

Gonadoblastoma

A noninvasive germ-cell neoplasm of dysgenetic gonads

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

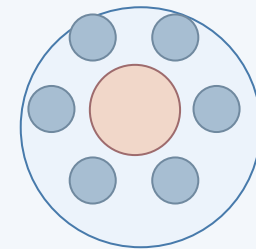
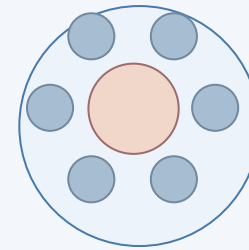
www.abusuraihsakhri.com

Learning outcomes

- Define gonadoblastoma and place it within the 2022 WHO tumour classification.
- Explain the association with gonadal dysgenesis, Y-chromosomal material and germ-cell maturation.
- Recognize characteristic morphology and interpret a two-compartment IHC panel.
- Distinguish precursor lesions from invasive germinoma and integrate pathology with DSD care.

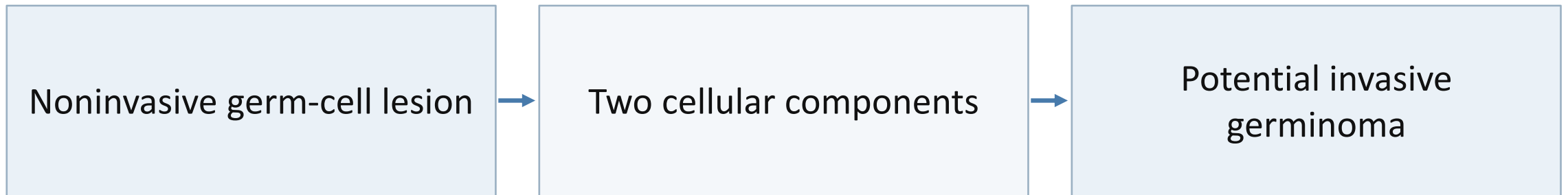
Diagnostic identity: A dual-cell lesion

- Noninvasive germ-cell neoplasia arising predominantly in abnormal or dysgenetic gonads.
- Contains neoplastic germ cells admixed with immature sex cord–stromal cells.
- Its clinical significance is the association with invasive germinoma: Seminoma or dysgerminoma.



Germ cells + sex cord cells
Schematic—not a histology image

The 2022 WHO classification changed the emphasis



- The 5th-edition WHO testicular tumour classification lists gonadoblastoma among noninvasive precursor lesions.
- The germ-cell population is the neoplastic driver; Sex cord cells form an intimate accompanying matrix.
- A mixed cellular composition does not make it equivalent to an invasive mixed germ-cell tumour.

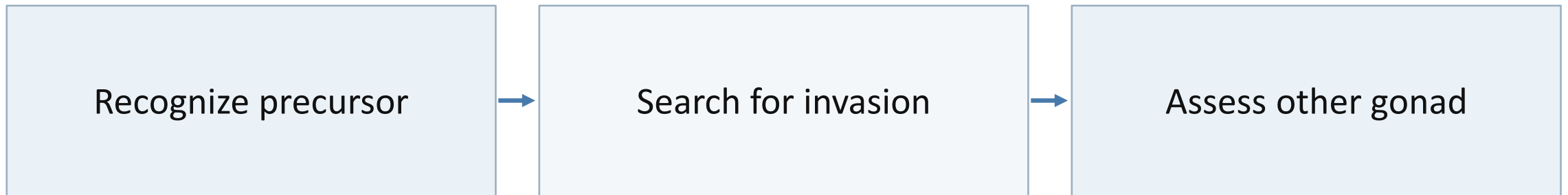
What “in situ” means here

- The germ cells are neoplastic, but the classical lesion is confined to its characteristic nests.
- Coexistent invasive germinoma must be assessed separately on tissue sections.
- A diagnosis of gonadoblastoma alone should not be reported as metastatic or invasive malignancy.



Defined noninvasive architecture

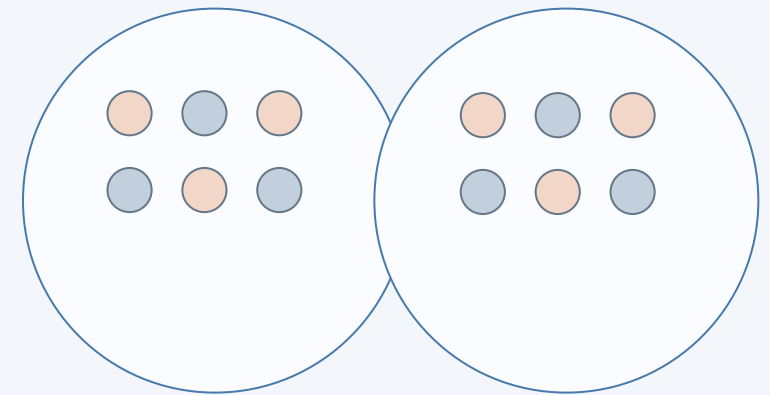
Why it matters despite being noninvasive



- Gonadoblastoma is a precursor to seminoma/dysgerminoma in susceptible gonads.
- It may already coexist with an invasive germ-cell tumour at diagnosis.
- Recognition prompts assessment of the remaining gonad and the underlying developmental condition.

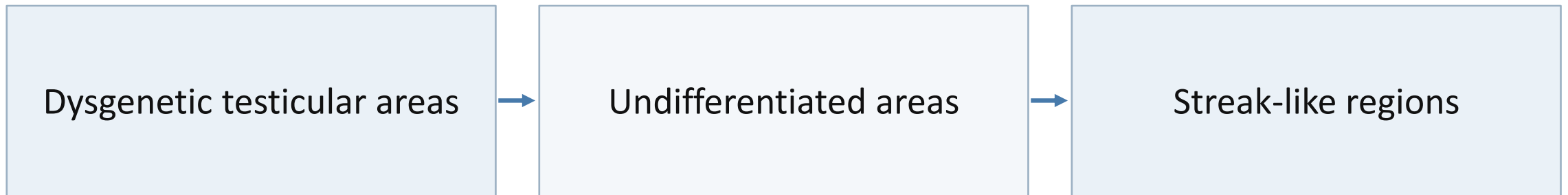
Predominant site: The dysgenetic gonad

- Typical setting is incomplete or abnormal gonadal differentiation in an individual with DSD.
- Gonads can contain testicular, ovarian, undifferentiated and streak-like areas in one specimen.
- Site nomenclature depends on gonadal anatomy; Do not infer identity solely from the patient's phenotype.



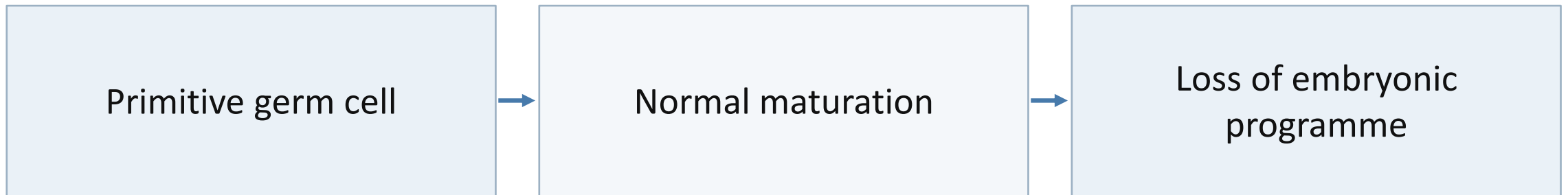
Heterogeneity can occur between—
and within—gonads

Anatomy is heterogeneous in gonadal dysgenesis



- A dysgenetic gonad may show disordered cords, germ cells, fibrous stroma and residual differentiated structures.
- Adjacent histologic patterns can vary within the same specimen.
- Representative mapping is essential because a small diagnostic focus may be overlooked.

