The British Association of Gynaecological Pathologists

19th Annual Meeting

- Pathology of the Vulva: Case Presentation
- Dr Katie Gardner, ST5 Histopathology Trainee
- (Supervisor: Dr Sarah Bell, Consultant Histopathologist)
- Forth Valley Royal Hospital, Larbert & Queen Elizabeth University Hospital, Glasgow
- Friday 9th June 2023

The British Association of Gynaecological Pathologists

Speaker disclosures

- ❑ I have no financial conflicts of interest to disclose
- ❑ I am not an expert

Case Presentation

"HPV-independent, p53-wild-type verruciform acanthotic Vulvar Intraepithelial Neoplasia"

Case Presentation

"**HPV-i**ndependent, **p53**-**w**ild-**t**ype **v**erruciform **a**canthotic **V**ulvar **I**ntraepithelial **N**eoplasia"

Case Presentation

HPVi(p53wt) vaVIN

Lecture Objectives

1) What is vaVIN?
2) Brief overview of terminology
3) Differential diagnoses to consider
4) Conclusion
5) Get everyone to lunch in time

What is vaVIN?

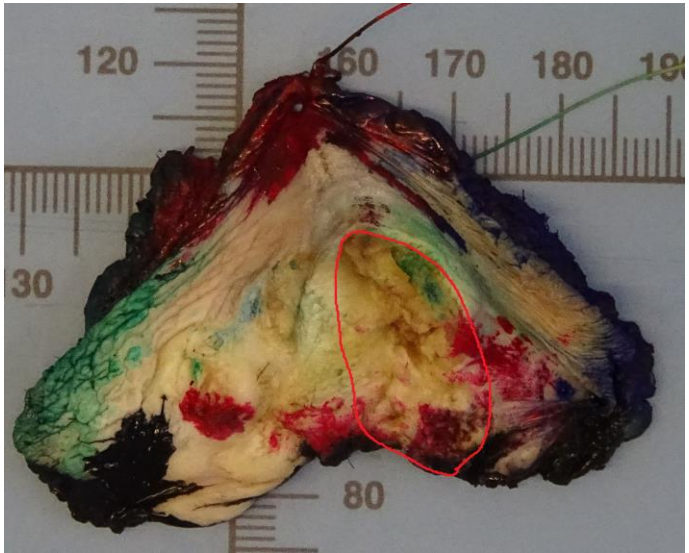
Patient Case

- 64 year old female presented with discrete vulvar lesion
  - Clinical concern for malignancy
  - No other significant PMHx

- Lesion previously biopsied
  - Markedly hyperkeratotic squamoproliferative lesion
  - Areas of hy**per**granulosis
  - DDX: Lichen simplex chronicus and HPVi(p53wt) vaVIN

Clinical Presentation

- Presents in patients aged 50+
  - (post-menopausal)
- Discrete lesion
- Most commonly solitary
- Raised white or erythematous mass
  - Exophytic
  - Flat plaque
- May be itchy or painful



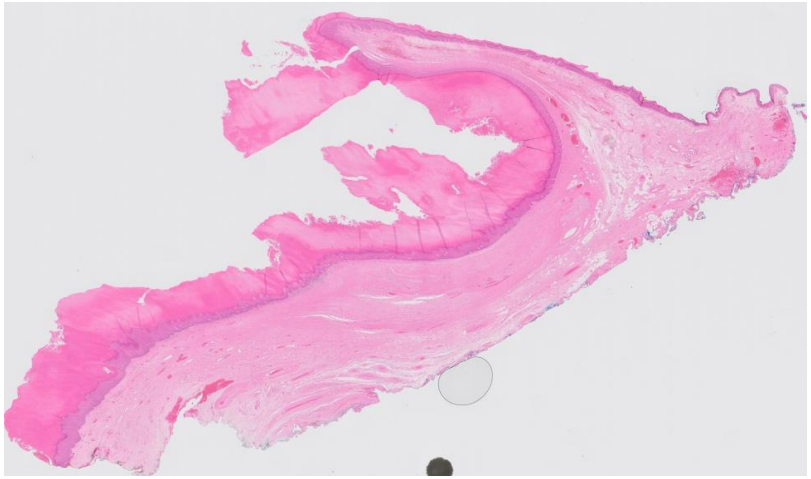
Histological Features

- Five criteria[1]:

