

Tumor markers

Principles, major marker families, interpretation, and liquid biopsy

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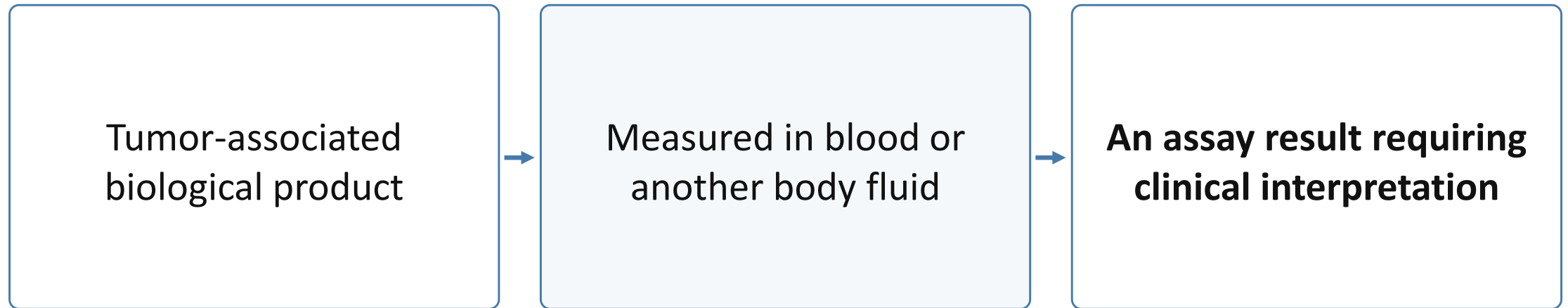
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Learning outcomes

- Explain why a positive circulating marker cannot by itself establish malignancy.
- Relate major tumor-marker classes to their associated neoplasms.
- Interpret marker persistence or recurrence after treatment without assuming specificity.
- Describe the rationale and limitations of cell-free DNA and RNA testing.

What a tumor marker measures



Association with cancer does not imply exclusive production by cancer.

The scope extends beyond serum proteins

Biochemical analytes

Hormones, enzymes,
antigens, immunoglobulins

Glycoproteins

Mucins and related
circulating markers

Molecular analytes

Tumor-associated cell-free
DNA and circulating RNA

The sampled molecule and specimen determine the assay—not its diagnostic certainty.

Tumor-associated is not tumor-specific

Association

- Marker may be elevated in malignancy
- Some tumor cells release measurable material

Limitation

- Non-neoplastic conditions may also elevate markers
- A marker alone does not prove the tissue contains cancer

Three distinct clinical questions

Detection

Does the result raise suspicion?

Treatment response

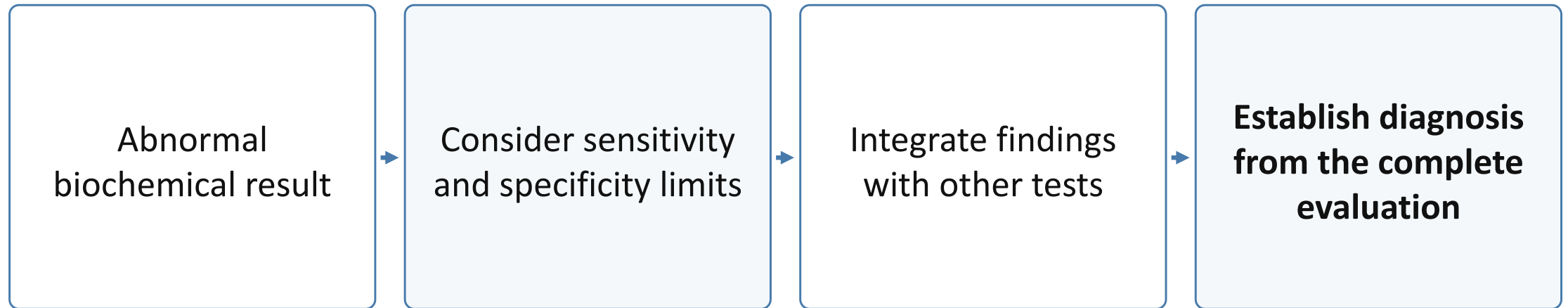
Does the level change after intervention?

Recurrence

Does a previously reduced marker reappear?

Follow-up more than stand-alone diagnosis.

Why a single assay does not diagnose cancer



A single positive result is a clinical clue, not a definitive diagnosis.

