Examples Of Immunohistochemistry Markers For Specific Vaginal Cancers

Intestinal-type adenocarcinoma

- **CK20** - **low molecular type I acidic keratin** and **intermediate filament protein** that maintains **keratin organisation in the epithelia**.
- It is encoded by ***KRT20* gene**. *KRT20* regulated by *CDX1* (a type of homeobox gene). It is commonly used in combination of CK7 to detect **site of origin for metastatic tumours.** It is commonly expressed in the **gastrointestinal epithelium, urothelium and Merkel cells (skin).** If there is loss of CK20 its associated with **microsatellite instability (DNA mismatch repair).**
- It is connected to **CK8 type II keratin** to form **heterpolymeric intermediate filaments** in **epithelial cell.**

- ***CDX2*** **-** It is a caudal type homeobox 2 protein transcription factor. It is expressed in the intestine **via the epithelial cell nuclei from duodenum to the rectum** and regulates **proliferation (growth)** and **differentiation (turn to specialised cells).** Sensitivity decreases in **poorly differentiated and high stage tumours**. It is linked to **gastrointestinal, bladder, and neuroendocrine tumours**. It is also commonly associated with the ***CDK7, CK20 and SATB2*** and villin to determine the site of origin. **Loss of CDX2 expression** linked to **methylation and repression of gene** rather than **somatic mutations of CDX2 gene.**

Mesonephric carcinomas

GATA3 (GATA binding protein 3): It encodes a **zing finger transcription factor**. This is needed for the **development of the embryo and for the differentiation of tissues especially mammary epithelium, urothelium (bladder), T lymphocytes (white blood cells) and the nervous system**. It helps to **regulate gene transcription** by **binding to DNA** and **facilitate chromatin remodelling.** It is useful in the detection of **urothelial carcinoma, salivary glands, thyroid, breast cancers and mesonephric lesions**. It helps to identfy the **site of origin in metastatic carcinoma** e.g. **mesonephric lesions in lower female genital tact.**

CD10 (cluster of differentiation 10) : It is a **cell membrane zinc dependent metalloendopeptidase (enzyme).** Its role is to **inactivate bioactive peptides e.g. atrial natrieuretic factor, endothelin, gastrin, and interacts with moesin proteins**. Loss of CD10 caused by **methylation** leads **to increased cell migration, growth and survival and contributes to neoplasm and progression**. CD10 is expressed in **early progenitor cells of the blood (haematopoietic cells) and haematopoietic neoplasms**. It is also distributed in the **normal and abnormal kidney tissue.** It helps to diagnose a type of blood cancer called **B lymphoblastic leulaemia and several types of lymphoma (cancer of the lymph nodes)**. It can detect **other types of cancers but staining is non-specific**. It helps to detect cancers of the **large intestine (colon) by apical cytoplasmic and surface staining**. It also helps to detect **melanoma, kidney, liver, urothelial and skin (squamous cell, basal cell) and hair (trichoblastoma) and vascular tumours.** CD10 is used with **prostate specific antigen (PSA) and prostate specific alkaline phosphatase (PSAP)** to confirm diagnosis in **uterus (womb) and vagina (CD10+ in cytoplasm of basal cell layer).** CD10 is also used with **smooth muscle actin (SMA), muscle specific actin (MSA) and desmin to differentiate endometrial stromal tumors (CD10+) from uterine smooth muscle tumors (CD10-, with rare exceptions**). It also helps to detect many other types of **gynaecological tumours like trophoblasts, choriocarcinoma and non-cancerous embryonal status (mesonephric remnant and mullerian system).**

TTF1 (thyroid transcription factor 1) **-** it is a types of **homeodomain containing transcription factor** that is expressed in the **thyroid, lung and brain (diencephalon) like neurohypophysis (pituitary), chordoid glioma and giant cell astrocytoma (glial cells**). It is not the same as transcription terminator factor 1 that stops the production of the **ribosomes (organelles that make protein).** It exclusively stains the **nucleus.**

Clear cell carcinoma

- **Napsin A**: This a type of **aspartic protease (enzyme) of the pepsin (protein-based enzyme found in the stomach and helps to break down proteins) family.** It is encoded by the ***NAPSA gene***. Its main role is involved in the **maturation of protein B** and helps to **combat infections by helping the macrophages (type of white blood cell) to engulf patthogenes (phagocytosis) and lysosomal protein catabolism (breaking down the lysosome) in the kidney cells** . It is mainly expressed in the cytoplasm of **type II pneumocytes, macrophages, renal tubules (proximal and convulated) and pancreas** (acinar cells where enzymes are made and the relevant ducts to induce their release in the duodenum (first part of the small intestine). It also helps to **detect small changes in the womb lining (endometrium) and is linked to chorion.**

