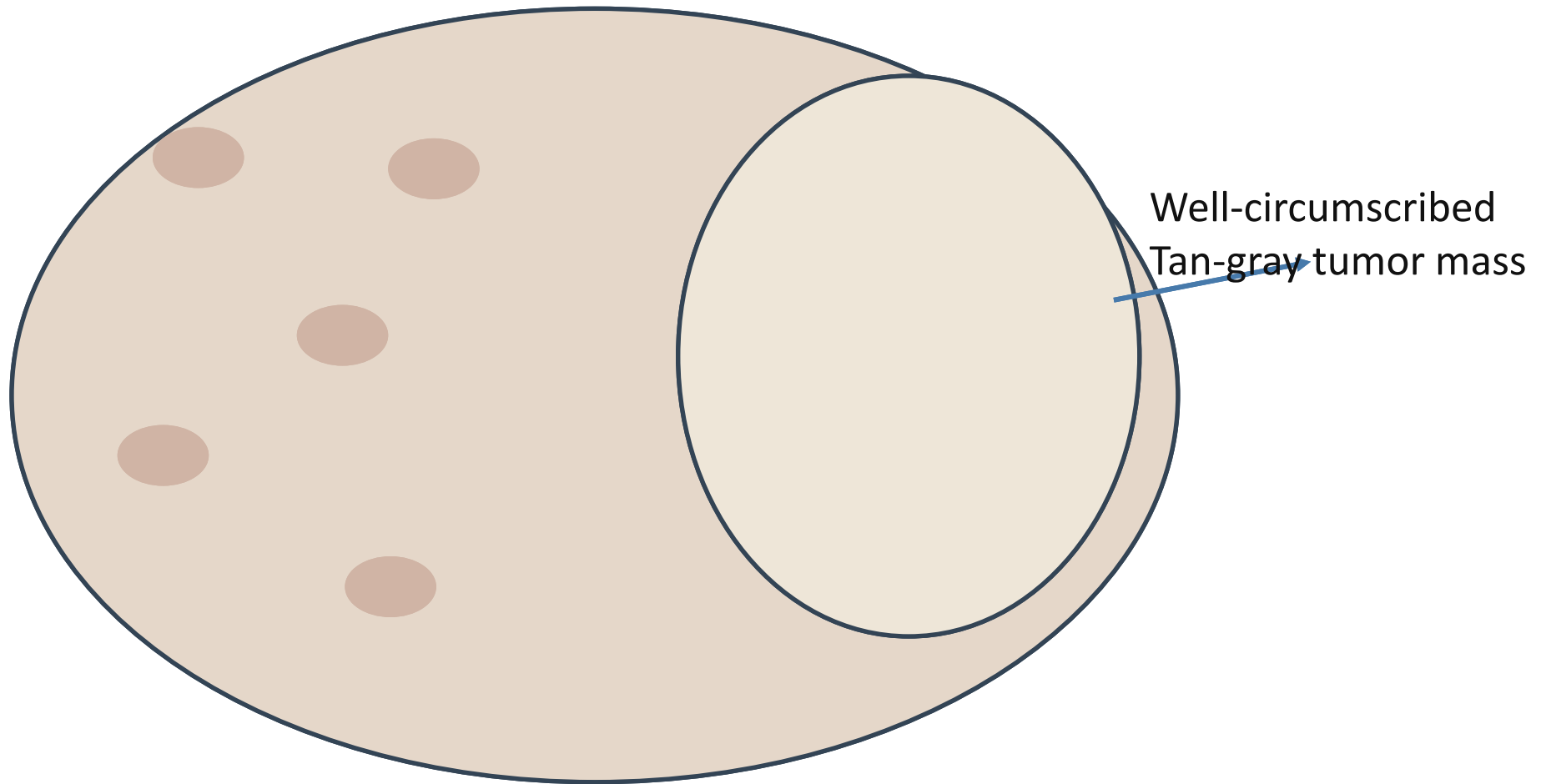
Alteration	Relevant consequence	Teaching interpretation
WT1 disruption	Abnormal nephrogenesis; predisposition	Developmental / tumor suppressor
11p15.5 imprinting	IGF2 overexpression	Growth-factor dysregulation
miRNA-processing genes	Impaired differentiation	Blastemal association
TP53 mutation	Anaplasia; drug resistance	Adverse prognosis

Each row is a distinct biological association; Categories are not mutually exclusive.