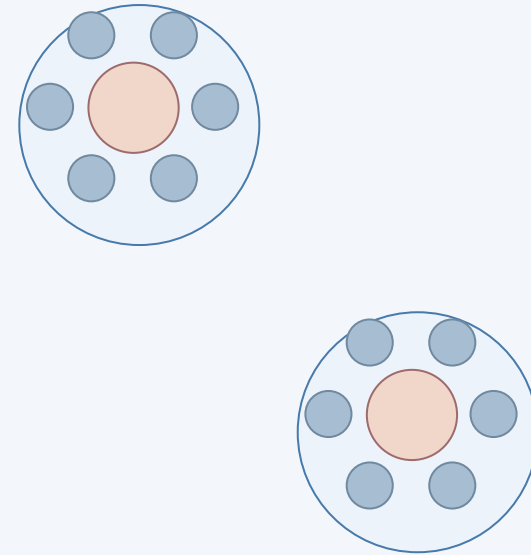
Germ-cell maturation is central to pathogenesis



- In normal development, primordial germ cells lose the embryonic pluripotency programme as they mature.
- Persistence of immature germ-cell features is an important observation in dysgenetic gonads.
- Delayed maturation is a biologic risk indicator, not by itself proof of malignancy.

Undifferentiated gonadal tissue (UGT)

- UGT contains germ cells within poorly organized gonadal stroma or immature cord-like structures.
- It is histologically non-neoplastic and can coexist with other dysgenetic patterns.
- UGT is proposed as a precursor setting for classical gonadoblastoma.



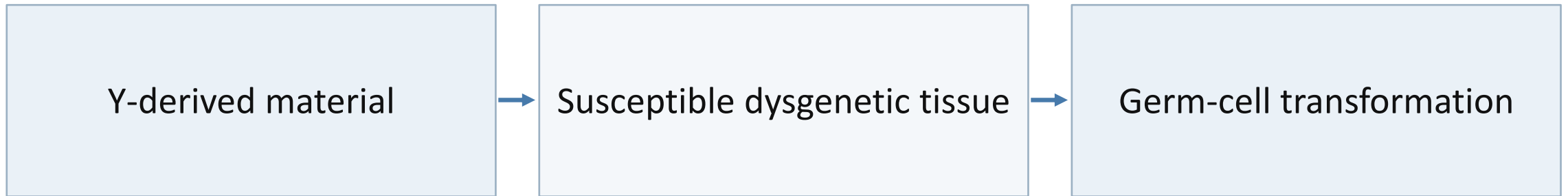
Poorly organised cells (schematic)
Schematic—not a histology image

Delayed maturation is not equal to neoplasia

Delayed maturation	Gonadoblastoma
Immature germ cells may persist	Characteristic cellular nests/cords
Non-neoplastic background possible	Germ-cell plus sex cord components
No obligatory circumscribed tumour nests	Neoplastic lesion

OCT4-positive immature germ cells may occur in dysgenetic gonads without a definitive tumour.

The Y chromosome association



- Most cases are associated with a Y chromosome or Y-derived material in the gonad.
- The gonadoblastoma susceptibility region (GBY) lies on the Y chromosome.
- Peripheral-blood karyotyping does not necessarily resolve all gonadal mosaicism.

TSPY: A candidate susceptibility gene

- TSPY1 encodes testis-specific protein, Y-linked 1, implicated in susceptibility.
- TSPY immunoreactivity may be seen in more mature germ-cell populations in this setting.
- Association with TSPY is not sufficient as a stand-alone diagnostic test.

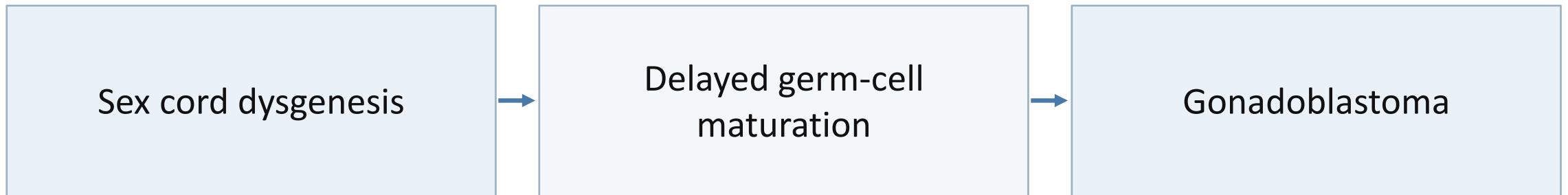
Y-derived material



TSPY1 susceptibility

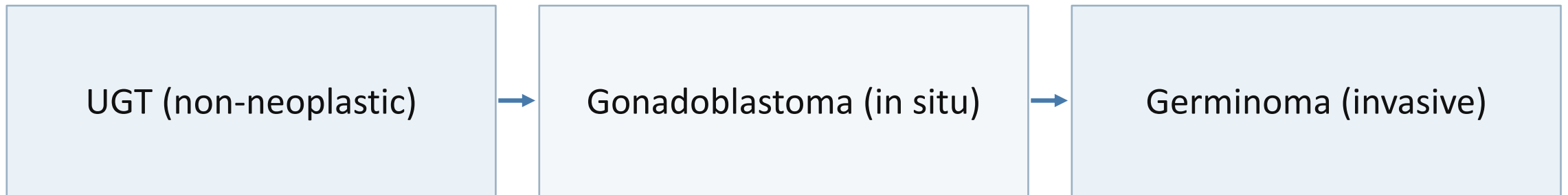
Association $\neq$ sufficient diagnosis

Proposed developmental mechanism



- Impaired sex cord differentiation creates an abnormal germ-cell microenvironment.
- Some germ cells retain an immature pluripotency-associated programme.
- Y-associated susceptibility may promote neoplastic transformation into gonadoblastoma.
- The sequence is a biologic model; Individual causal steps are not deterministically proven.

A conceptual progression model



- UGT is proposed as a precursor to classical gonadoblastoma.
- Classical and dissecting patterns can be linked histologically.
- Invasive germinoma may arise within or alongside the noninvasive lesion.
- Not every retained dysgenetic gonad follows this sequence.

Karyotype is a clue—not the entire diagnosis

- Many patients have 46,XY or sex-chromosome mosaicism, such as 45,X/46,XY.
- The presence, absence and distribution of Y-derived material must be interpreted in clinical context.
- Rare reported 46,XX cases demonstrate that the usual association is not absolute.

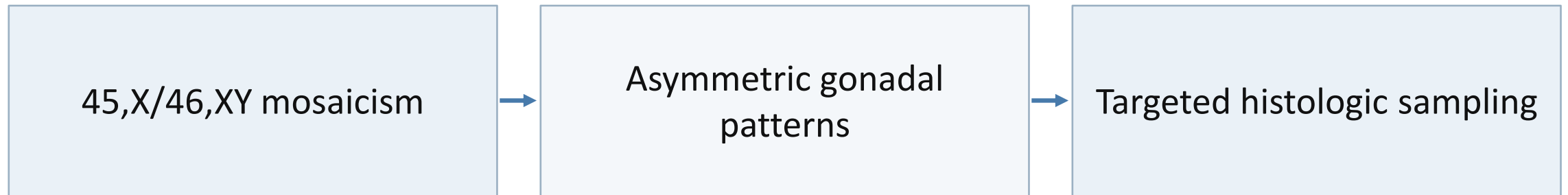
Y-derived material



TSPY1 susceptibility

Association ≠ sufficient diagnosis

Mixed gonadal dysgenesis: An instructive setting



- Sex-chromosome mosaicism can produce markedly asymmetric gonadal development.
- A streak-like gonad may coexist with dysgenetic testicular tissue.
- The gonad containing the least differentiation may still harbor the relevant precursor lesion.