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Skene gland adenocarcinoma	• **Prostate specific antigen (PSA)**- A tumour marker for **prostate cancer** or related conditions like **prostatic hypertrophy (enlargement of the prostate gland).** This is detected via **blood test**. It helps facilitate when doing a **genetic test where faulty version of *BRCA2* gene raises risk.** • **Prostatic acid phosphatase:** This is a type of **enzyme (non-specific tyrosine phosphatase)** that removes substrates under acidic conditions (pH 4 to 6). This enzyme prevents prostate cancer by **dephosphorylation (**removing a phosphate group) of ERBB2) and **deactivating cellular pathway MAPK.** It can create adenosine from AMP **to surpress pain.** it can also function as **ecto-5'nucleotidase in dorsal root ganglion neurones.** • **NKX3.1**. This is a type of transcription factor that is expressed in the **prostate, lining of the prostaate and the ducts**. Its expression is regulated in **androgen specific.** It can help detect **basal cell carcinoma of the cervix, ovarian teratoma and vaginal tubulosquamous polyps**. It can also help **detect prostate cancer**. **Low levels is linked to prostatic intraepithelial neoplasmia** due to **gene loss, methylation or posttranscriptiona; silencing.** The prostate lesions can mimic **urothelial carcinoma (bladder cancer).** It can be detected as **nuclear stain**. It is important to inform that staining can be **positive for normal status, prostate, testis, salivary glands, kidneys (ureter)** but also positive for disease such as **prostatic adenocarcinoma., adenoid basal cell carcinoma, ovarian Sertoli-Leydig cell tumor, breast cancerous and trachea (windpipe0).** Negative staining for the **basal cell carcinoma, testicular cancers and bone cysts.**
Rhabdomyosarcoma (RMS)	• Embryonal RMS • **Desmin:** This is a **major muscle-specific intermediate filament protein.** It is highly expressed in the **cardiac tissue (heart tissue)** and helps with the development of the heart. Desmin represents 2% of cellular protein in **myocytes (muscle cells).Smooth muscle cells** which are commonly found in the **gastrointestinal tract, blood vessels and other areas, contains desmin with the cytoplasmic dense bodies and subplasmalemmal dense plaques.** Skeletal/striated muscles have **desmin filaments associated with sarcomeric Z disks** • **Myogenin and myoD1 (skeletal muscle markers)** • **Myogenin** is a transcription factor that is expressed in **myotubes. Ir helps in the differentiation stages of making muscle cells (myogenesis), muscle re-generation and activation of genes involved in myogenesis.** The procedure involved the **mononuclear muscle precursor cells leave the cell cycle, differentiate, connect with existing myofibers** or together to make **new myofibers.** • **MyoD1** is a gene that encodes for the **transcription factor** that is important for the production of **muscles (myogenesis).** • **The MYOD1 transcription factor** activates its **own transcription, muscle-related genes and helps to leave the cell cycle. It is also involved in the differentiation of the skeletal muscle.**
Melanoma	• **S100 positive:** It is from its **solubility in 100% saturated ammonium sulfate at neutral pH.** Family of multigenic group of **nonubiquitous cytoplasmic homologous intracellular Ca2+ (calcium ion) binding proteins with EF hand motifs.** It looks similar at **protein and genomic levels.** It helps with detecting **tumours of unknown origin** and to show **nerve sheath involvement. It is presented as positive cytoplasmic and nuclear staining**. **It helps to elucidate perineural involvement. How?** • **It can detect the difference between benign nerve sheath tumours that presented with S100 strong and diffuse, but on the other hand, malignant peropheral nerve sheath tumours that present with weak or negative S100.** • S100 can serve as a **myoepithelial cell marker** and **identification of tumours with myoepithelial cells. It can help to evaluate sentinel lymph nodes (first lymph node affected) in melanoma.** • **S100 can help detect cancer of the Schwann cells (schwannnoma). It is coveredwith myelin sheath (fatty layer) to help insulate the nerve on axon. All cells are stained** • **It also helps detect other glial cancers.** • **It can detect neurofibroma - it is stained with positive and negative cells and can be compared with schwannoma.** • **It can help detect Langerhans cell histiocytosis from other syndromes.** • **HMB45 Human melanoma black (HMB) antibody that targets a premelanosome protein called gp100. This HMB45 is found in early progenitor and activated melanocytes and evaluates the primary melanocytic lesions** along a screening panel with other melanocytic markers. • **HMB45 aberrant expression in** some tumours without **melanocytic differentiation (angiomyolipoma, perivascular epithelioid cell tumour [PEComa], lymphangioleiomyomatosis, *TFE* and *TFEB* rearranged renal cell carcinoma)**

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Melanoma continued

- **Melan A: It is a melanocyte specific cytoplasmic protein essential for the melanocyte development more specifically the stage II melanosomes from expression to stability and processing.**
- **Normal status: It is expressed in the skin, eye (retina), adrenal, testis and ovary.**
- Disease status:They can help evaluate **sentinel lymph nodes for melanoma with S100** and serve as a marker for **melanin-producing cells (melanocytes) and schwann cells.** It can also **evaluate nerve sheath tumors and metastatic melanoma.**
- **Most primary melanoma are Melan A positive (cytoplasmic staining)**
- **Desmoplastic melanoma** is the exception that is melan A **negative.**
- **Other cancers helps to detect are non-melanocytic:**

Angiomyolipoma, PEComa, lymphangioleiomyomatosis, sex cord tumours, and adrenal tumours (adrenal cortical adenoma [cortex]), schwannoma, clear cell sarcoma of the soft tissue.

