

NUT Carcinoma

A fusion-driven, poorly differentiated malignancy

Molecular pathogenesis · diagnostic pathology · clinicopathologic correlation

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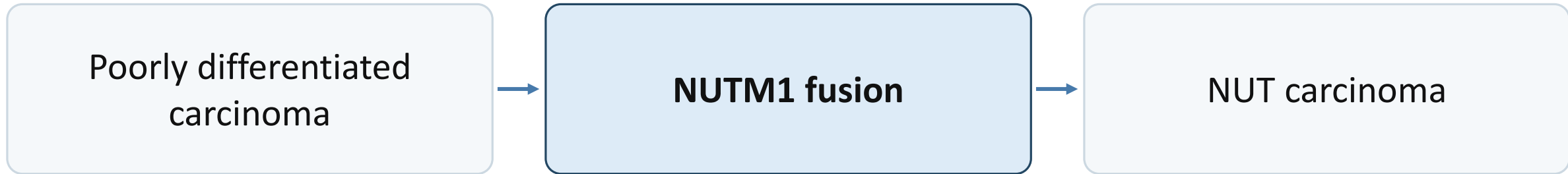
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Learning outcomes

- Recognize clinical and microscopic settings that warrant NUT testing.
- Explain how NUTM1 fusion proteins disrupt chromatin regulation and differentiation.
- Construct a focused immunohistochemical and molecular diagnostic pathway.
- Interpret key management and prognosis limitations.

NUT carcinoma is molecularly defined

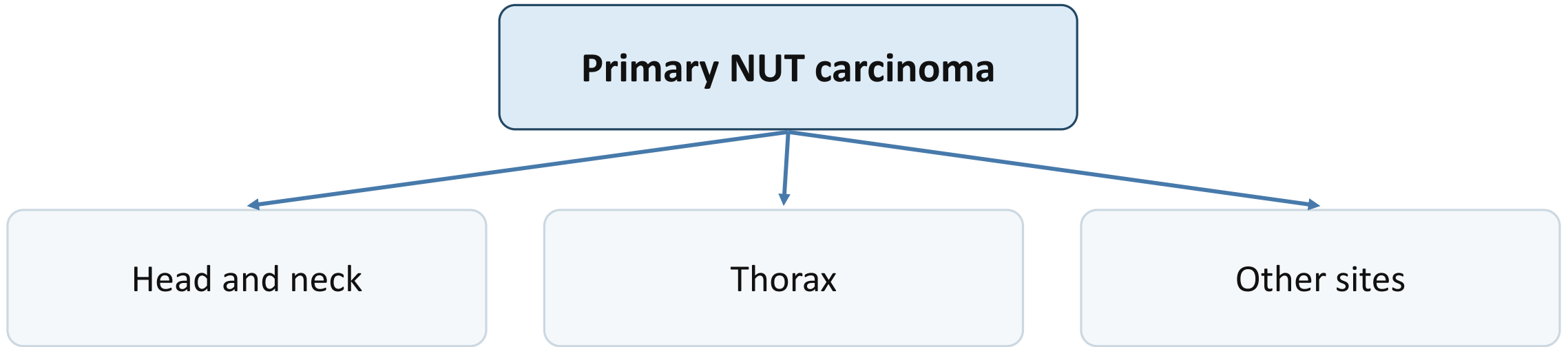


- A rare, aggressive carcinoma driven by an oncogenic NUTM1 rearrangement.
- The defining alteration is more specific than a site, age, or conventional histologic pattern.
- The malignant cells commonly appear poorly differentiated, with variable squamous features.

Why this entity is underrecognized

- The tumor can closely resemble conventional squamous cell carcinoma.
- Unusual site and age distributions can obscure the diagnosis.
- Morphology alone cannot reliably identify the molecular entity.

Anatomic distribution is broad



- Head and neck sites include sinonasal tract, nasopharynx, and salivary glands.
- Thoracic and mediastinal primary tumors are also well documented.
- Other visceral or extranodal sites occur; “midline” is not an absolute restriction.

Historical “midline carcinoma” is a misnomer

- The historical label reflects the first-recognized thoracic and upper aerodigestive cases.
- NUTM1-rearranged carcinomas can arise outside the midline.
- “NUT carcinoma” is the preferred broad term for this entity.

There is no age-based exclusion

Clinical assumption	Diagnostic correction
Pediatric-only tumor	May occur across the lifespan
Young adults only	Older patients also affected
Age confirms diagnosis	Molecular or NUT IHC evidence is required

- Cases range from infancy to late adulthood.
- A young patient with a rapidly growing undifferentiated carcinoma warrants heightened suspicion.
- Advanced age does not exclude NUT carcinoma.

True population incidence remains uncertain

- Disease rarity and histologic mimicry complicate ascertainment.
- Selective use of NUT testing creates underdiagnosis and referral bias.
- Published case-series proportions should not be presented as population incidence.

No established environmental cause



- No specific exogenous cause of the NUTM1 fusion has been established.
- A NUTM1 rearrangement is generally a somatic tumor event, not a hereditary syndrome.
- Smoking, EBV, and HPV are not established drivers of this entity.

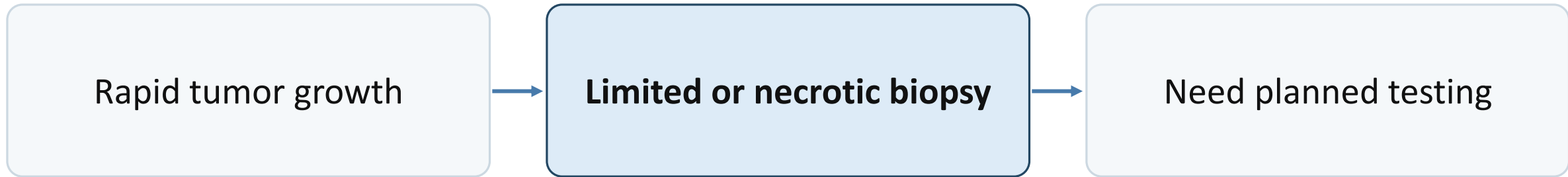
Head and neck presentation depends on site

- Sinonasal lesions may present with nasal obstruction or epistaxis.
- Nasopharyngeal or salivary-region masses can produce compressive symptoms.
- These symptoms are nonspecific; Rapid progression should raise diagnostic urgency.