46,XY gonadal dysgenesis

- Dysgenetic gonadal development occurs despite a 46,XY chromosomal constitution.
- Phenotypic appearance can be female, male or atypical, depending on developmental effects.
- Tumour risk must be assigned according to the specific gonadal condition rather than the karyotype alone.

Gonadal differentiation

Y-derived material

Anatomic location

Rare exception: Reported 46,XX gonadoblastoma

- Gonadoblastoma with dysgerminoma has been documented with 46,XX peripheral karyotype.
- A published case investigated sex-chromosomal material and a CYP17A1-related endocrine disorder.
- Such reports are uncommon and do not invalidate the strong usual association with Y material.

Usual association

Rare exceptions

Recheck assumptions

Clinical phenotypes are not uniform

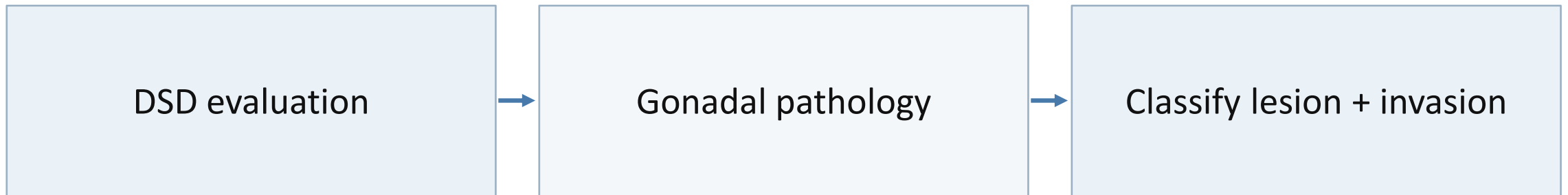
- Predominantly phenotypically female patients, with some phenotypically male cases.
- Presentations may include delayed puberty, primary amenorrhea or atypical genital development.
- Tumours may be detected during assessment of DSD or following symptoms of an invasive associated tumour.

Phenotype

Gonadal function

Shared-care decisions

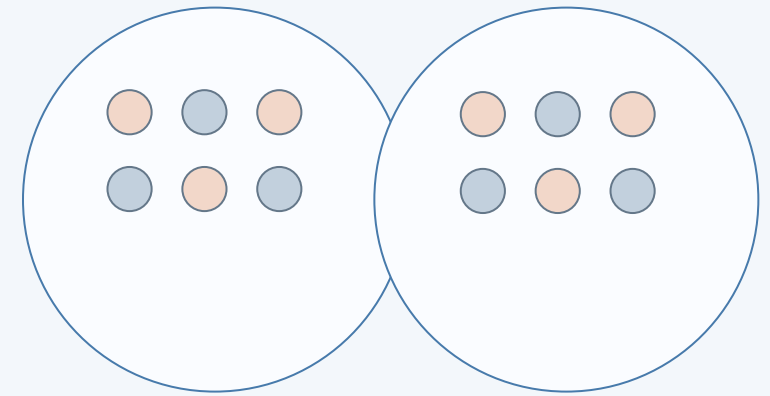
How gonadoblastoma comes to attention



- Incidental finding in prophylactically excised or diagnostically sampled dysgenetic gonads.
- A gonadal/pelvic mass may reflect an accompanying invasive germ-cell tumour.
- Clinical and imaging findings do not establish the histologic diagnosis of a microscopic precursor.

The contralateral gonad matters

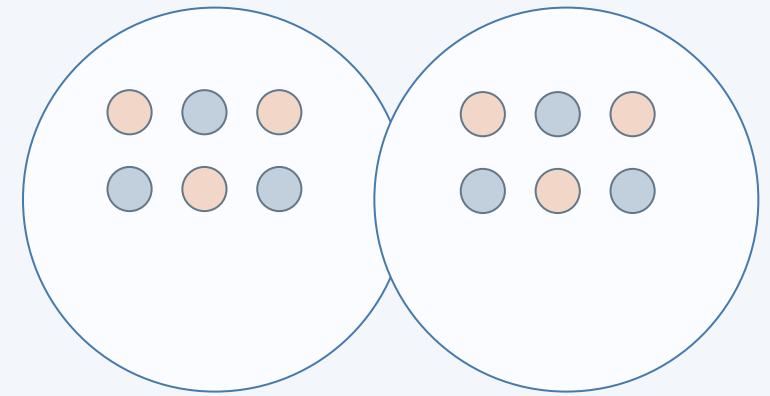
- Gonadoblastoma can occur bilaterally, including microscopic or occult lesions.
- Published pathology series describe bilaterality in a substantial subset; Selection biases limit generalization.
- Pathology findings should be communicated for specialist assessment of the opposite gonad.



Heterogeneity can occur between—
and within—gonads

Macroscopy: Do not expect a large mass

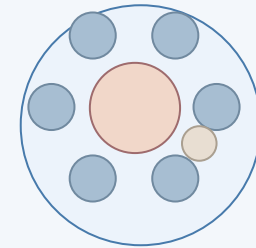
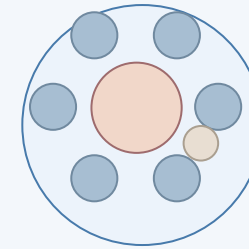
- Classical gonadoblastoma may form tiny, inconspicuous foci in dysgenetic tissue.
- Calcification can draw attention, but a grossly calcified nodule is not synonymous with gonadoblastoma.
- A bulky mass should trigger careful search for an associated invasive component.



Heterogeneity can occur between—
and within—gonads

Low-power architecture is diagnostic

- Classical gonadoblastoma consists of multiple rounded, discrete cellular islands.
- Nests contain both germ cells and small immature sex cord cells.
- Basement membrane-like hyaline material often participates in a recognisable pattern.

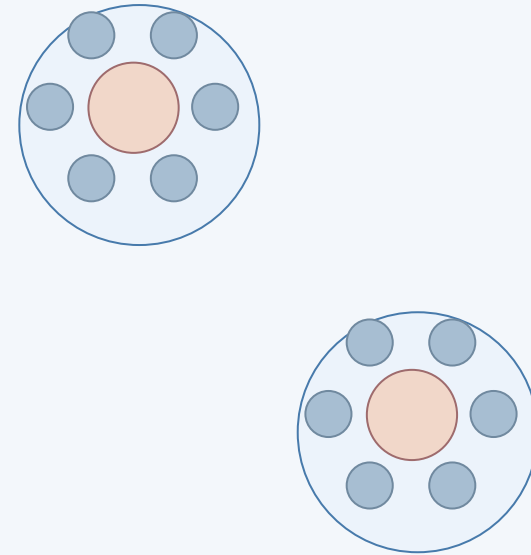


Dual-cell nests (schematic)

Schematic—not a histology image

Cell type one: The germ cells

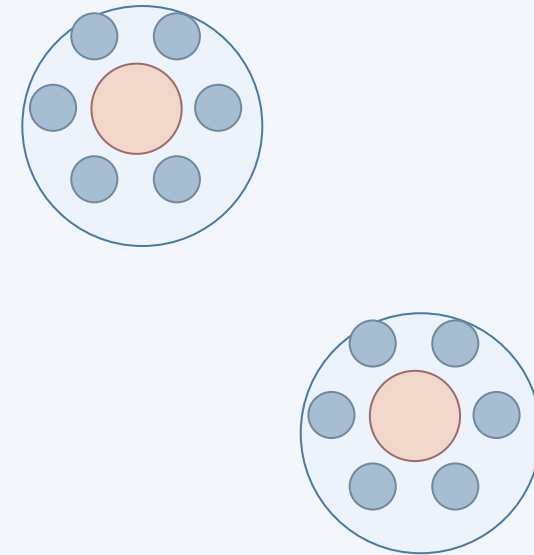
- Relatively large cells with pale cytoplasm and conspicuous nuclei may resemble germinoma cells.
- These cells represent the neoplastic germ-cell component.
- Their appearance must be evaluated with the smaller sex cord cells within the same nests.