It can help detect **neurotized melanocytic nevi (MelanA+) from neurofibroma (MelanA-).**

it is more sensitive marker than HMB45 to detect metastatic melanoma in sentinel lymph nodes.

- SOX10. It is a **SRY-related HMG box 10 protein** and serves as a **transcription factor for neural creast and maintained by Schwann cells and melanin-producing cells (melanocytes).** Therefore, it can be expressed in **benign nevi and benign tumours of the Schwann cell lines.**
- It is also detected by **the lining of the breast. It can be combined with GATA3 to detect breast cancers and more aggressive cases.**
- Other areas are luminal cells of **the sweat and salivary glands, smooth muscle and bone forming cells (osteoblasts).**
- It is **a positive marker for most melanomas and is more sensitive than S100 to identify metastatic melanoma.**
- A **positive nuclear stain**
- It can help in complex cases of **GATA3 negative metastases.**

Yolk Sac Tumour (Vaginal)

- High levels of serum AFP
- This should be measured at diagnosis and during treatment.

AFP is a protein formed in the **liver and yolk sac of the fetus.** It is present in the **fetal serum and secondarily in maternal blood.** It is vital during reproductive system as it is used as **prenatal screening between 15th and 20th week of pregnancy. Ultrasongraphy** is performed if there is **unexpected levels of high or low.** Levels of AFP is linked by **length of gestation and mothers weight.** AFP is linked to **liver tumours and teratomas.**

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Granular cell tumours	• **AFP** • **S100 positive** • **PLAP (Placental-like alkaline phosphatase)** is an immunohistochemical marker of **germ cell tumour**, **testicular cancer (seminoma), ovarian (embryonal, dysgerminoma). Soft tissue tumours (rhaabdomyosarcoma, leiomyoma and desmoplastic small round cell tumour).** It can also detect **germ cell neoplasia in situ (GCNIS) but not specific**. Under laboratory conditions using cells (in vitro) the role of PLAP is to catalyse the **breakdown of the monoesters of phosphoric acid.** It also is **a transphosphorylation reaction in large concentration of phosphate acceptors.** However, in animal **studies (in vivo) it is expressed in the synctiotrophoblast of the placenta** functioning **as phosphomonoesterase that help with nutrient transport. It is also expressed in the lining of the womb (endometrium).** A **positive stain of PLAP would support the membrane and cytoplasm**. It holds frequent **low intensity and focal expression in embryonal carcinoma and yolk sac tumour**s in most cases. • **Glypican-2: Cell surface proteoglycan** that has **heparan sulfate**. It helps **develop neurons (nerves). The proteoglycan is a combination of proteins anf glycosaminoglycan (sugar) and are commonly found in the extracellular matrix between the cells** • They interact with **growth factors where signalling molecules help to build growth factors, protect them** and ensure they are **presented to the correct receptors.** For example, **fibroblast growth factor (FGF) is bound to its receptor with the support of heparan sulfate. FGF helps with wound healing, blood vessels formation and development.** • **Glypican** helps with **cell adhesion, migration, differentiation during development and repair.** They help with **cell to cell communication and response. In cancer state**, it can help **promote or restrain cell division by altering the cancer signalling pathways.** • **Neuron specific enolase**. This is a type of enzyme that is found in **the central and periopheral neurons and neuroendocine cells.** It is released into the **cerebrospinal fluid when nerves are injured.** However it is not specific for **neuroendocrine differentiation** as it can be found in any neoplasm. To detect neuro specific anolase it requires a combined approach with **chromogranin and synaptophysin.** • **Peripheral nerve myelin proteins: Myelin** is a complex membrane structure that is formed **by glial cells** that help axon **transmit the nerve message or impulse** and help with **electrical conduction**. Myelin can be detect by **immmunofluorescence** based on **antibodies against major myelin proteins.** • **Vimentin: It** helps to detect **mesenchymal origin of tumours**. Most **carcinomas and epithelial tumours** are **negative. Vimentin** is an **intermediate filament protein**. It can help **endothelial cells, fibroblasts, muscle cells, blood and immune cells endometrial cells (womb) and the testes (leydig cells and sertoli cells).** • The cytoplasm is mainly stained and the **absence of vimentin staining may confirm that fat-like or other spaces actually lack a cellular lining. Vimentin also helps to distinguishes endocervical adenocarcinoma (vimentin negative) and endometrial carcinoma (vimentin positive), as part of panel.**

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Immunohistochemistry Microscopic slides can be seen in following links below:

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