Thoracic disease can be clinically silent early

- Mediastinal or pulmonary masses may cause cough, pain, or dyspnea.
- Patients may present with bulky locoregional disease.
- Clinical presentation cannot distinguish NUT carcinoma from common lung tumors.

Aggressive local growth has diagnostic consequences

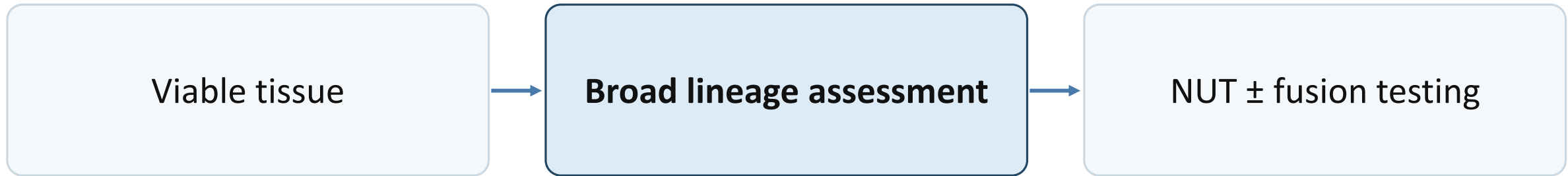


- Rapid expansion may compromise airway or adjacent organs.
- Necrosis and crush artifact are frequent challenges in limited biopsies.
- Early pathology communication can preserve tissue for molecular work-up.

Dissemination often occurs early

- Regional nodes and distant deposits may be present at diagnosis.
- Thoracic and extrathoracic primaries both require appropriate staging assessment.
- The presence of metastases does not resolve the differential diagnosis.

Biopsy strategy: Maximize useful viable tumor



- Select a viable region whenever possible, avoiding exclusively necrotic tissue.
- Obtain sufficient material for morphology, immunostains, and potential sequencing.
- Discuss differential diagnosis with the sampling team if NUT carcinoma is suspected.

Histology: Primitive epithelial malignancy

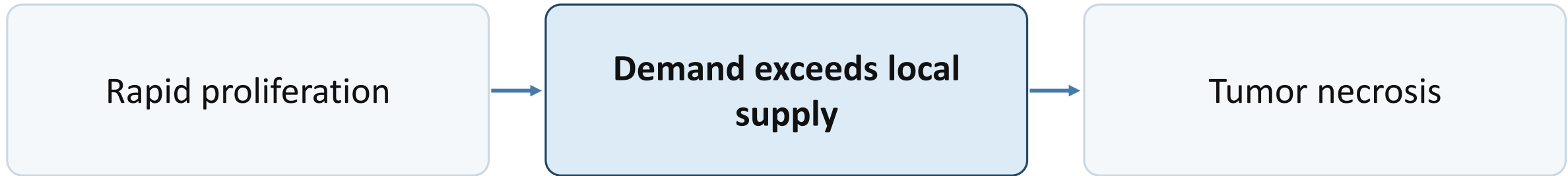
- Sheets, nests, or lobules of monotonous poorly differentiated cells are common.
- Architectural differentiation may be minimal or absent.
- Cellular morphology often resembles basaloid squamous carcinoma.

The nuclear appearance can be deceptively uniform

Observation	Interpretation
Monotonous cells	Primitive appearance
Prominent nucleoli	High-grade cytology
Limited pleomorphism	Does not imply low-grade biology

- Nuclei may be round to oval, with open chromatin and evident nucleoli.
- Pleomorphism may be less striking than expected for an aggressive tumor.
- Nuclear monotony is a clue, not a diagnostic criterion.

High turnover produces necrosis and mitoses



- Brisk proliferation commonly accompanies extensive viable tumor.
- Confluent necrosis may occur within cellular sheets.
- A small sample dominated by necrosis may obscure the epithelial pattern.

Abrupt keratinization is an important clue

Primitive component	Differentiated component
Basaloid cells	Keratinizing squamous nests
Limited cytoplasm	Eosinophilic keratinization
High proliferation	Abrupt morphologic transition

- Well-differentiated squamous foci may directly abut primitive cells.
- The shift can occur without an extended maturation gradient.
- This feature is helpful but neither constant nor specific.

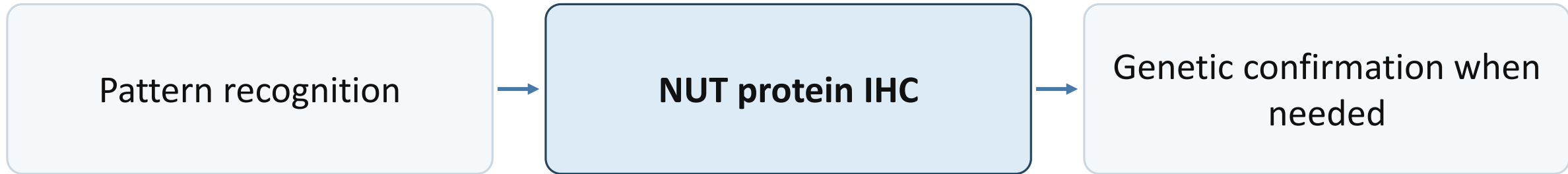
Absence of keratinization does not exclude NUT

- Some tumors lack visible squamous maturation entirely.
- Small biopsies may miss an otherwise focal squamous component.
- NUT testing must follow the total clinicopathologic impression, not one morphologic sign.