Sensitivity: Cancer may escape detection

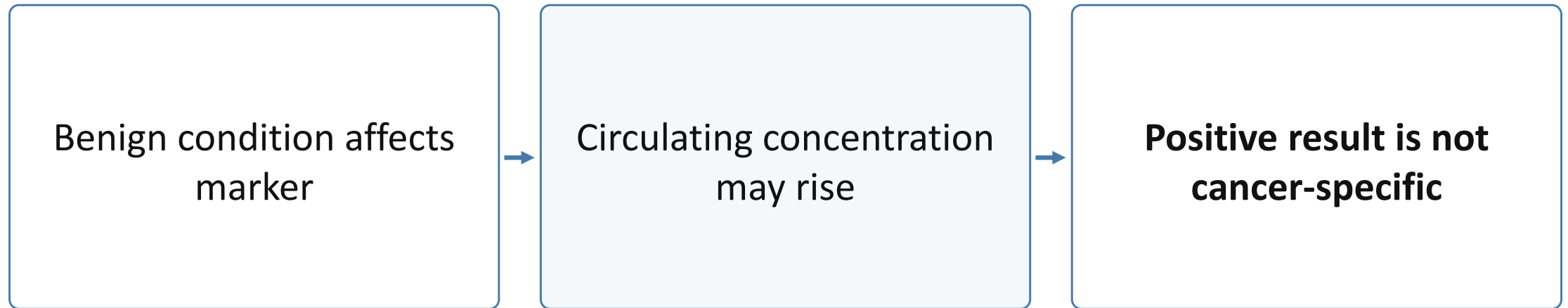
General principle

- Cancer can be present without a sufficient measurable signal
- A negative result cannot universally exclude malignancy

Textbook example

- PSA is the explicit textbook example
- No PSA concentration guarantees freedom from prostate cancer

Specificity: Benign disease can mimic cancer



PSA and benign prostatic hyperplasia illustrate this problem.

Why population screening is difficult

- Cancer-associated analytes may occur in people without cancer.
- Some cancers fail to produce a detectable marker signal.
- A test aimed at one analyte may lack the specificity needed for broad screening.
- Accurate, sensitive, specific early-detection tests as an active research goal.

Context determines the interpretation

Before diagnosis

An abnormal marker prompts correlation, not a final label

With known cancer

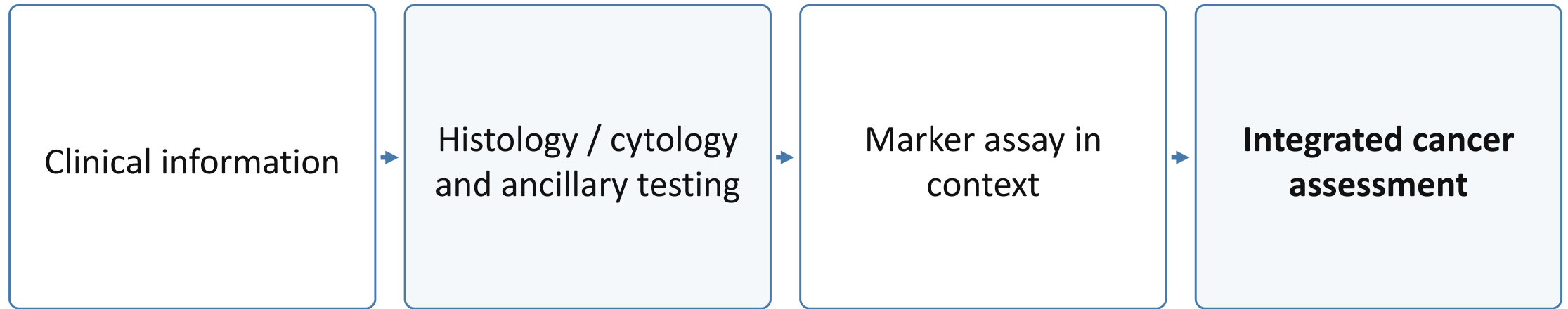
A relevant marker can supplement the tumor assessment

After treatment

A longitudinal result may inform response or recurrence evaluation

The same analyte can have different clinical utility at different time points.

Tumor markers complement tissue evaluation

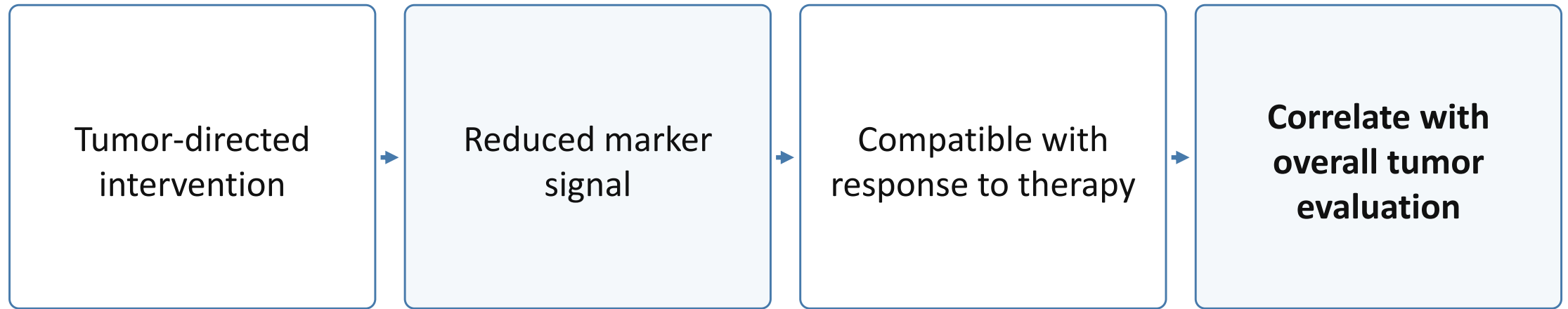


The adjacent Robbins laboratory-diagnosis section identifies morphology as the diagnostic foundation.