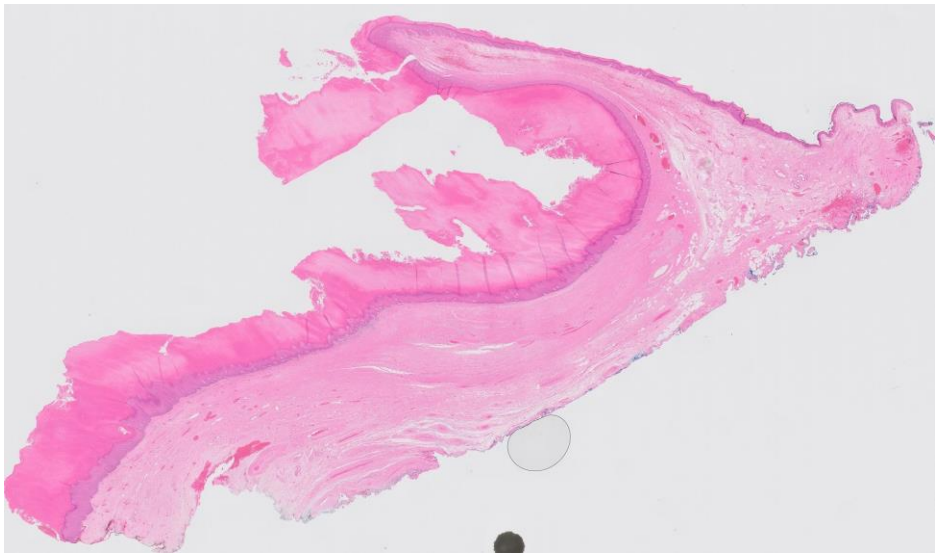
1) Verruciform and/or Acanthotic architecture
2) Altered squamous differentiation
3) Absence of cytological atypia
4) Negative (or patchy) P16 staining
5) Wild-type p53 expression

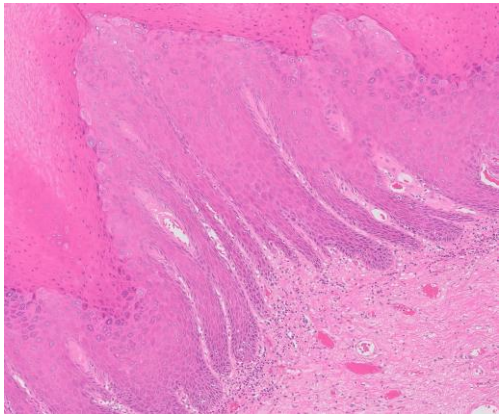
1) Verruciform and/or Acanthotic architecture

- **Verruciform** – elongation and irregularity of rete
- **Acanthotic** – thickened epidermis
- **Exophytic** – variably sized epithelial projections which may be squared, bulbous or pointed
- **Flat Plaque**