Stroma and inflammatory cells can vary

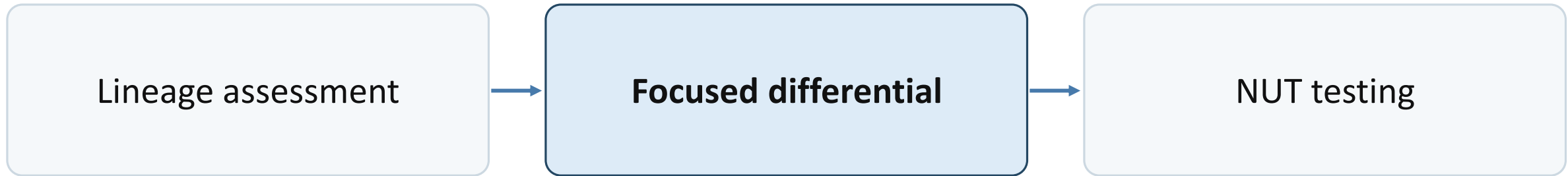
- Stroma may be fibrous, edematous, or myxoid.
- Intratumoral neutrophils are described and may be conspicuous.
- Neither stromal pattern nor inflammatory phenotype is independently diagnostic.

H&E findings are a trigger—not proof



- Poor differentiation, necrosis, and focal squamous features form a useful pattern.
- The same pattern can occur in several unrelated malignancies.
- A molecularly specific assay is needed to distinguish the entity.

Small biopsy pitfalls require a deliberate sequence



- First establish carcinoma versus lymphoma, melanoma, or other round-cell tumor.
- Then assess squamous and neuroendocrine lineage as indicated.
- Order NUT IHC early when the tumor remains unusually primitive.

Squamous lineage is not sufficient to subtype it

Marker class	What it establishes
Broad cytokeratin	Epithelial differentiation
P40 / p63	Squamous differentiation
NUT nuclear staining	Supports NUT carcinoma in context

- Cytokeratin, p40, or p63 positivity may support epithelial/squamous differentiation.
- Conventional basaloid SCC can share these markers.
- Only NUT-specific testing resolves the molecular classification.

The genetic hallmark is a NUTM1 fusion

Normal chromosomal segments

BRD4 · 19p13

NUTM1 · 15q14

BRD4 :: NUTM1 fusion protein

Schematic: Rearranged chromosome produces a chimeric transcriptional regulator.

BRD4 is the major fusion partner

Most commonly identified fusion

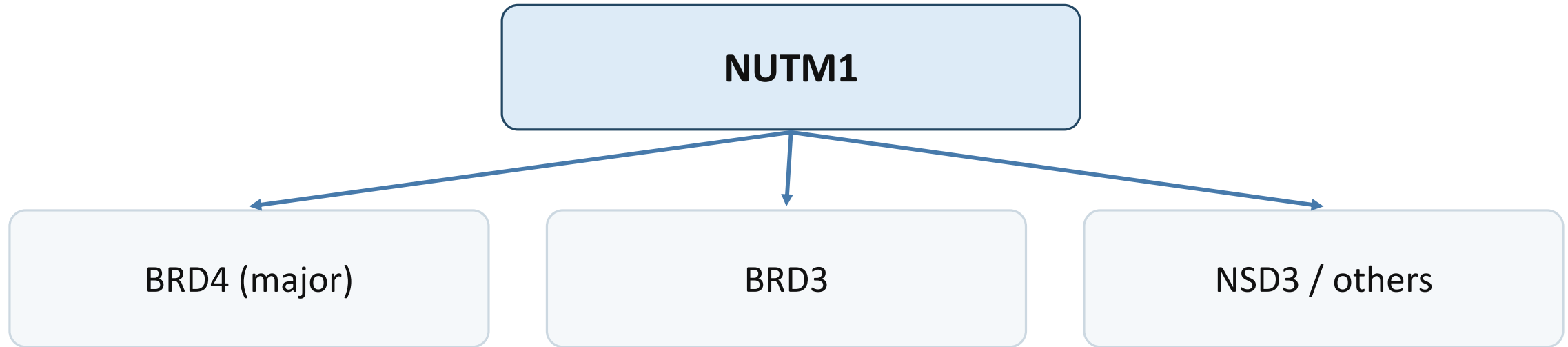
BRD4::NUTM1

Other partners

Predominant fusion; Approximately 70% in published series

- BRD4 lies at chromosome 19p13 and encodes a BET chromatin reader.
- BRD4::NUTM1 accounts for the majority of characterized cases.
- Partner identification helps explain mechanism and may inform clinical studies.

Other partners use related chromatin machinery



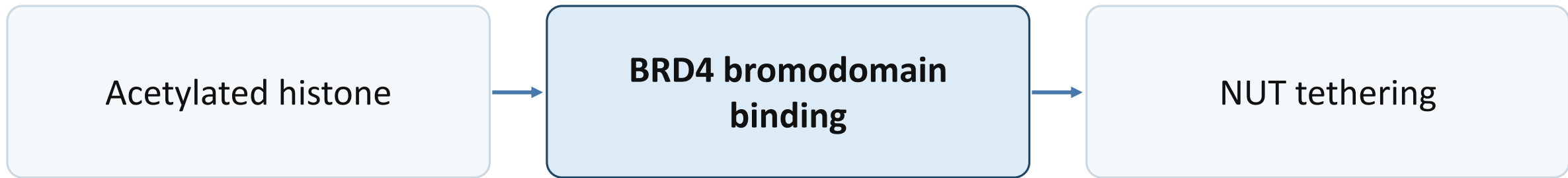
- BRD3::NUTM1 and NSD3::NUTM1 are established variants.
- ZNF-related and other rare NUTM1 partners have been reported.
- Not every NUTM1-rearranged neoplasm is classifiable as NUT carcinoma.