Serial monitoring is a principal use

- A marker secreted by an established tumor may provide a trackable biochemical signal.
- Successful therapy can be accompanied by loss of detectable circulating marker.
- Persistence or reappearance raises concern for residual or recurrent tumor.
- The interpretation must remain tied to the tumor type and other clinical evidence.

A falling marker is evidence, not a verdict



A conceptual sequence; No patient-level measurement or response magnitude is assumed.

Marker persistence after resection

CLINICAL APPLICATION

After resection of a marker-producing malignancy, the tumor-associated analyte remains measurable.

What is the main teaching implication?

Persistent marker may indicate tumor remaining; Confirm using the complete clinical assessment.

The marker cannot localize or independently characterize the residual lesion.

Reappearance after initial decline

CLINICAL APPLICATION

A circulating marker decreases after treatment and is later detected again in follow-up.

Why does this result matter?

Reappearance as a signal that can suggest tumor recurrence.

Do not equate a biochemical signal alone with confirmed anatomic recurrence.

Marker families

Hormones

HCG; Calcitonin;
Catecholamines

Oncofetal antigens

AFP; CEA

Proteins / glycoproteins

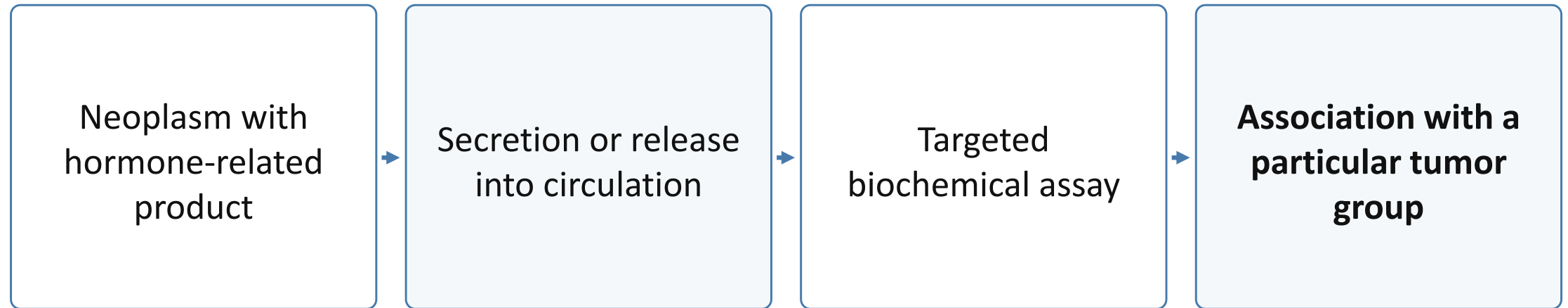
Immunoglobulins;
PSA/PSMA; CA-series
markers

Molecular markers

Cell-free mutant DNA;
Circulating RNA

The biomarker classes reflect different biological sources and assay targets.

Hormonal markers reflect tumor production



A hormonal marker is not automatically specific to a single diagnosis.

Human chorionic gonadotropin (hCG)

Hormone

HCG

Trophoblastic tumors

**Nonseminomatous testicular
tumors**

HCG among tumor-associated hormonal markers.

HCG links two different tumor settings

Trophoblastic

- Trophoblastic neoplasia
- Tumor group explicitly associated with hCG

Germ cell

- Nonseminomatous testicular tumors
- HCG included among relevant marker associations

Calcitonin: Thyroid lineage association

Hormone

Calcitonin

Medullary carcinoma of the thyroid

The marker association is specific to the named tumor type in Table 7.12.

Catecholamines and metabolites

Hormonal analytes

Catecholamines

Pheochromocytoma

Related tumors

The measurable target can include biochemical metabolites, not only a secreted hormone.