Germ cells + sex cord cells
Schematic—not a histology image

Cell type two: Sex cord cells

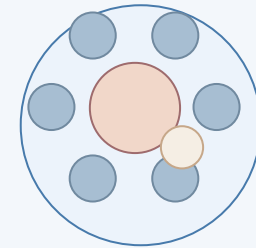
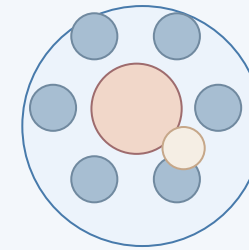
- Small immature supporting cells intimately surround or intermix with germ cells.
- These cells show sex cord differentiation by morphology and selected immunostains.
- Recognition of the second population prevents overcalling a solid nest as pure germinoma.



Germ cells + sex cord cells
Schematic—not a histology image

Hyaline globules and basement membrane material

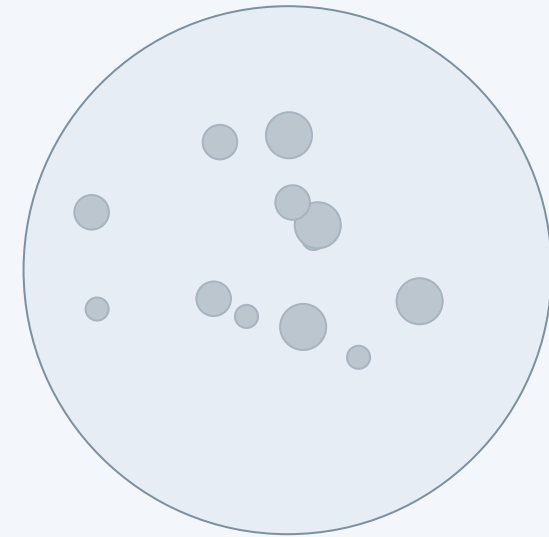
- Eosinophilic, hyaline basement membrane-like deposits can form globules or central bodies.
- Hyaline material helps organise the distinctive nest architecture.
- It is supportive rather than sufficient in isolation for the diagnosis.



Basement membrane bodies
(schematic)
Schematic—not a histology image

Calcification can be a useful clue

- Calcific deposits are commonly encountered in classical lesions.
- Progressive involution may leave largely calcified remnants.
- Calcification alone cannot distinguish active gonadoblastoma from another mineralised gonadal lesion.



Calcification may remain after marked involution

How to scan the H&E slide

Low power: Nests



Higher power: Two cell types



Search: Adjacent invasion

- Start at low power: Identify circumscribed rounded nests and their stromal context.
- Move to intermediate power: Verify germ cells plus smaller supporting sex cord cells.
- At high power: Inspect hyaline material, calcification and any adjacent invasive sheets.

Classical versus dissecting gonadoblastoma

Classical pattern	Dissecting pattern
Rounded discrete islands	Irregular/cord-like architecture
Hyaline bodies may be prominent	May resemble a germinoma infiltrate
Two cell lineages	Look for supporting sex cord elements

Classical pattern: Rounded nests with an intermingled dual-cell population.

The dissecting variant is a diagnostic trap

- Irregular distribution of tumour cells can look invasive at low magnification.
- Search for residual sex cord cells surrounding or accompanying germ cells.
- Use architecture, full sampling and an appropriately targeted IHC panel before declaring invasion.

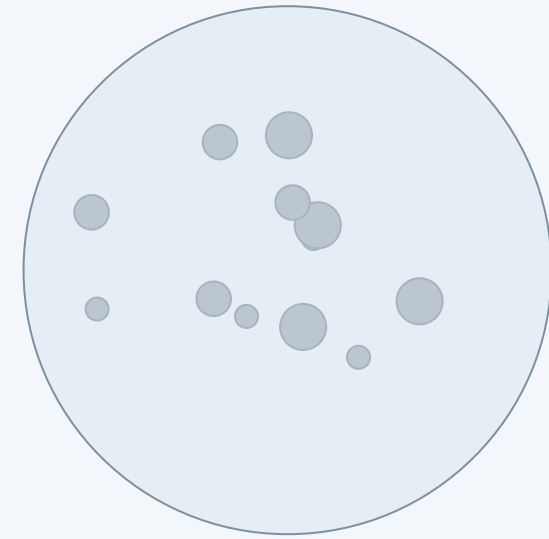
One positive marker



Not equivalent to an
Invasive diagnosis

Involuted gonadoblastoma

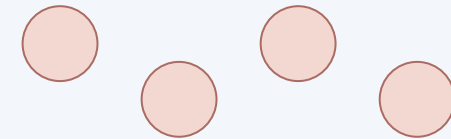
- Some lesions show extensive hyalinisation and calcification with loss of viable cells.
- An acellular calcified focus may represent an involuted lesion in the correct context.
- The report should reflect what was actually found; Do not infer viable tumour or invasion without evidence.



Calcification may remain after marked involution

The invasive partner: Dysgerminoma / seminoma

- An invasive germinoma can coexist with gonadoblastoma.
- In the ovarian context the conventional name is dysgerminoma; In testicular tissue, seminoma.
- The invasive tumour requires its own staging and management assessment.



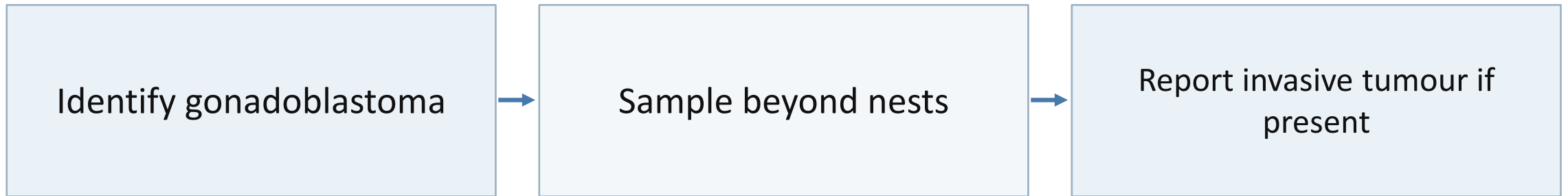
Loss of noninvasive arrangement

Recognising invasive germinoma morphologically

Gonadoblastoma	Invasive germinoma
Germ + sex cord elements	Germ-cell sheets and nests
Characteristic hyaline globules	Lacks integrated sex cord framework
Premalignant / noninvasive	Invasive malignant neoplasm

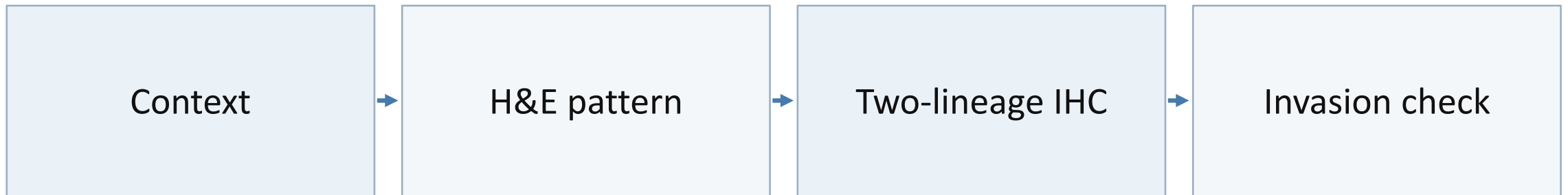
Invasive nests or sheets may contain large fairly uniform germ cells with prominent nucleoli.