Fusion terminology matters in the report

Laboratory result	Appropriate wording
Diffuse NUT IHC	NUT carcinoma supported
NUTM1 break-apart FISH	NUTM1 rearrangement detected
RNA fusion assay	Named partner::NUTM1 fusion

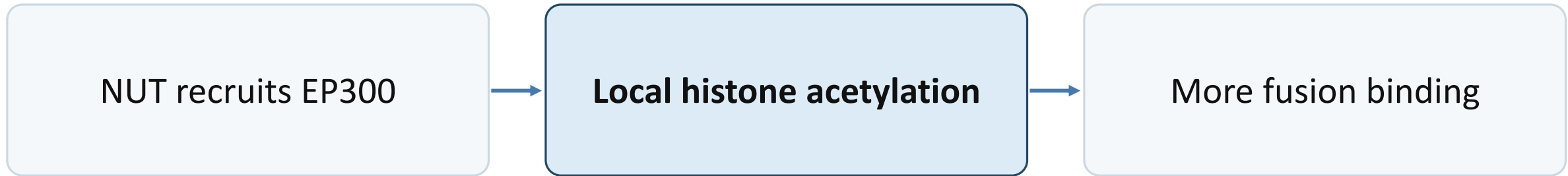
- Use “NUTM1 rearranged” for a demonstrated locus alteration.
- Use “BRD4::NUTM1” only when that partner is actually identified.
- Do not infer BRD4 solely from positive NUT immunohistochemistry.

BRD4 reads acetylated chromatin



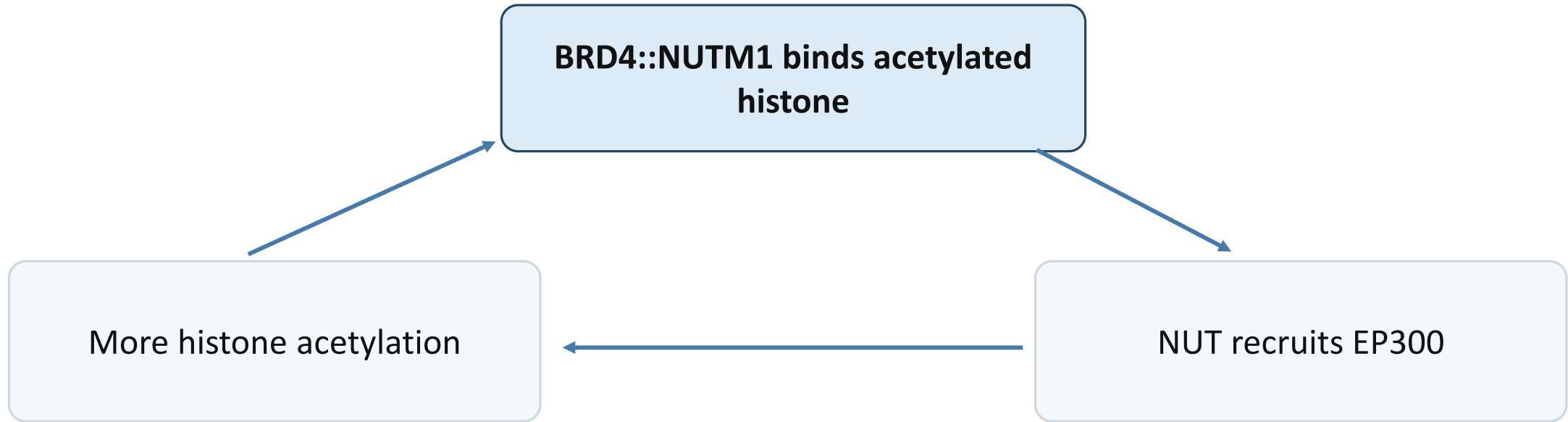
- BET bromodomains recognize acetylated lysines on histones.
- This property anchors BRD4-containing complexes to active chromatin.
- In the fusion protein, the chromatin reader is coupled to NUT activity.

The NUT moiety recruits acetylation machinery



- The NUT component interacts with EP300, a histone acetyltransferase.
- EP300 increases local histone acetylation at bound chromatin.
- More acetylation favors further recruitment of BET-containing fusion protein.

Feed-forward acetylation builds megadomains



- BRD4::NUTM1 binds acetylated chromatin and recruits EP300.
- EP300 acetylates neighboring histones, extending binding sites.
- Repeated recruitment produces large hyperacetylated chromatin domains.

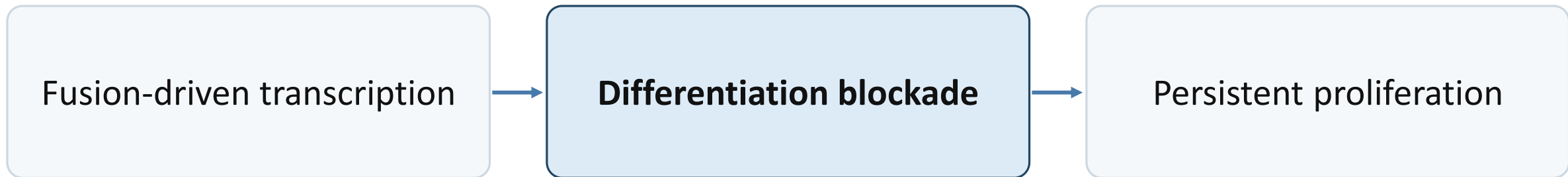
Feed-forward chromatin acetylation is a mechanism; Not a measured patient-specific pathway.