Ectopic hormone production differs in purpose

Assay association

- Tumor-associated hormonal product
- May serve as a circulating marker

Clinical consequence

- Ectopic hormonal action
- May produce a clinical paraneoplastic syndrome

Paraneoplastic endocrine examples

ACTH / ACTH-like

Cushing syndrome in
associated tumors

Antidiuretic hormone

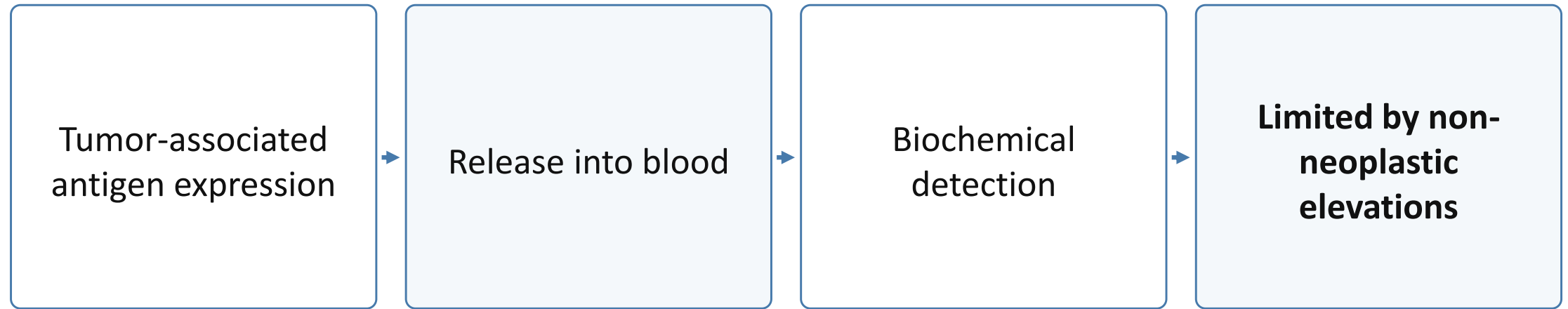
Syndrome of inappropriate
ADH secretion

PTH-related protein

One mechanism of
malignancy-associated
hypercalcemia

Examples Table 7.11; A hormone-mediated syndrome is not interchangeable with a tumor-specific test.

Oncofetal antigens as circulating markers



AFP and CEA are the central examples in this family.

Alpha-fetoprotein: Hepatocellular tumors

Oncofetal antigen

AFP

Hepatocellular carcinoma

Elevated AFP is an association; The textbook does not support using it as a stand-alone diagnosis.

AFP: Nonseminomatous germ cell tumors

Oncofetal antigen

AFP

Yolk sac tumors

Some teratocarcinomas

**Some embryonal
carcinomas**

The associations in the source do not imply expression in every germ cell tumor.

AFP joins distinct tumor lineages

Hepatic

- Liver cell cancer
- Hepatocellular carcinoma

Germ cell

- Germ cell neoplasia
- Yolk sac and selected nonseminomatous types

AFP is not a universal screening result

- AFP is produced by several tumor types in the Robbins discussion.
- Non-neoplastic conditions can also increase serum AFP.
- An elevated AFP therefore does not, by itself, establish cancer.
- Its useful role can include assessment of treatment response in an appropriate patient.

Carcinoembryonic antigen: Tumor spectrum

Digestive tract

Colon, pancreas, stomach

Other epithelial tumors

Lung and breast carcinomas

These are associated tumor sites, not proof of tissue of origin from a serum result.

CEA is not restricted to colorectal cancer

Common association

- Colorectal carcinoma is a major association
- CEA can contribute to serial monitoring

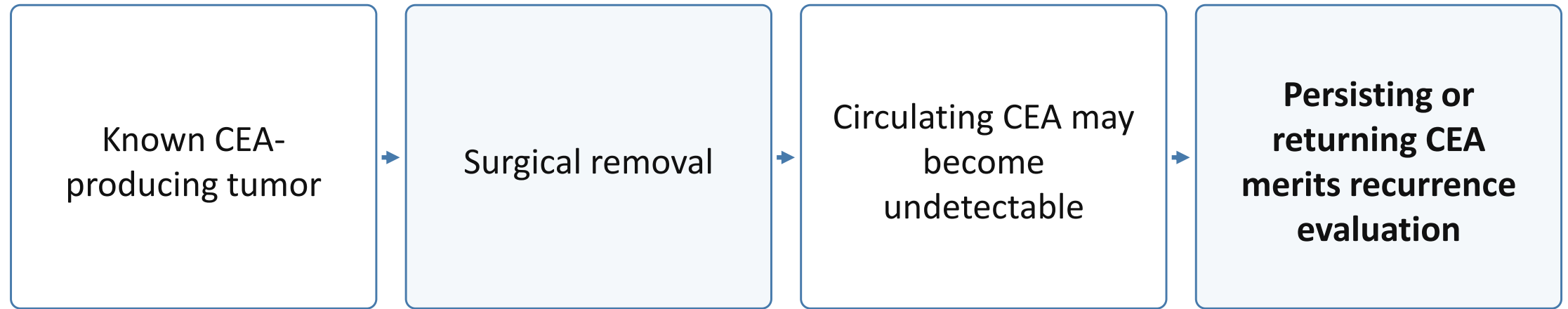
Why it matters

- Other carcinomas can also produce CEA
- A serum value alone does not localize the primary tumor

CEA elevations may be non-neoplastic

- Robbins explicitly cautions that CEA may increase in non-neoplastic conditions.
- This undermines the value of an isolated result as a screening test.
- Interpretation requires context, including whether a CEA-producing tumor is already known.

CEA after successful tumor resection



Clearance and reappearance as longitudinal surveillance concepts.

CEA and AFP: Shared interpretation rule

Property	CEA	AFP
Marker family	Oncofetal antigen	Oncofetal antigen
Tumor associations	Several carcinomas	Hepatocellular and selected germ cell tumors
Non-neoplastic elevation	Possible	Possible
Useful context	Response / recurrence monitoring	Response / recurrence monitoring

Immunoglobulins: Lineage-associated markers

Lineage-specific proteins

Immunoglobulins

Multiple myeloma

**Other secretory plasma
cell tumors**

**Other gammopathies
(Table 7.12)**

The measured protein reflects a secretory cellular lineage.