1) Verruciform and/or Acanthotic architecture

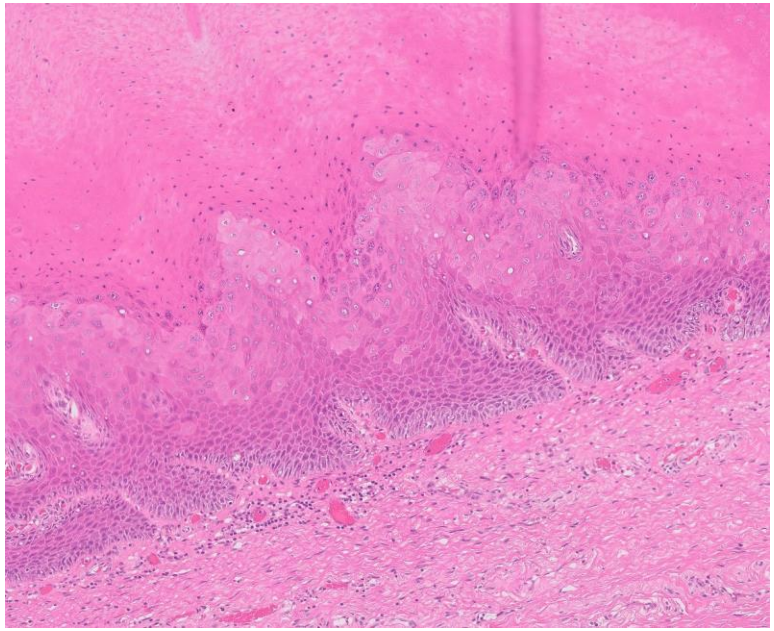






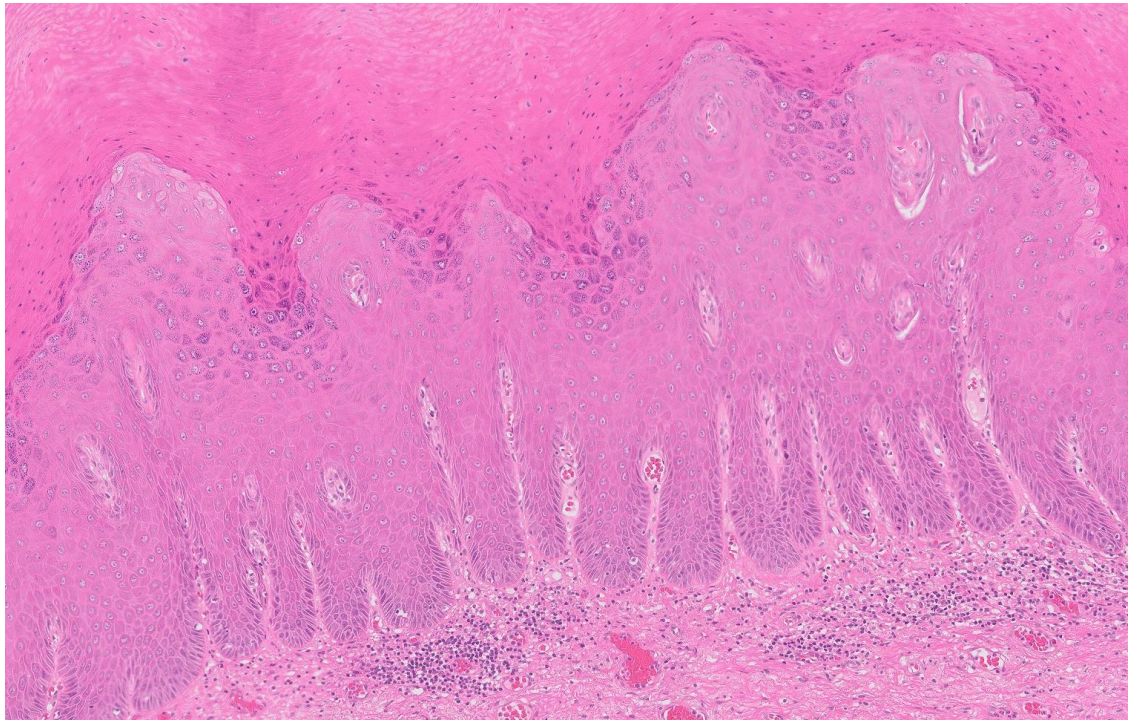
2) Altered squamous differentiation

- "Squamous maturation is retained but altered"
  - Hyperkeratosis and parakeratosis
  - Partial or complete hyp**o**granulosis (typically patchy)
  - Hyp**er**granulosis (less common)
  - Pallor of upper/mid epithelial layers