Megadomains reorganize transcription

Megadomain-associated chromatin	Other chromatin regions
Enriched acetylation	Relative hypoacetylation
Fusion-protein enrichment	Reduced fusion occupancy
Oncogenic gene expression	Differentiation programs impaired

- Hyperacetylated domains concentrate oncogenic transcriptional activity.
- Regions outside these domains may become relatively hypoacetylated.
- The combined effect favors proliferation and represses differentiation programs.

Differentiation arrest is central to oncogenesis



- The fusion protein helps maintain a primitive proliferative state.
- MYC, SOX2, and TP63 are implicated in experimental models.
- Molecular and cell-line evidence must not be mistaken for a validated patient-level biomarker.

Experimental removal of fusion function restores maturation

Experimental perturbation	Observed cell-model effect
Fusion suppression	Differentiation resumes
BET displacement	Growth arrest / differentiation
Clinical treatment	Benefit remains limited / under study

- Fusion knockdown can cause growth arrest and squamous differentiation in models.
- BET bromodomain blockade can displace fusion complexes from chromatin.
- This is compelling target biology, not proof of clinical survival benefit.

NUT immunohistochemistry is the frontline assay



- NUT IHC is practical on formalin-fixed diagnostic material.
- A strong, diffuse nuclear pattern in an appropriate carcinoma is highly informative.
- The assay should be interpreted alongside morphology and controls.

The characteristic NUT pattern is nuclear

Supports NUT carcinoma	Requires caution
Diffuse nuclear staining	Isolated cytoplasmic staining
Speckled intranuclear pattern	Weak focal nuclear signal
Concordant morphology	Poor preservation / artifact

- Strong nuclear labeling frequently has a punctate or speckled quality.
- Cytoplasmic staining alone should not be accepted as diagnostic.
- Evaluate distribution and intensity in viable tumor nuclei.

IHC interpretation must remain contextual

- Diffuse strong nuclear staining is commonly treated as highly specific in carcinoma.
- Test characteristics vary by antibody, sample quality, and population.
- Equivocal or discordant staining warrants molecular adjudication.

Epithelial immunophenotype is variable

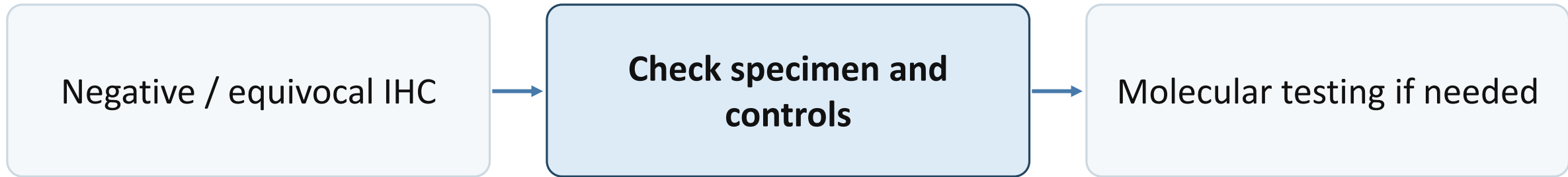
- Broad-spectrum keratins often support carcinoma.
- P40 and p63 may be expressed, sometimes incompletely.
- Negative or limited squamous markers do not reliably exclude this entity.

Neuroendocrine marker expression can mislead

Shared observation	Necessary discriminator
Primitive cells	Lineage panel plus NUT
Necrosis / brisk mitoses	Not exclusive to neuroendocrine tumors
Focal neuroendocrine marker	Does not overrule NUTM1 driver

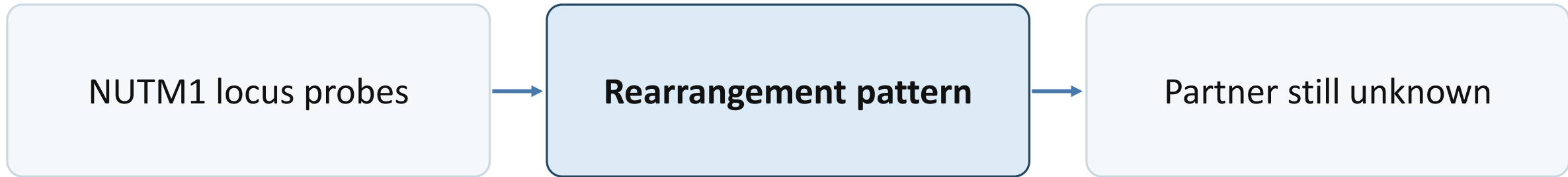
- Some NUT carcinomas express individual neuroendocrine markers.
- A small-cell–like morphology does not establish small cell neuroendocrine carcinoma.
- Combined morphology and NUT testing can prevent misclassification.

A negative NUT stain is not the end of work-up



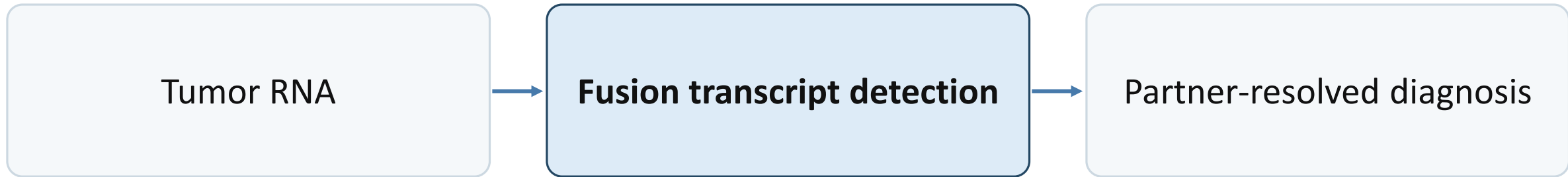
- Review whether viable tissue and assay controls were adequate.
- Consider rare antigenic variants, fixation issues, and sampling limitations.
- With strong suspicion, request NUTM1 rearrangement or fusion testing.