The key distinction: Demonstrate or exclude invasion



- Do not designate a specimen “pure gonadoblastoma” until adjacent tissue is examined.
- Search for destruction of the noninvasive architecture and invasive expansion of germ cells.
- Use clinical staging only for an established invasive malignant component.

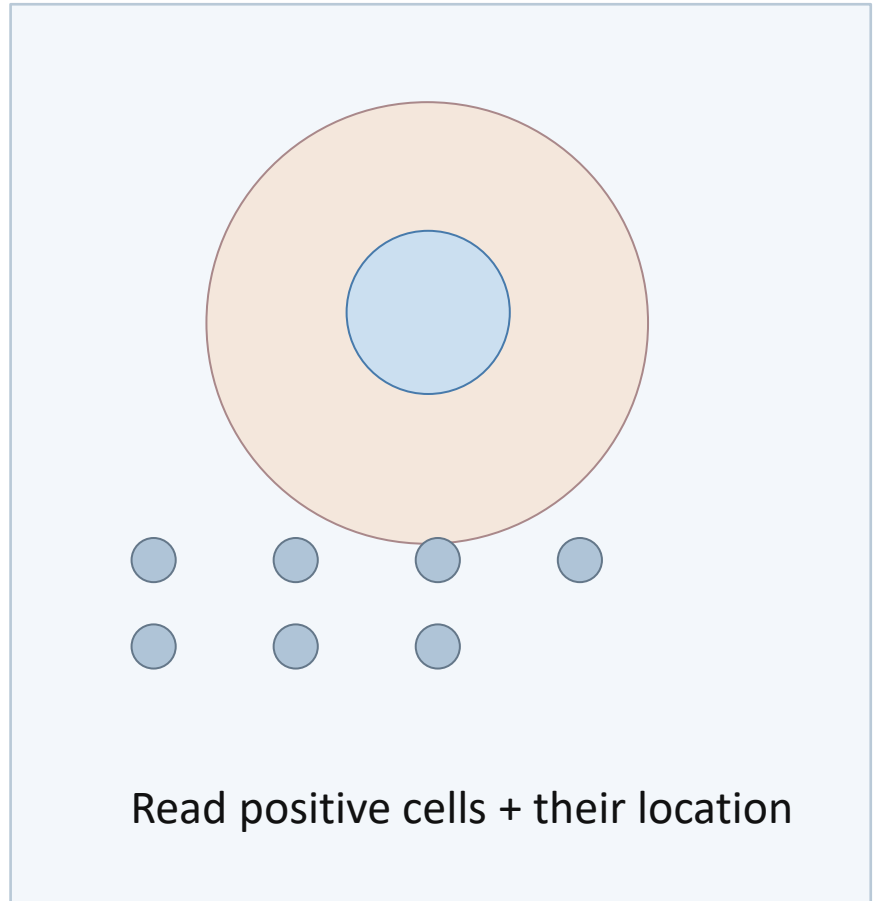
An efficient diagnostic workflow



- Establish developmental and anatomic context of the sampled gonad.
- Identify dual-lineage tumour nests on H&E.
- Demonstrate germ-cell and sex cord populations with complementary markers.
- Determine whether invasive germinoma or other malignant components coexist.

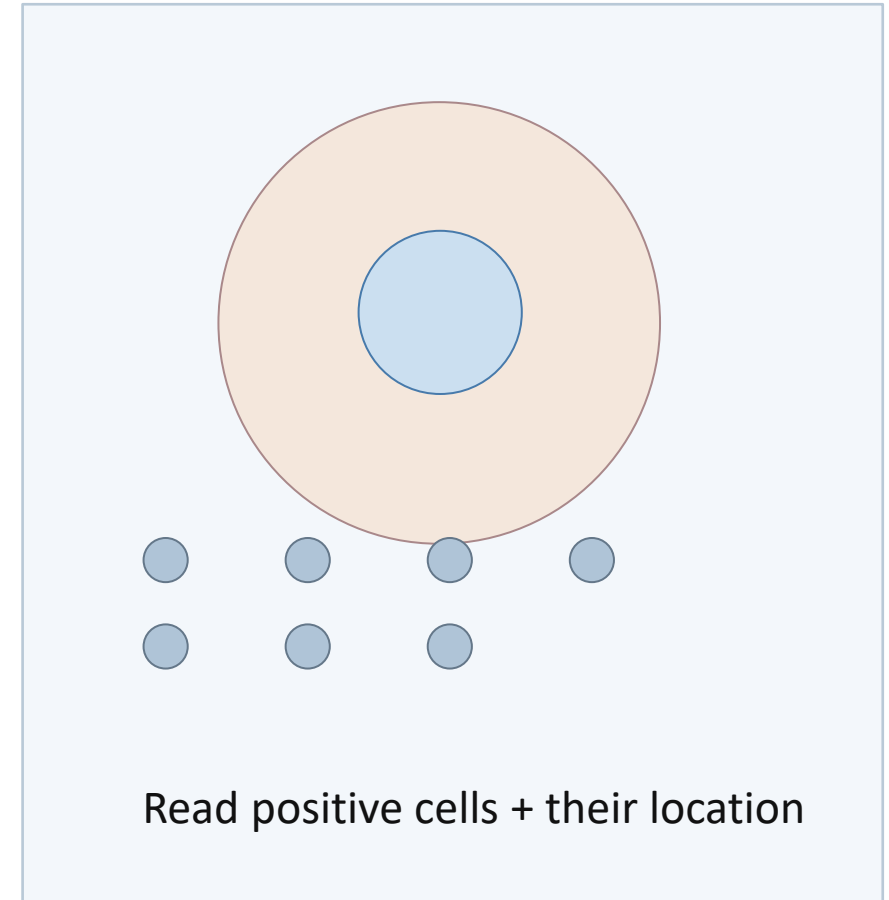
IHC must answer a cellular question

- Use markers of the germ-cell compartment and separately of the supporting sex cord compartment.
- The distribution and location of staining matter more than a binary positive/negative label.
- A single stain does not distinguish delayed maturation, gonadoblastoma and invasive tumour.