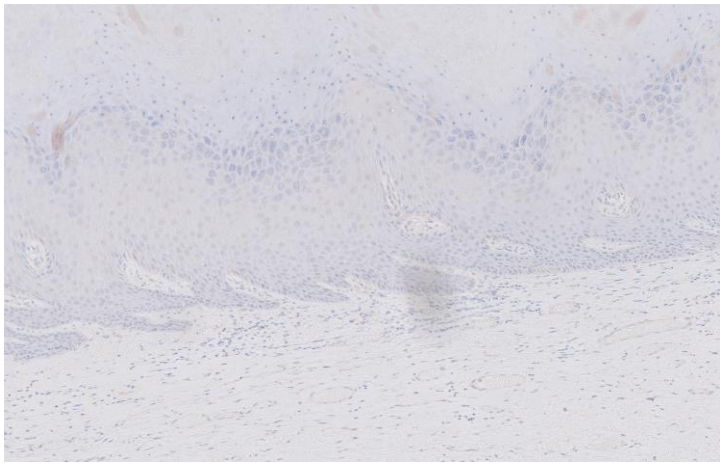
3) Absence of cytological atypia

- Usually low mitotic activity
  - Confined to basal and parabasal layer

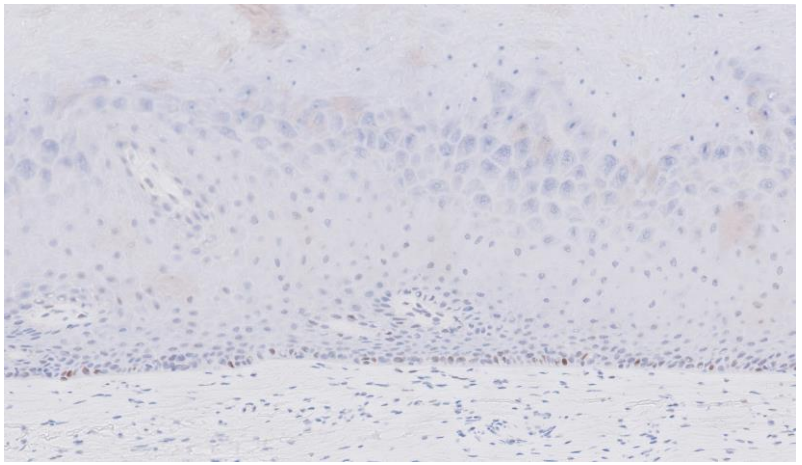


4) Negative for P16 and 5) Wild-type P53

P16

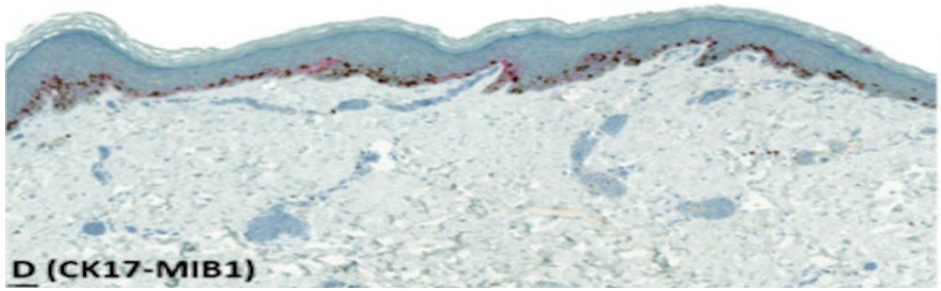


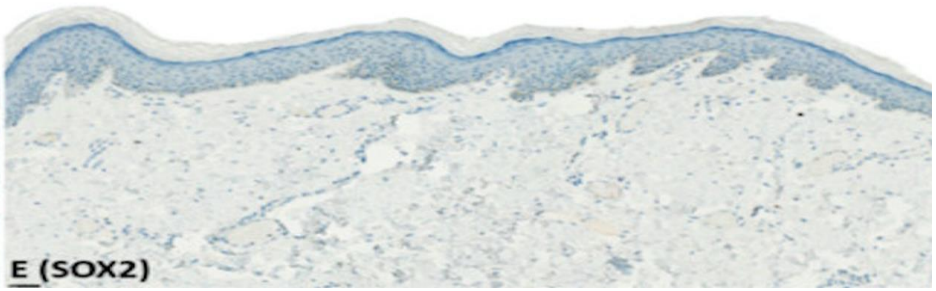
P53



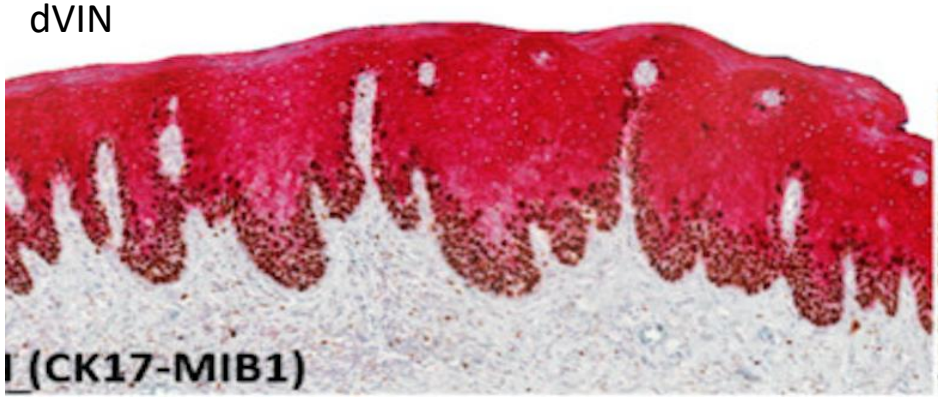
Potential Immunohistochemistry adjuncts[2]