Gross appearance: The typical renal mass

- Usually large, solitary and well circumscribed.
- Soft, homogeneous tan-gray cut surface.
- May contain hemorrhage, cystic degeneration or necrosis.
- About 10% are bilateral or multicentric at diagnosis in the morphologic summary.

Gross anatomy: Simplified renal cut-section schematic



Schematic: Contour and scale are illustrative, not specimen evidence.

Gross heterogeneity may be present

Baseline appearance

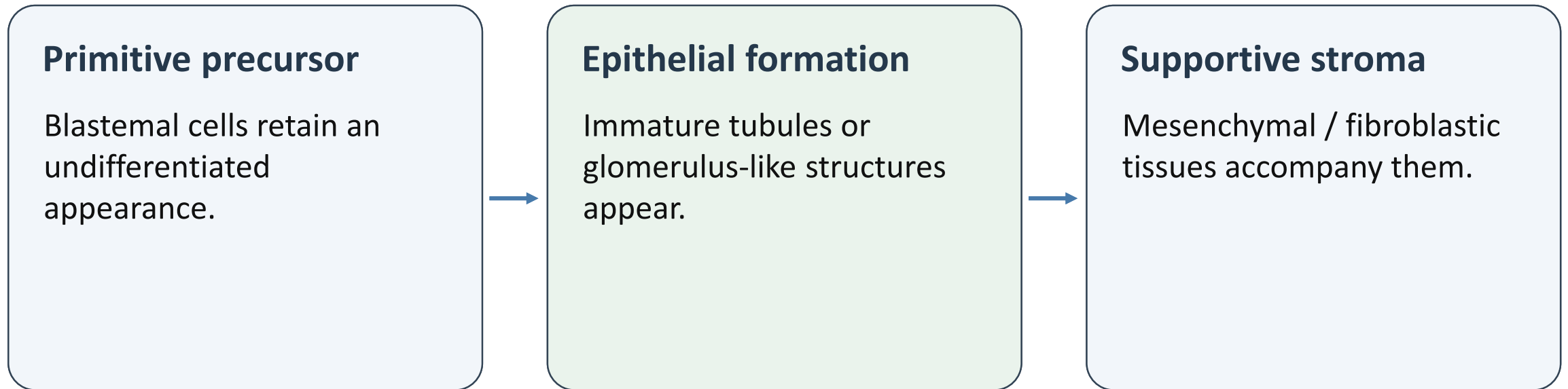
Soft, relatively homogeneous tan-gray tissue with a circumscribed interface.

Secondary changes

Foci of hemorrhage, necrosis and cyst formation may interrupt the uniform appearance.

Gross appearance is compatible with—but does not establish—the histologic diagnosis.

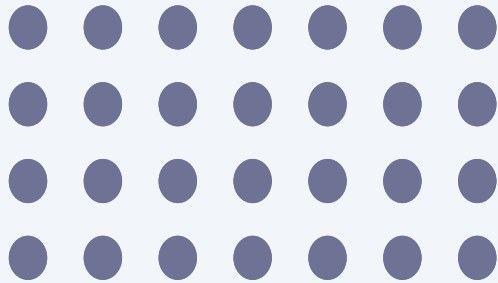
Wilms tumor attempts to recapitulate nephrogenesis



The three differentiation programs explain the classic triphasic pattern.