An immunoglobulin result requires context

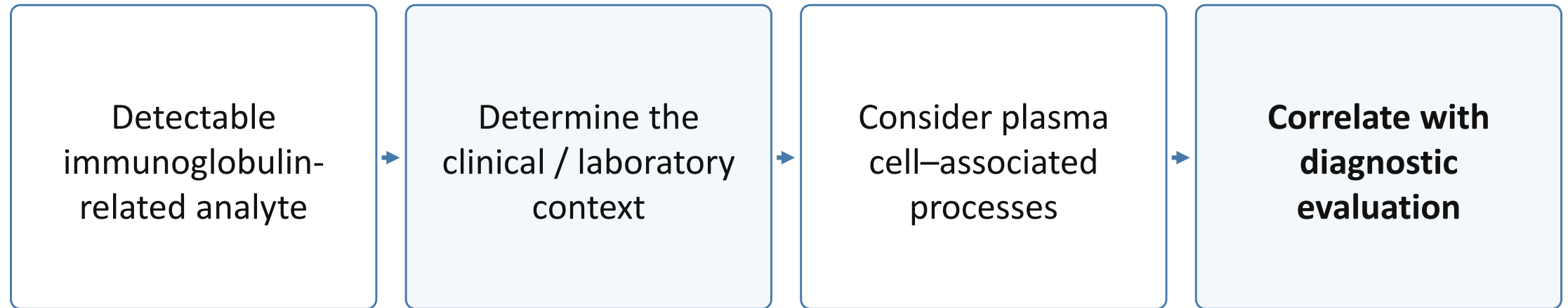


Table 7.12 lists immunoglobulins in myeloma and other gammopathies; It does not make a standalone diagnostic rule.

Prostate-specific antigen: A useful model

Lineage-specific protein

PSA

Prostatic adenocarcinoma

PSA is common in clinical practice but sharply illustrates specificity and sensitivity limitations.

Benign prostatic hyperplasia can raise PSA

Malignant cause

- Prostate carcinoma may elevate PSA
- Cancer remains a possible explanation

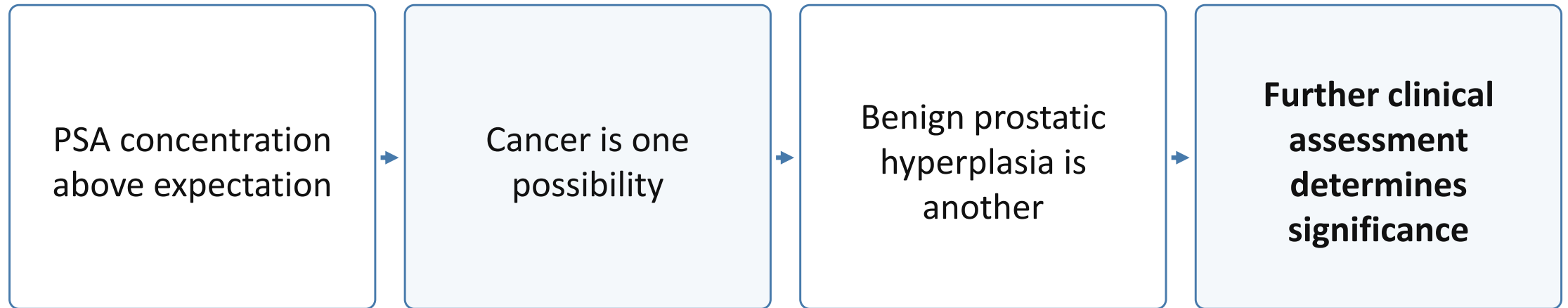
Benign cause

- Benign prostatic hyperplasia may elevate PSA
- An elevated value does not establish malignancy

No PSA value excludes all prostate cancer

- The textbook explicitly states that no serum PSA level ensures absence of cancer.
- An apparently reassuring result is therefore not an absolute exclusion test.
- The finding must be interpreted with the rest of the prostate evaluation.

How to interpret an elevated PSA



Do not invent an absolute PSA cutoff: None is specified in the topic excerpt.

PSA and PSMA are grouped in the table

Protein	Robbins association	Teaching distinction
PSA	Prostate cancer	Serum marker discussed in main text
PSMA	Prostate cancer	Listed as a lineage-specific marker in Table 7.12