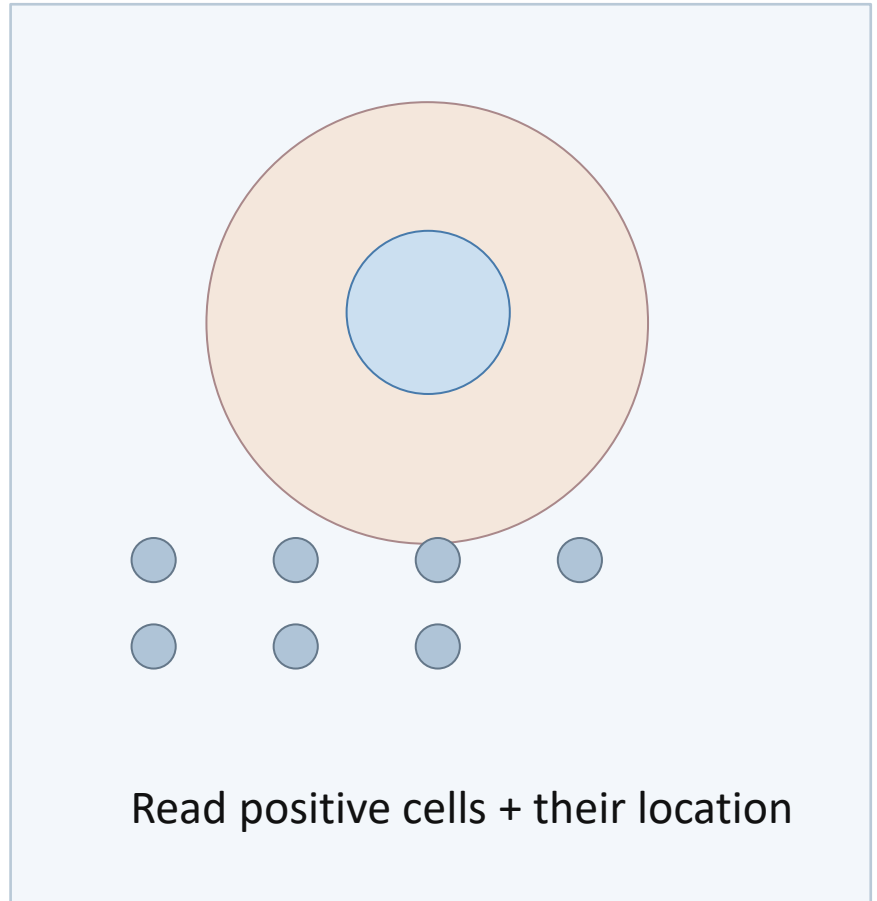
OCT3/4: Immature germ-cell programme

- OCT3/4 (POU5F1) shows nuclear staining in primitive neoplastic germ cells.
- It also can label germ cells exhibiting delayed maturation in dysgenetic gonads.
- Therefore, OCT3/4 demonstrates phenotype but cannot alone establish tumour boundaries.



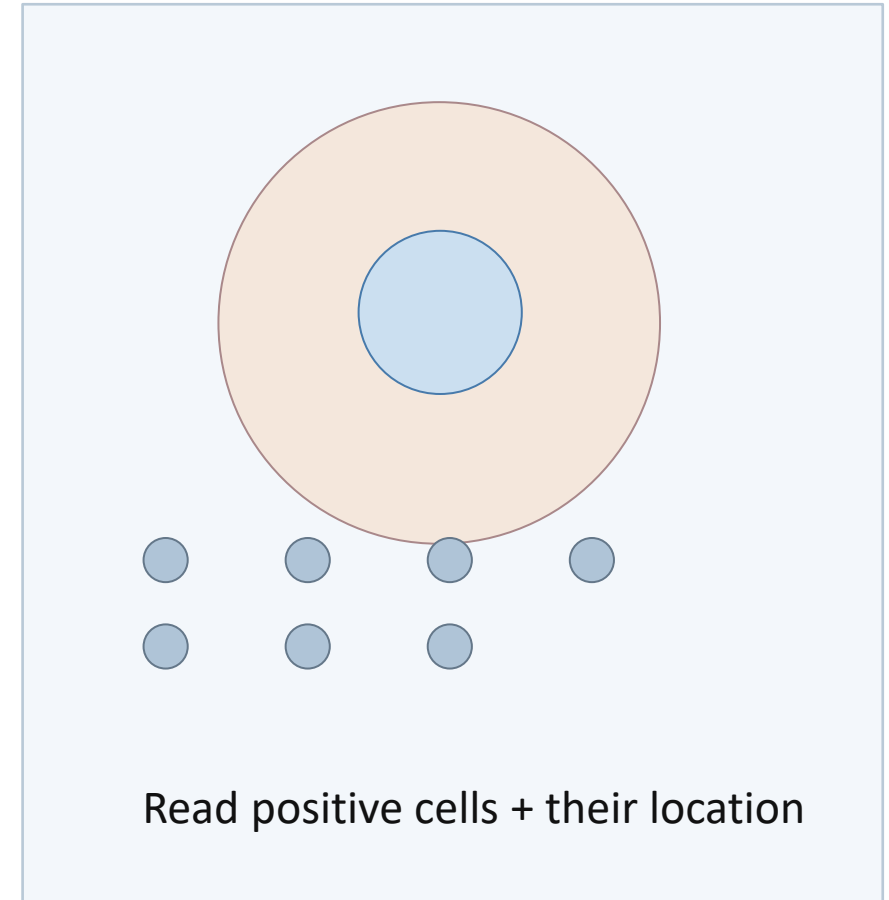
SALL4: Broad germ-cell lineage support

- SALL4 commonly labels germ-cell tumour components and supports germ-cell identity.
- It must be interpreted within the biphasic nests and not used in isolation.
- Positivity is not uniquely specific to gonadoblastoma.



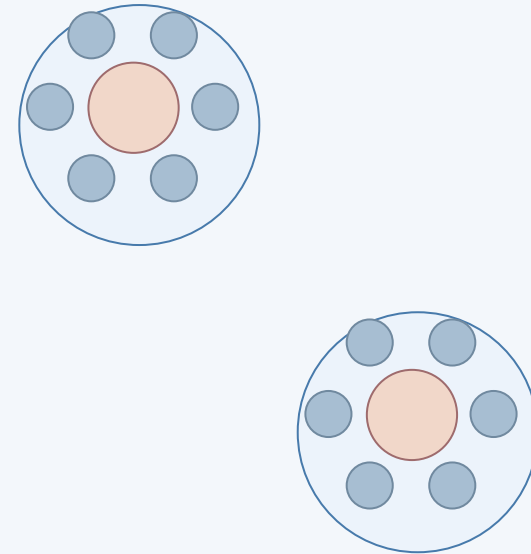
KIT/CD117: Useful but not a standalone discriminator

- KIT can highlight germ-cell elements of germinoma and associated lesions.
- A positive KIT stain cannot establish whether the germ-cell population is invasive.
- Correlate with H&E architecture and accompanying sex cord differentiation.



Inhibin and SF1 highlight sex cord differentiation

- α -Inhibin and steroidogenic factor 1 (SF1/NR5A1) support sex cord–stromal differentiation.
- In gonadoblastoma, the smaller supporting cells—not the germ cells—are the relevant population.
- Their presence helps distinguish the biphasic lesion from a pure invasive germinoma.



Germ cells + sex cord cells

Schematic—not a histology image

FOXL2 and SOX9: Interpret lineage carefully

FOXL2	SOX9
Sex cord cells; Ovarian pathway	Testicular supporting-cell pathway
May highlight supporting cells	Helps map gonadal differentiation
Localisation matters	Not a stand-alone tumour marker

FOXL2 supports granulosa-like/ovarian differentiation in the sex cord compartment.

TSPY immunostaining: Molecular context

- TSPY can mark germ-cell subsets in Y-associated dysgenetic gonads.
- Expression may coexist with OCT4 in a small population, reflecting heterogeneity.
- A negative result cannot by itself exclude exceptional gonadoblastoma presentations.