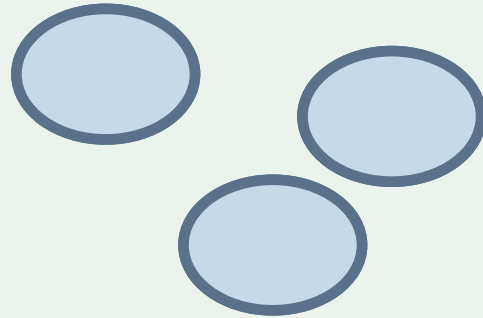
The classic triphasic pattern

Blastemal



Small, densely packed
primitive cells

Epithelial



Abortive tubules / primitive
glomeruli

Stromal



Fibroblastic or myxoid
mesenchyme

Original editable conceptual schematic — not a microscopic specimen.

Blastemal component

- Sheets of primitive small blue cells.
- Little overt differentiation; High nuclear density.
- May dominate in tumors with certain microRNA-processing abnormalities.
- Blastemal predominance alone is not synonymous with anaplasia.

Epithelial component

- Primitive or abortive tubules are characteristic.
- Immature glomerular structures may be identified.
- Epithelial features reflect partial recapitulation of renal nephron development.
- The fraction of epithelial differentiation varies between tumors.

Stromal component

- Usually fibroblastic or myxoid.
- Skeletal muscle differentiation is not uncommon.
- The mesenchymal nature can be especially apparent in stromal-rich tumors.
- Stromal dominance does not exclude Wilms tumor.

Occasional heterologous differentiation

- Squamous or mucinous epithelium.
- Smooth muscle, adipose tissue or cartilage.
- Osteoid and neurogenic elements can also occur.
- These uncommon elements reflect broad differentiation capacity.

Triphasic does not mean equal proportions

Classic pattern

Blastemal, epithelial and stromal elements can all be recognized.

Observed variability

The relative abundance of each component varies widely; Some may be sparse in a given sample.

Recognizing developmental lineage is more important than expecting a fixed 1:1:1 ratio.

Define anaplasia morphologically

- Approximately 5% of Wilms tumors are anaplastic in the source.
- Markedly enlarged, pleomorphic tumor cell nuclei.
- Prominent nuclear hyperchromasia.
- Abnormal mitotic figures.
- Do not confuse brisk ordinary mitoses with atypical mitotic figures.

Favorable versus anaplastic histology

Without anaplasia

Tumor may show brisk proliferation and primitive blastema, but diagnostic nuclear atypia is not present.

Anaplastic morphology

Marked nuclear pleomorphism and hyperchromasia, with atypical mitoses; Often associated with TP53 alteration.

The prognostic interpretation depends on correctly recognizing true anaplasia.

Why anaplasia matters during chemotherapy

DNA damage

Cytotoxic therapy can trigger cell death pathways.



P53 response

Functional p53 helps signal apoptosis after DNA injury.



TP53 dysfunction

Loss of this response may promote chemotherapy resistance.

This provides a biological explanation for the adverse association of anaplastic histology.

Nephrogenic rests: Suspected precursors

- Persistent foci of embryonal renal tissue in postnatal parenchyma.
- Regarded as putative preneoplastic lesions.
- Often located adjacent to Wilms tumor.
- Some rests share molecular alterations with the associated tumor.

Nephrogenic rests accompany many tumors

25–40%

Unilateral cases

Rests identified in adjacent renal parenchyma.

Nearly 100%

Bilateral cases

Rests reported in bilateral Wilms tumor cases.

Values represent approximate proportions in the primary textbook.