Break-apart FISH detects locus rearrangement



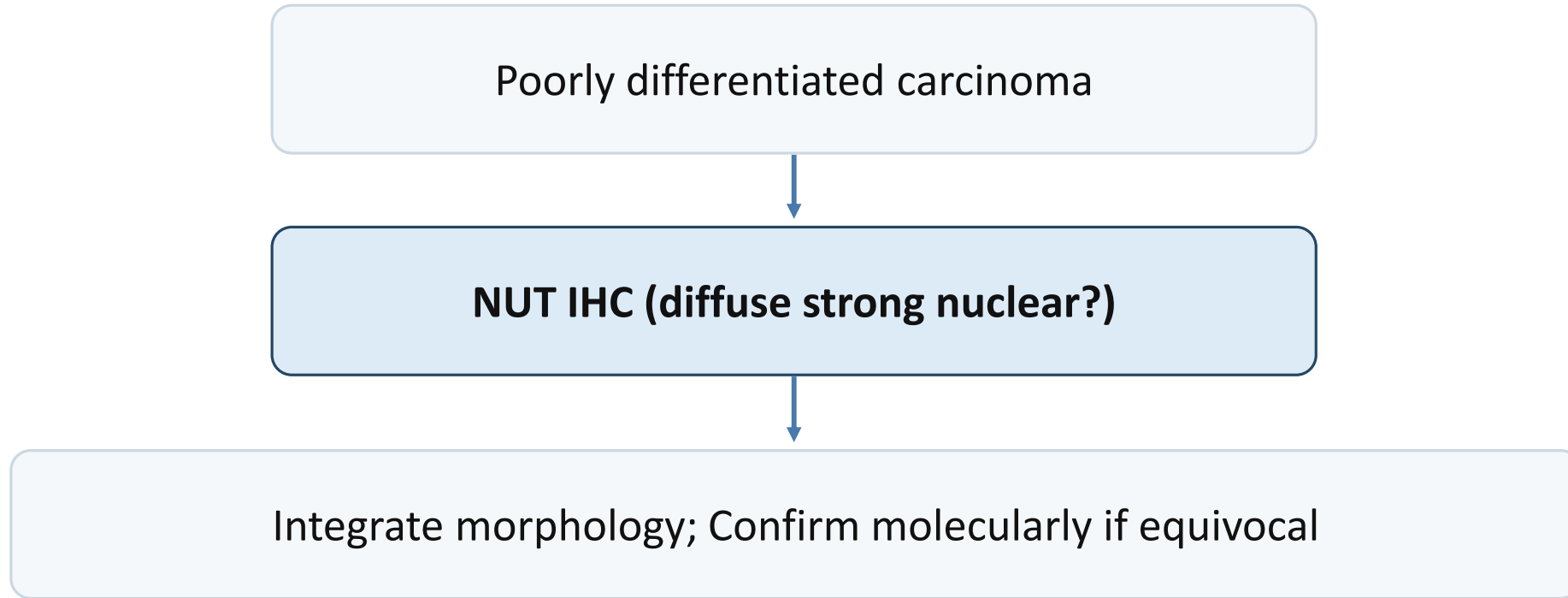
- Separate probes flank NUTM1; An abnormal split signal supports rearrangement.
- FISH does not routinely identify the fusion partner.
- Preanalytical failure or cryptic rearrangements can require alternative testing.

RNA-based methods can identify the partner



- Targeted RNA sequencing may detect the expressed fusion transcript.
- Partner-resolved results distinguish BRD4, BRD3, NSD3, and rare variants.
- Analytic success depends on RNA quality and assay design.

Use an integrated diagnostic algorithm



- Identify a poorly differentiated carcinoma and characterize lineage.
- Use NUT IHC when histology or clinical context is suspicious.
- Use NUTM1 FISH / RNA testing if staining is absent, equivocal, or discordant.

Basaloid SCC is a major morphologic mimic

Basaloid SCC	NUT carcinoma
Often site-related carcinoma	Can arise in multiple organs
Variable squamous differentiation	Variable squamous differentiation
No defining NUTM1 fusion	NUTM1 rearrangement defines entity

- Both tumors may show monotonous basaloid cells, necrosis, and squamous markers.
- Abrupt keratinization can also occur outside NUT carcinoma.
- A diffuse nuclear NUT stain or defining fusion resolves the distinction.

Small cell carcinoma enters the differential

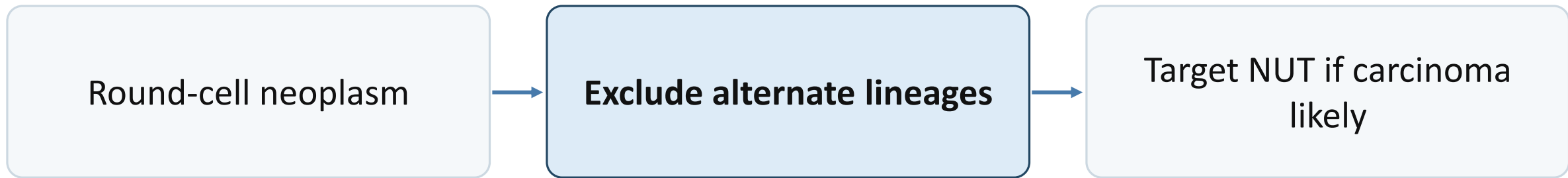
- Crush artifact, necrosis, and primitive round cells can overlap.
- High-grade neuroendocrine lineage requires an integrated marker profile.
- NUT expression should be assessed when morphology or markers are atypical.