Y-derived material



TSPY1 susceptibility

Association $\neq$ sufficient diagnosis

Two compartments, two interpretive questions

Germ-cell component	Sex cord component
OCT3/4; SALL4	Inhibin; SF1
KIT/CD117; TSPY in context	FOXL2 or SOX9 in context
Interpret neoplastic and immature states	Look for intimate admixture in nests

Germ-cell stains: Where are primitive germ cells and how are they distributed?

IHC pitfall: Immature benign germ cells

- OCT4 expression in developmentally delayed germ cells is a known false-positive pitfall for malignancy.
- Neoplasia requires supporting architecture and a coherent cellular distribution.
- Evaluate marker localisation, age, gonadal maturity and whole-slide context.

One positive marker



Not equivalent to an
Invasive diagnosis

Differential 1: UGT versus gonadoblastoma

Undifferentiated gonadal tissue	Classical gonadoblastoma
Poorly organised germ cells/cords	Rounded islands with two cell types
No definitive classical tumour nests	Hyaline deposits are supportive
Developmental lesion	Noninvasive germ-cell neoplasia

UGT is developmentally abnormal but not itself a neoplastic lesion.

Differential 2: GCNIS versus gonadoblastoma

GCNIS	Gonadoblastoma
Neoplastic germ cells in tubules	Dual-population nests / cords
Existing testicular tubule framework	Undifferentiated or dysgenetic gonad
Testicular differentiation setting	Variable stromal arrangement

Germ cell neoplasia in situ (GCNIS) occurs within seminiferous tubules of testicular differentiation.

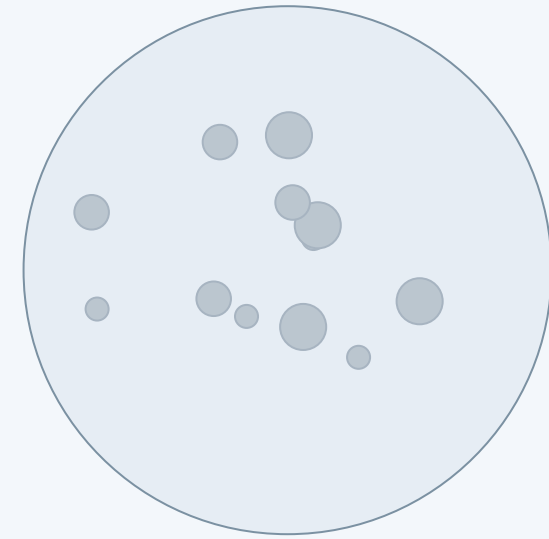
Differential 3: Invasive germinoma

Dissecting gonadoblastoma	Invasive germinoma
Irregular dual-lineage lesion	Invasive germ-cell tumour
Supporting cells detectable	Integrated sex cord pattern absent
Noninvasive variant	Malignant stage-relevant lesion

Invasive germinoma may be contiguous with or separate from gonadoblastoma.

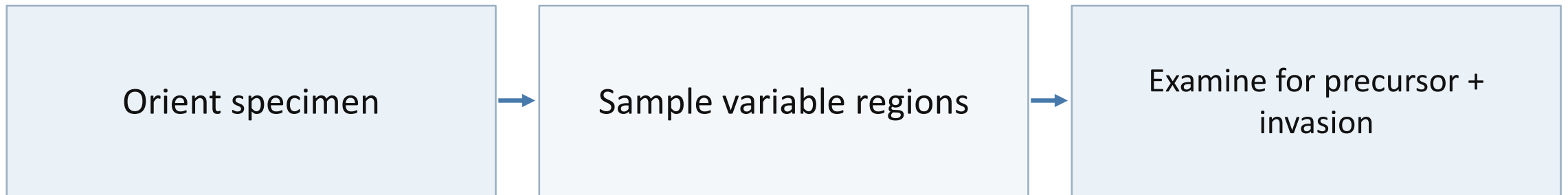
Differential 4: An isolated calcified gonadal focus

- A heavily involuted gonadoblastoma may be nearly acellular.
- Other causes of gonadal calcification must be considered; The finding is not pathognomonic.
- Report uncertainty if adequate viable diagnostic cellular elements are absent.



Calcification may remain after marked involution

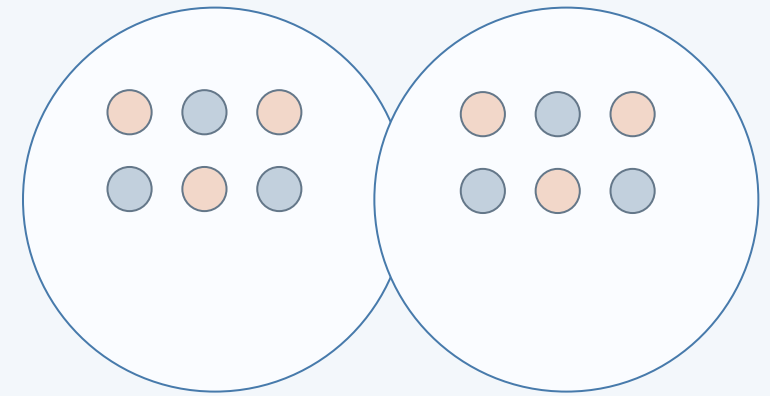
Sampling a dysgenetic gonad



- Review gross and histologic heterogeneity; Submit representative regions rather than only a single calcified nodule.
- Target suspicious nodules and adjacent gonadal tissue for precursor and invasive disease.
- The exact sampling plan should be adapted to specimen size and institutional protocols.

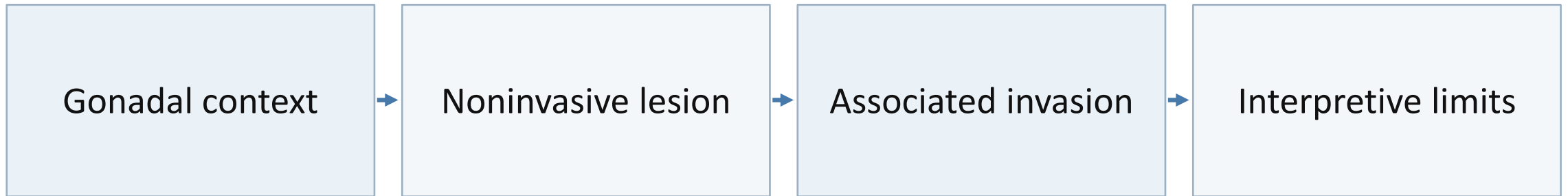
Communicate any contralateral risk

- Presence of gonadoblastoma signals that the other gonad may share the developmental susceptibility.
- Do not infer that the opposite gonad is affected without examination.
- Recommend multidisciplinary discussion informed by genotype, age, gonadal location and function.



Heterogeneity can occur between—
and within—gonads

A focused pathology report



- Record specimen side, gonadal tissue pattern and whether gonadoblastoma is identified.
- Document whether invasive dysgerminoma/seminoma or another malignant component is present.
- State relevant calcification, IHC findings and limitations in sampling when they alter confidence.
- Avoid attaching an invasive stage to a purely noninvasive lesion.

Risk stratification: Neither binary nor universal

- Malignancy risk varies by the specific DSD diagnosis and degree of gonadal dysgenesis.
- Y-chromosome material and intra-abdominal gonadal location may increase concern in selected groups.
- Tumour-related recommendations must distinguish a premalignant focus from overall lifetime gonadal risk.