Morphologic spectrum of nephrogenic rests

Hyperplastic rest

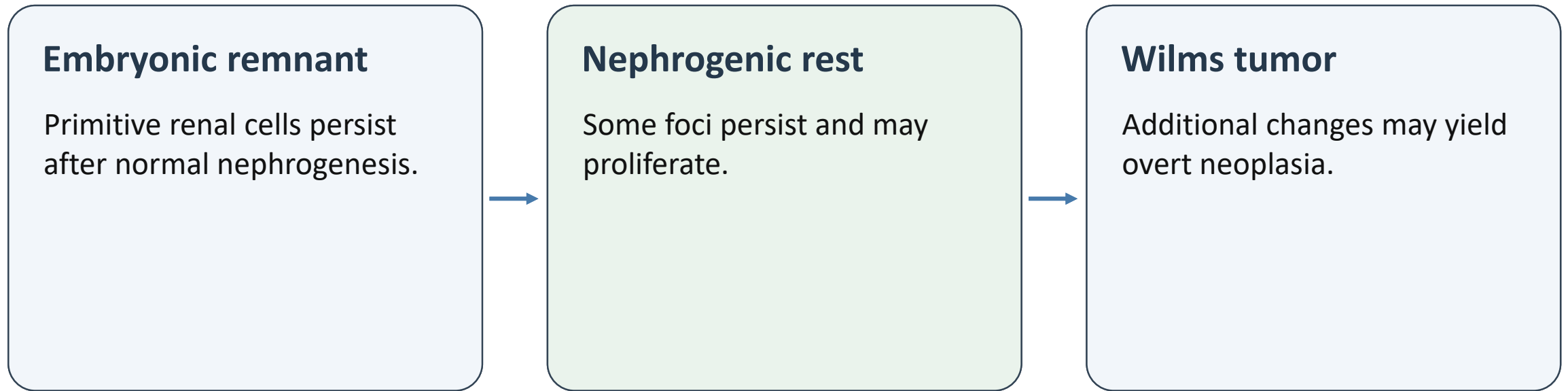
Expansile lesion that may resemble a small Wilms tumor.

Sclerotic rest

Fibrous tissue with scattered immature tubules or glomeruli.

The appearances represent a spectrum; Appearance alone does not prove progression.

Nephrogenic rest to Wilms tumor: Conceptual continuum



Supported by shared alterations in some paired rests and tumors; Progression is not universal.

Why finding nephrogenic rests matters

- Rests in a resection specimen indicate a field of renal tumor predisposition.
- A remaining contralateral kidney may later develop Wilms tumor.
- The source recommends regular surveillance for many years.
- The pathologist should document nephrogenic rests in the specimen.

Clinical presentation: Abdominal mass

- The most common presentation is a large abdominal mass.
- The mass can be unilateral or extend across the midline.
- Very large lesions may descend into the pelvis.
- Clinical examination detects the consequence of substantial renal enlargement.

Additional clinical manifestations

- Hematuria can occur.
- Abdominal pain may follow minor trauma.
- Intestinal obstruction is a possible presentation.
- Hypertension is another recognized clinical feature.

Localized symptoms and dissemination

Primary tumor effects

Abdominal enlargement, hematuria, pain, compression and hypertension.

Metastatic disease

Pulmonary metastases may already be present at diagnosis in a considerable subset.

Clinical symptoms do not reliably indicate tumor spread.

Histology drives prognostic assessment

- Anaplastic histology is a major adverse prognostic feature.
- Even anaplasia confined to the kidney increases recurrence/death risk.
- Accurate histologic recognition has direct treatment implications.
- Do not substitute molecular association for morphologic identification.

Adverse molecular correlates

- Loss of heterozygosity at chromosome 1p.
- Loss of heterozygosity at chromosome 16q.
- Gain of chromosome arm 1q.
- These abnormalities correlate with worse outcomes in the source.

Use pathology features for different questions

Feature	Interpretive role	Caution
Triphasic elements	Support morphologic identity	Not necessarily equal in abundance
Nephrogenic rests	Indicate precursor background / risk	Not identical to invasive tumor
Anaplasia	Major adverse prognostic finding	Requires specific nuclear/mitotic changes
1p/16q LOH; 1q gain	Adverse molecular correlation	Not the same as primary diagnosis

Terminology and clinical management criteria can vary by protocol; This slide is a textbook synthesis.