Olfactory neuroblastoma is site-specific mimic

Olfactory neuroblastoma	NUT carcinoma
Neuroectodermal lesion	Epithelial carcinoma
Fibrillary matrix often present	Sheets / nests of primitive cells
Neuroendocrine markers support	NUTM1 fusion defines

- Sinonasal location and small blue cells create overlap.
- Olfactory neuroblastoma often has lobules, fibrillary neuropil, and neuroendocrine markers.
- NUT carcinoma requires NUT-specific molecular or immunophenotypic evidence.

Lymphoma and other round-cell neoplasms



- Lymphoma may produce diffuse sheets of blue cells without gland formation.
- Melanoma and selected sarcomas can also lose obvious lineage morphology.
- A limited first-pass lineage panel avoids a false epithelial assumption.

SWI/SNF-deficient sinonasal carcinoma

SWI/SNF-deficient carcinoma	NUT carcinoma
Loss of SWI/SNF protein	NUT nuclear labeling
SMARCB1 / SMARCA4 alteration	NUTM1 fusion
Overlapping primitive phenotype	Overlapping primitive phenotype

- SMARCB1- or SMARCA4-deficient tumors may also be very poorly differentiated.
- Loss of INI1 or BRG1 supports a distinct SWI/SNF-deficient category.
- Fusion-based classification should not be replaced by appearance alone.

EBV-associated nasopharyngeal carcinoma

EBV-related nasopharyngeal carcinoma	NUT carcinoma
EBER positivity supports	NUTM1 fusion supports
Common lymphoid background	Variable inflammatory background
Defined EBV association	No established EBV causation

- A nasopharyngeal primary may raise EBV-related carcinoma as an alternative.
- Nonkeratinizing nasopharyngeal carcinoma often has a lymphocyte-rich background.
- EBER in situ hybridization and NUT testing answer different etiologic questions.

Germ cell tumor staining is a special pitfall

- Normal NUT expression occurs in germ cells, and some germ-cell neoplasms can stain.
- Weak or focal staining is different from diffuse strong tumor nuclear reactivity.
- Morphology, germ-cell lineage markers, and NUTM1 testing settle conflicts.

Report the diagnosis with test provenance

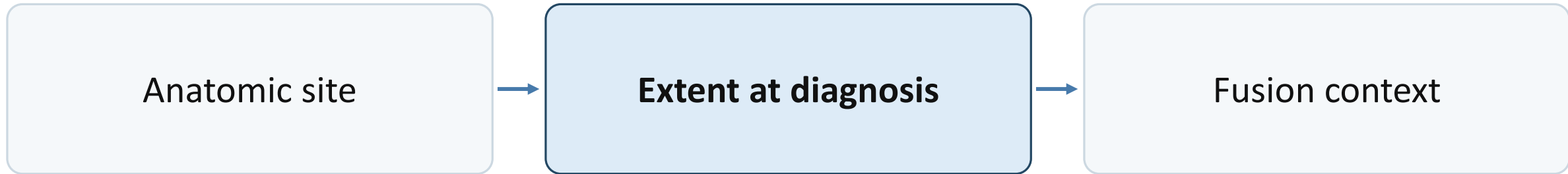
Report component	Example information
Morphology	Poorly differentiated carcinoma
Diagnostic evidence	Diffuse nuclear NUT positivity
Genetics (if tested)	BRD4::NUTM1 transcript detected

- State tumor type and anatomic site, including certainty about origin.
- Specify NUT antibody pattern and/or NUTM1 fusion method.
- Name the fusion partner only if directly demonstrated.

Stage assessment is clinical and site dependent

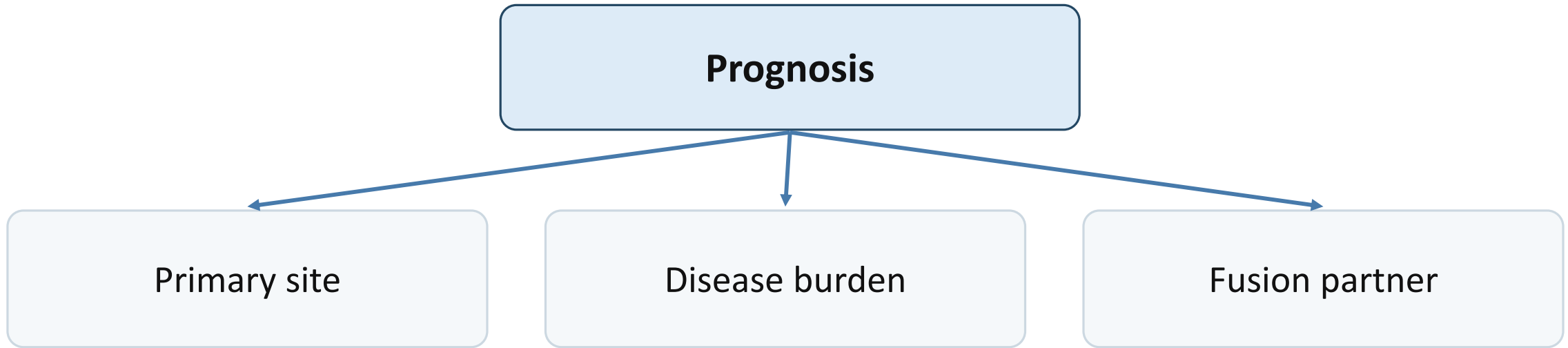
- There is no single universal anatomic staging rubric for all NUT carcinoma sites.
- Document primary site, local invasion, nodal disease, and distant metastases.
- Staging and treatment planning require the appropriate organ-specific multidisciplinary team.