Mucins and related glycoproteins

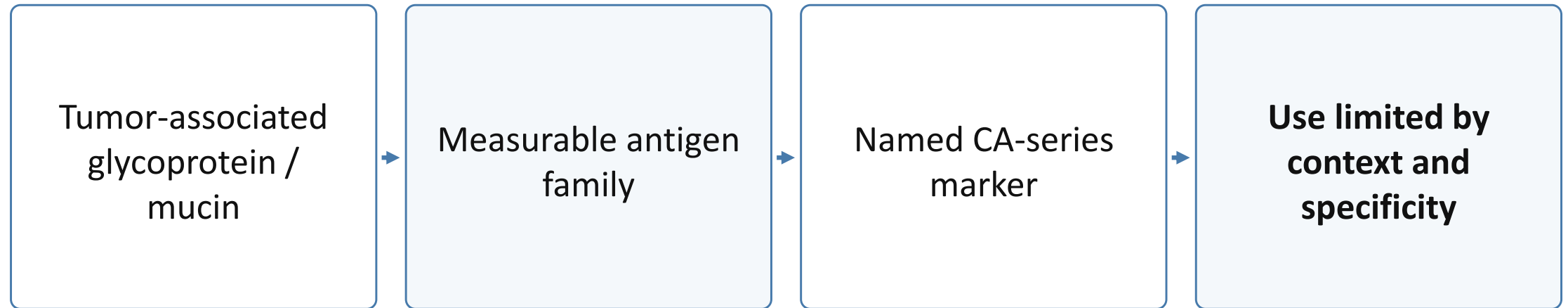


Table 7.12 lists CA-125, CA-19-9, and CA-15-3.

CA-125: Ovarian cancer association

Mucin / glycoprotein

CA-125

Ovarian cancer

A tumor-marker association is not, by itself, a screening or diagnostic guarantee.

CA-19-9: Gastrointestinal associations

Mucin / glycoprotein

CA-19-9

Pancreatic cancer

Colon cancer

The Robbins table associates this marker with more than one tumor site.

CA-15-3: Breast cancer association

Mucin / glycoprotein

CA-15-3

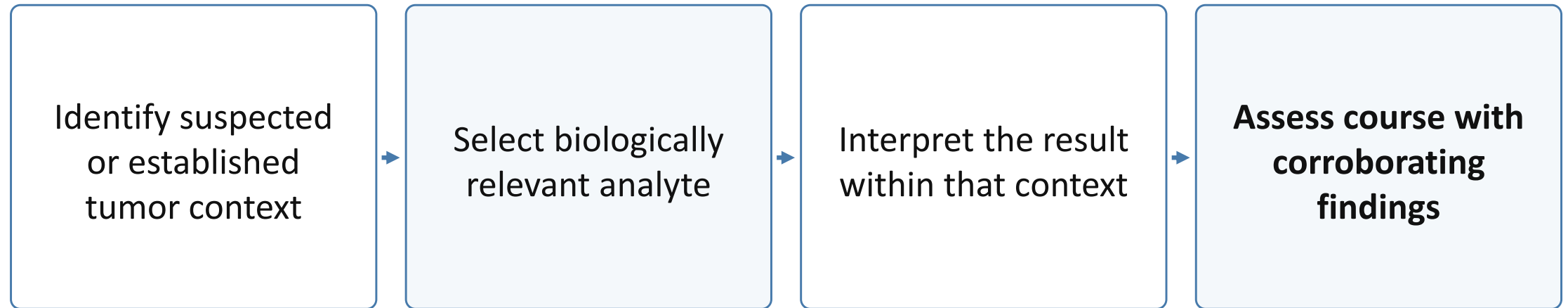
Breast cancer

The source identifies association, without providing a standalone diagnostic cutoff.

Compare the CA-series associations

Marker	Associated tumor(s) in Table 7.12	Interpretive limit
CA-125	Ovarian	Association $\neq$ diagnosis
CA-19-9	Pancreatic and colon	More than one tumor type
CA-15-3	Breast	Not a universal screening test

Marker selection follows the clinical problem



Conceptual workflow synthesized marker roles; Not a formal clinical guideline.

Markers do not supply tumor morphology

Circulating marker

- Biochemical result
- Suggests production of an associated analyte

Tissue / cytology

- Pathology assessment
- Characterizes cells, architecture and tumor type

A blood marker rarely resolves tumor origin

CLINICAL APPLICATION

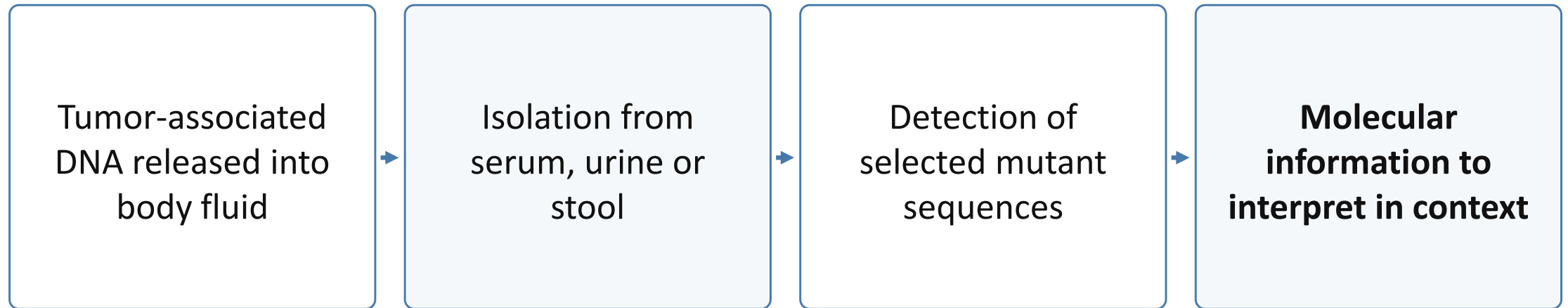
A patient has an increased CEA concentration, but the primary lesion has not been characterized.