Gonadal differentiation

Y-derived material

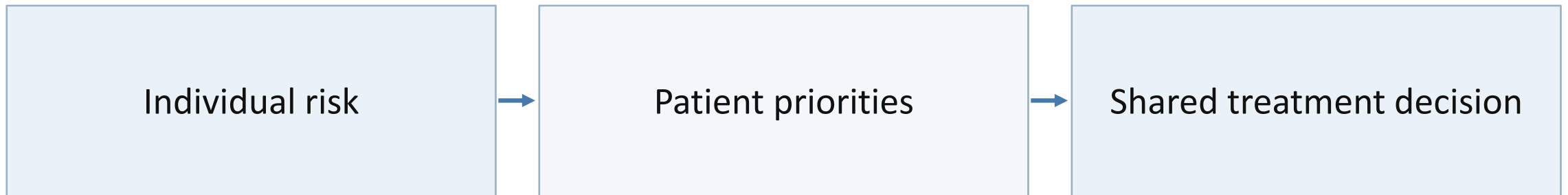
Anatomic location

Clinical surveillance has limitations

Useful for	Not reliable for
Mass localisation on imaging	Excluding occult microscopic lesions
Evaluation of invasive GCT markers	Certifying absence of premalignancy
Longitudinal clinical assessment	Replacing histologic diagnosis

Serum AFP, hCG and LDH may help evaluate an established germ-cell tumour but cannot reliably exclude microscopic gonadoblastoma.

Gonadectomy decisions require individualisation



- Historically, dysgenetic gonads with suspected Y-associated risk were often removed prophylactically.
- Contemporary guidance weighs actual risk against hormonal function, fertility potential and patient autonomy.
- The choice and timing should be made through a specialist DSD team and shared decision-making.

Consequences beyond neoplasia

- Removal or retention of gonadal tissue can affect sex-hormone production and fertility potential.
- Clinical assessment should include developmental anatomy, endocrinology and psychosocial wellbeing.
- Pathology supplies a tumour diagnosis; It does not independently determine appropriate sex assignment or care goals.

Phenotype

Gonadal function

Shared-care decisions

Prognosis depends on what is present

- An excellent prognosis for completely excised isolated gonadoblastoma.
- A coexistent invasive germ-cell tumour changes the clinical question and requires separate evaluation.
- Avoid extrapolating invasion-related outcomes to a purely noninvasive lesion.



Defined noninvasive architecture

Case 1: Microscopic gonadal lesion

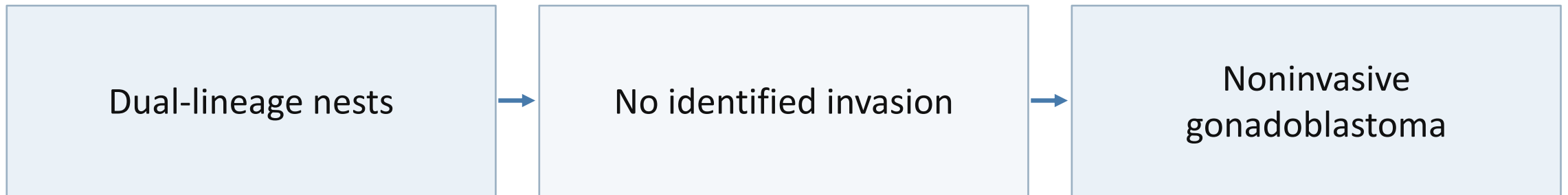
A patient with 45,X/46,XY mosaicism has a dysgenetic gonad removed during multidisciplinary assessment.

Histology shows multiple rounded nests of large germ cells and small supporting cells.

Hyaline bodies and focal calcification are present, without an invasive component in examined sections.

What is the most defensible diagnosis?

Case 1: Interpretation



- The dual-cell nests with hyaline material favour classical gonadoblastoma.
- Appropriate IHC would identify germ-cell and sex cord components if morphology is uncertain.
- Report noninvasive gonadoblastoma; Assess sampling adequacy and convey contralateral relevance.

Case 2: A mass in an atypical context

A phenotypically female child has a unilateral pelvic mass, low sex steroids and an apparent 46,XX karyotype.

Sections show gonadoblastoma adjacent to dysgerminoma.

The appropriate conclusion is not that a Y chromosome is necessary in every reported case.

What additional developmental and molecular evaluation is justified?

Case 2: Interpretation and limitation



- Recognise the invasive dysgerminoma separately from gonadoblastoma.
- Investigate the underlying endocrine/DSD context and possible mosaicism as clinically appropriate.
- Rare 46,XX reports are evidence of exceptions, not a basis for revised population risk estimates.

Diagnostic checkpoint

A dysgenetic gonad has OCT4-positive germ cells but no rounded biphasic tumour nests.

Which statement is defensible?

- A. OCT4 positivity proves invasive dysgerminoma.
- B. Delayed germ-cell maturation must remain in the differential.
- C. Gonadoblastoma is proven without H&E architecture.

Checkpoint answer: B

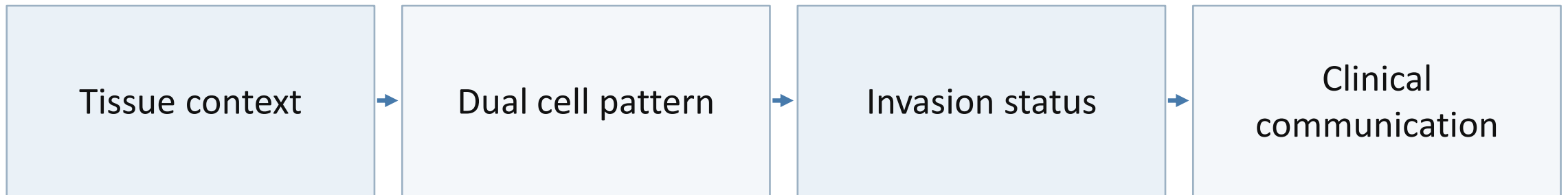
- OCT4 is a germ-cell maturation/pluripotency marker, not an independent invasion test.
- The distinction requires histologic pattern, cellular context and possibly additional stains.
- Overcalling a precursor or malignant lesion can directly alter surgical and oncologic care.

One positive marker



Not equivalent to an
Invasive diagnosis

Synthesis: Four decisions for the pathologist



- Determine whether the gonadal tissue is dysgenetic and how it is organised.
- Recognise dual germ-cell and sex cord compartments in the lesion.
- Actively exclude associated invasive germinoma or other malignant elements.
- Communicate context and limitations to the multidisciplinary treating team.

Primary textbook source

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026).
- Textbook framework: A noninvasive germ-cell lesion in dysgenetic gonads.
- Related ovarian pathology: Association with an invasive dysgerminoma.
- The book's descriptions provide core identity and clinical significance; Subsequent sources extend mechanisms and diagnostic practice.

Classification, pathogenesis and diagnosis: Sources

- Berney DM et al. WHO 5th-edition testicular tumour classification. Histopathology. 2022. Doi:10.1111/his.14675.
- Roth LM et al. Gonadoblastoma: Origin and outcome. Hum Pathol. 2020. Doi:10.1016/j.humpath.2019.11.005.
- Roth LM et al. Classical and dissecting gonadoblastoma. Histopathology. 2018. Doi:10.1111/his.13387.
- Yin M et al. 46,XX case report. Front Endocrinol. 2022. Doi:10.3389/fendo.2022.989695.

Clinical context and limitations: sources

- Cools M et al. Caring for individuals with DSD: consensus. Nat Rev Endocrinol. 2018. doi:10.1038/s41574-018-0010-8.
- Clinical practice guidelines for management of DSD in Japan (2025). PMC12779382.
- Biphasic histology photomicrographs: Yin et al. (2022), Fig. 1, open access CC BY 4.0: doi:10.3389/fendo.2022.989695.
- No histology figure is reproduced here: the original open-access micrographs should be consulted during microscopy teaching.