Prognosis is poor but not uniform



- Extreme aggressiveness and survival usually shorter than one year.
- Selection, stage, site, fusion partner, and treatment patterns affect reported cohorts.
- Avoid promising individual outcomes from small retrospective series.

Site and fusion partner may stratify risk

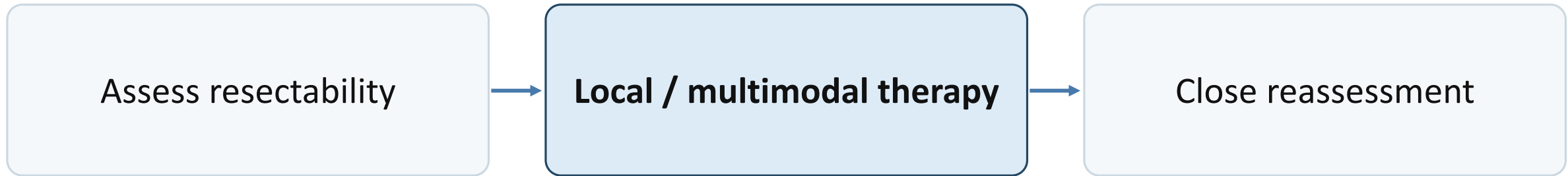


- Retrospective data suggest thoracic primaries often fare worse than nonthoracic disease.
- Among nonthoracic tumors, fusion partner may correlate with survival.
- These observations are prognostic associations, not validated treatment selection rules.

Conventional therapy is often insufficient

- Surgery, radiation, and systemic therapy are used in multimodal combinations.
- Transient initial responses may be followed by early progression.
- No regimen has established a reliable disease-wide cure rate.

Management of potentially resectable disease



- Discuss complete local resection when anatomically feasible.
- Radiation and systemic therapy are considered according to site and extent.
- Rarity favors consultation with a specialized multidisciplinary team.

Advanced disease requires a trial-minded approach



- Treatment is individualized; Rapid clinical deterioration is possible.
- Systemic therapy and local palliation may both be appropriate.
- Clinical trials and expert-center referral should be explored early.

BET inhibitors are mechanism-directed



- They compete with acetyl-lysine recognition at BET bromodomains.
- This can displace BRD4::NUTM1 from chromatin in experimental models.
- Clinical activity has been limited by durability, toxicity, and heterogeneous responses.

Additional epigenetic strategies remain investigational

Strategy	Current interpretation
HDAC modulation	Preclinical differentiation signal
BET-based combinations	Clinical investigation
Protein degradation approaches	Emerging research

- HDAC inhibitors have produced differentiation-related effects in preclinical models.
- Combinations and protein degraders are active areas of research.
- Experimental rationale does not equate to a licensed or effective routine treatment.

Evidence limitations affect clinical recommendations

- Most published cohorts are retrospective and relatively small.
- Therapies, sites, case ascertainment, and fusion types are heterogeneous.
- Rare-disease collaborative registries and prospective studies are important.

Applied case: A rapidly growing sinonasal mass

Clinical scenario (hypothetical)

- A young adult has a destructive sinonasal mass and a primitive carcinoma on biopsy.
- The cells form sheets with necrosis and a small focus of squamous maturation.
- Question: What next diagnostic test most directly addresses NUT carcinoma?

Discussion question: Establish the next test before revealing the answer.

Case resolution: Immunophenotype and fusion



- Perform NUT immunohistochemistry early rather than relying on p40 alone.
- Diffuse strong nuclear staining supports the molecular diagnosis.
- If the result is equivocal, evaluate a NUTM1 rearrangement or transcript.

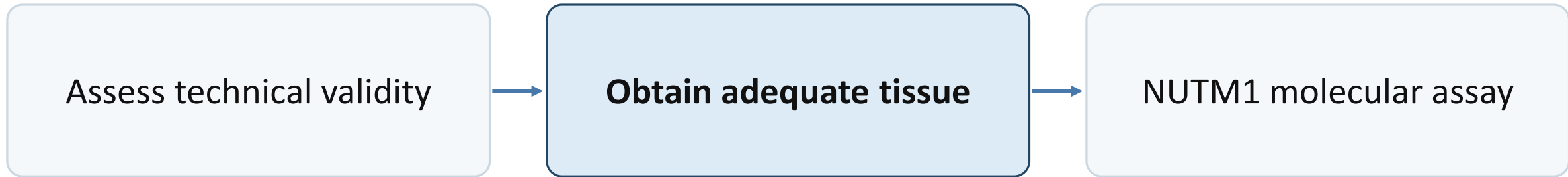
Applied case: Negative stain, persistent concern

Clinical scenario (hypothetical)

- An undifferentiated mediastinal carcinoma remains unexplained after an initial panel.
- A technically limited specimen shows negative NUT IHC.
- Question: Does this result definitively exclude NUT carcinoma?

Discussion question: Establish the next test before revealing the answer.

Case resolution: A negative IHC may be provisional



- Check preservation, controls, and viable tumor content.
- Re-biopsy or use an alternate block if needed for adequate testing.
- If suspicion persists, molecular testing helps settle discordance.

Diagnostic sign-out checklist

- Is the histologic impression a poorly differentiated carcinoma with an adequate differential?
- Was diffuse nuclear NUT expression or a NUTM1 rearrangement demonstrated?
- Are fusion partner, site, stage, and diagnostic limitations reported accurately?

Five high-yield conclusions

- NUT carcinoma is defined by a NUTM1 fusion rather than a unique H&E pattern.
- BRD4::NUTM1 disrupts chromatin regulation and blocks differentiation.
- Diffuse nuclear NUT IHC is an efficient initial diagnostic test.
- Negative or equivocal IHC with high suspicion warrants molecular testing.
- Disease is highly aggressive; Treatment evidence remains limited.

Selected references

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