Can the source of the tumor be assigned from CEA alone?

No. Several tumor types and non-neoplastic conditions are associated with CEA.

Use morphologic and clinical correlation rather than reverse-diagnosing from one marker.

Cell-free DNA expands the marker concept



The source discusses mutation detection across several body fluids.

Why mutation-based assays attract interest

- Cancer is associated with genetic driver alterations.
- Highly sensitive methods can detect selected mutant sequences in cell-free DNA.
- Blood and other accessible fluids offer opportunities for molecular assessment.
- Robbins still cautions against assuming population-screening performance from a single marker.

EGFR mutants in serum: Lung cancer

Cell-free DNA marker

EGFR mutation

Lung cancer

Serum specimen listed in Table 7.12

This is a tumor-associated sequence example; Performance estimates are not given in the source.

Colon cancer: Several DNA targets

TP53

Mutant sequences may be
assayed

APC

Mutant sequences may be
assayed

RAS

Mutant sequences may be
assayed

The table links these targets to stool and serum specimens in colon cancer.

Pancreatic cancer: Stool and serum DNA

Cell-free DNA marker

TP53 / RAS

Pancreatic cancer

Stool and serum samples

Marker candidates are not equivalent to a validated population screening program.

Lung cancer: Sputum and serum DNA

Cell-free DNA marker

TP53 / RAS

Lung cancer

Sputum and serum samples

Tumor-associated variants may be sought in different fluid matrices.

Bladder cancer: Urine-based DNA example

Cell-free DNA marker

TP53 mutation

Bladder cancer

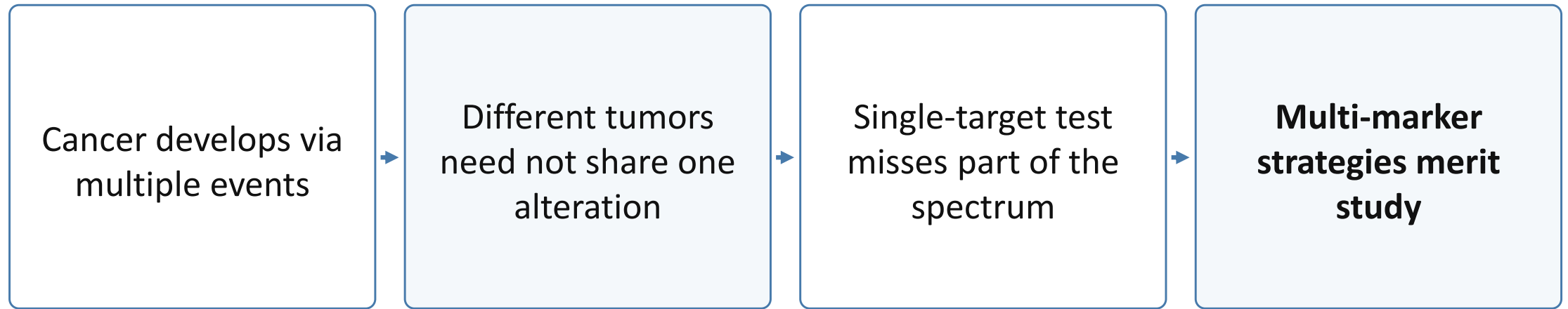
Urine specimen

Urine illustrates that a liquid biopsy need not use blood.

Body fluids used for mutant DNA assays

Specimen	Source-listed tumor examples	DNA targets mentioned
Serum	Lung, colon, pancreas	EGFR; TP53/APC/RAS
Stool	Colon, pancreas	TP53/APC/RAS
Sputum	Lung	TP53/RAS
Urine	Bladder	TP53

One molecular target may not be enough



Robbins explicitly argues single-marker population screening may lack adequate specificity.

Multi-analyte liquid biopsy rationale

Multiple DNA variants

Look for several driver mutations

Additional analytes

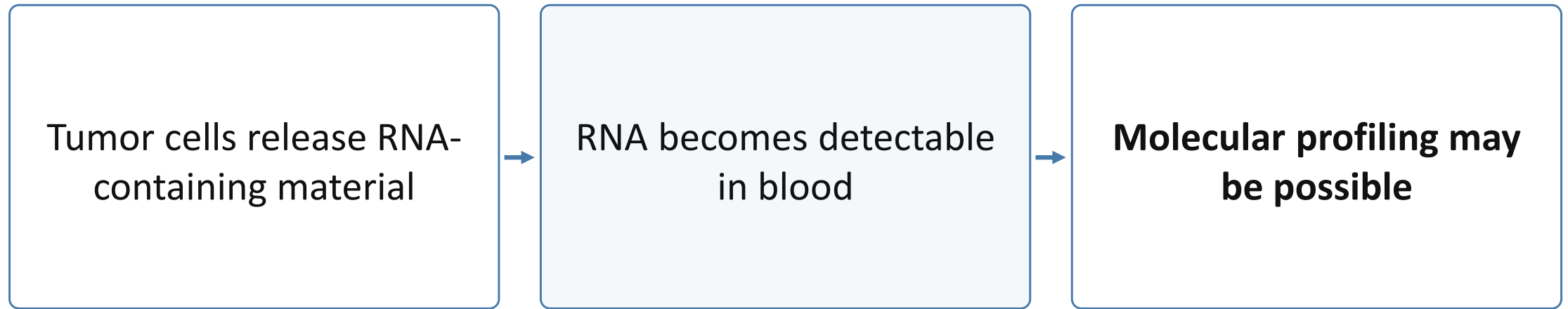
Potentially combine different cancer-associated markers