Treatment outcomes improved dramatically

~30%

Historical cure rate

As low as this in earlier decades, per textbook.

~90%

Contemporary cure rate

Approximate value reported in the 11th edition.

The gain reflects one of the major success stories of pediatric oncology.

Late effects matter after cure

- Long-term survivors have an increased risk of second primary tumors.
- Reported second tumors include bone and soft tissue sarcomas.
- Leukemia, lymphoma and breast cancer are also described.
- Both inherited predisposition and cancer therapy contribute to risk.

Why radiotherapy requires a risk–benefit balance

Benefit

Radiotherapy may form part of effective multimodal cancer management.

Long-term cost

Radiation exposure can contribute to later second malignancies, especially within treated fields.

The source emphasizes judicious use; It does not specify a treatment protocol.

Case 1: Congenital aniridia and renal tumor

Clinical vignette

A young child with bilateral aniridia and genitourinary anomalies is found to have a renal mass. A constitutional deletion at 11p13 is documented.

Which additional gene, beyond PAX6, is central to tumor predisposition?

Case 1: Molecular interpretation

WT1 deletion explains the Wilms tumor predisposition.

- PAX6 loss contributes to aniridia; WT1 is a neighboring tumor-suppressor locus.
- This phenotype is consistent with the WAGR contiguous-gene deletion.
- Tumor development typically involves further WT1 inactivation.

Case 2: Overgrowth and tumor predisposition

Clinical vignette

An infant with macroglossia, asymmetric somatic overgrowth and an omphalocele develops a renal mass. Molecular workup demonstrates altered imprinting at 11p15.5.

Which growth-factor gene is implicated by this parent-of-origin mechanism?

Case 2: Imprinting interpretation

IGF2 is the key growth-factor example.

- Normally, paternal IGF2 is expressed and the maternal allele is imprinted.
- Maternal re-expression or paternal uniparental disomy can increase IGF2 output.
- This is conceptually distinct from WT1 two-hit inactivation.

Case 3: Primitive renal tumor

Clinical vignette

A pediatric kidney tumor contains densely packed small blue cells, primitive tubules and fibroblastic/myxoid tissue. No large pleomorphic nuclei or abnormal mitoses are identified.

Name the three morphologic compartments and the missing adverse feature.

Case 3: Histologic interpretation

Classic triphasic Wilms tumor without identified anaplasia.

- Blastemal component: Undifferentiated small blue cells.
- Epithelial component: Abortive tubules and immature glomerular structures.
- Stromal component: Fibroblastic / myxoid mesenchyme.
- Anaplasia is not established by ordinary mitotic activity alone.

Case 4: Unfavorable morphology

Clinical vignette

A renal tumor shows markedly enlarged hyperchromatic pleomorphic nuclei with abnormal mitoses, even though its imaging suggests a kidney-confined lesion.

Why is the histologic feature prognostically important?

Case 4: Prognostic interpretation

Anaplasia is associated with adverse risk even without extra-renal spread.

- Anaplastic tumors are frequently associated with TP53 abnormalities.
- Defective DNA-damage apoptosis helps explain chemoresistance.
- Anaplasia must be recognized and reported accurately.

Integrated pathology review

- An embryonal renal malignancy that recapitulates nephrogenesis.
- WT1 and 11p15.5 imprinting reveal distinct predisposition mechanisms.
- Blastemal, epithelial and stromal differentiation define the classic morphologic pattern.
- Nephrogenic rests mark risk; Anaplasia and selected cytogenetic changes signal worse prognosis.

Principal source and scope

Robbins, Cotran & Kumar

Pathologic Basis of Disease • 11th edition (2026)

Chapter 10: Diseases of Infancy and Childhood

“Wilms Tumor,” printed pp. 437–439

Content follows the supplied textbook excerpt; original source figures are not reproduced.