Interpretation

Screening utility still requires validation

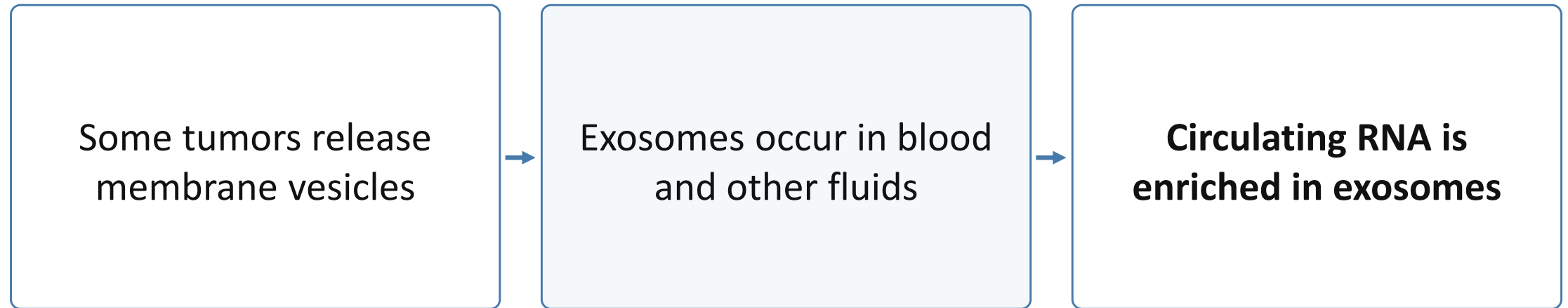
Conceptual research strategy; Not a claim of established clinical accuracy.

Circulating tumor-associated RNA



Evidence that circulating RNA can be profiled.

Exosomes as carriers of circulating RNA



An original native schematic of the relationship described on page 301.

Liquid biopsy: Promise versus evidence gap

Technical opportunity

- Accessible bodily fluid
- Molecular mutations and RNA can be assayed
- Multiple markers may broaden information

Clinical restraint

- Early detection remains a research challenge
- One analyte may not screen populations adequately
- Assay detectability $\neq$ demonstrated clinical benefit

Case: An abnormal PSA in isolation

CLINICAL APPLICATION

A person without a confirmed cancer diagnosis has an elevated serum PSA.

What can be concluded?

Prostate malignancy is possible; Benign prostatic hyperplasia is also a recognized cause.

Do not convert one result into a definitive cancer diagnosis.

Case: An unremarkable PSA result

CLINICAL APPLICATION

A clinical evaluation raises concern for prostate malignancy, but PSA is not elevated.

Does the marker rule out the tumor?

No. There is no PSA value that guarantees absence of prostate cancer.

The remainder of the assessment still matters.

Case: CEA returns after resection

CLINICAL APPLICATION

CEA fell after surgery for a known CEA-producing carcinoma; A later sample detects it again.

What hypothesis should be investigated?

Recurrence or persistent tumor becomes an important concern.

A serum marker is not sufficient to determine the location or extent of tumor.

Case: An AFP elevation

CLINICAL APPLICATION

A serum AFP result is elevated in a patient with an undiagnosed lesion.

Why is a single-test diagnosis inappropriate?

AFP is associated with more than one tumor type and may rise in non-neoplastic conditions.

Correlate the laboratory result with the broader evaluation.

Case: A mutant sequence in body fluid

CLINICAL APPLICATION

A molecular assay detects a tumor-associated variant in a fluid sample.

Is this proof that population screening is solved?

No. Detecting a mutation and demonstrating sufficient screening specificity are separate claims.

Broad early-detection deployment as an active research challenge.

A practical interpretive checklist

Biological source

Which tumor(s) or benign conditions can produce it?

Intended role

Detection, response assessment, or recurrence monitoring?

Time context

Single sample or a serial post-treatment observation?

Corroboration

What independent clinical / pathologic evidence exists?

A disciplined checklist reduces overinterpretation of tumor-associated analytes.

Core teaching conclusions

- No circulating tumor marker discussed here independently establishes cancer.
- Some conventional markers are valuable when followed after treatment in known tumors.
- Associations are marker- and tumor-dependent, and benign elevations matter.
- Cell-free DNA, circulating RNA and multi-marker assays are promising, but screening validity remains a separate requirement.

Principal reference

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026). Chapter 7, “Clinical Aspects of Neoplasia,” section “Tumor Markers,” pp. 300–301; Table 7.12.

Related context: “Laboratory Diagnosis of Cancer” (pp. 296–300) and Table 7.11 (paraneoplastic endocrine syndromes).