Lichen sclerosus



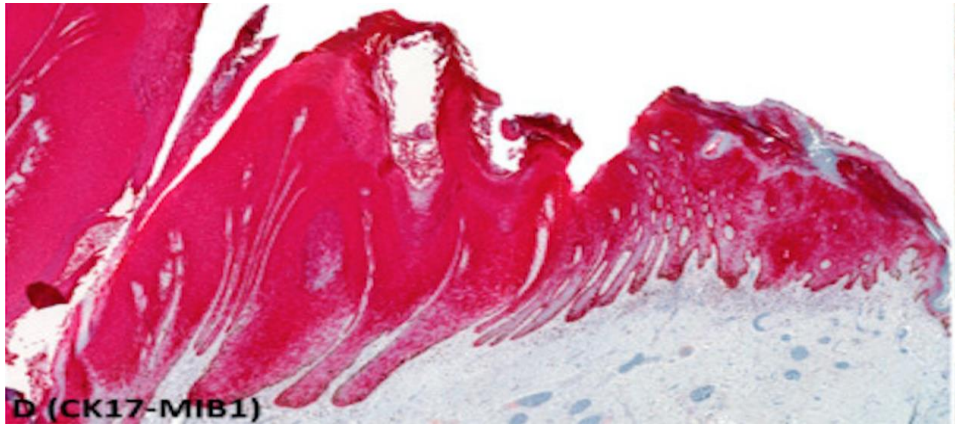


dVIN





DEVIL





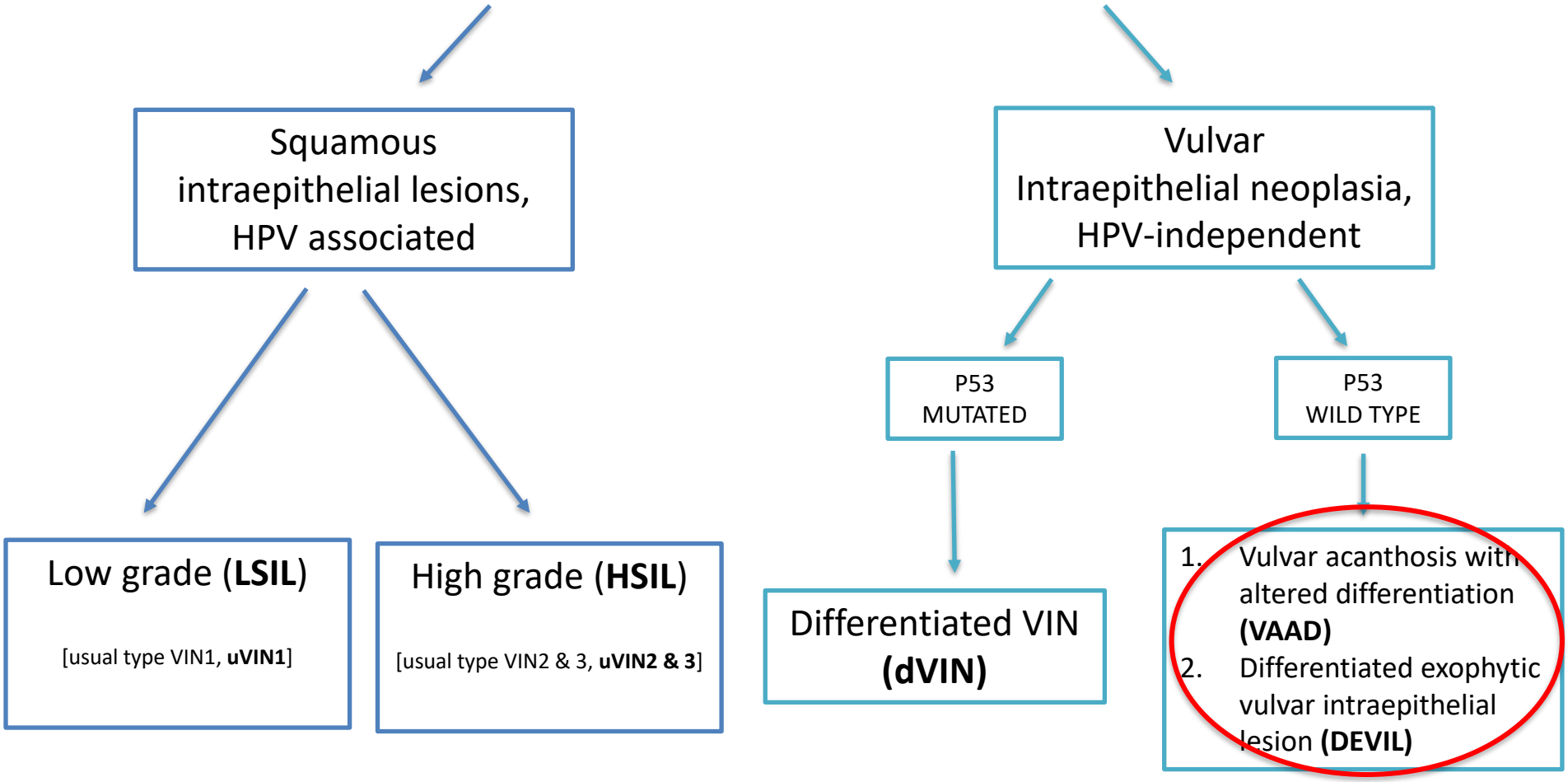
Molecular

- Associated with mutations in:
  - PIK3CA
  - ARID2
  - HRAS

- Absence of these mutations **does not** preclude the diagnosis

Brief overview of terminology

SQUAMOUS CELL PRECURSOR LESIONS OF THE VULVA[3]



VAAD

Vulvar **A**canthosis with **A**ltered **D**ifferentiation[4]

1) Marked acanthosis with variable verruciform architecture
2) Loss of granular cell layer with superficial epithelial pallor
3) Multilayered parakeratosis

Associated with HRAS (71.4%) and NOTCH1 (28.6%) mutations[5]

DEVIL

Differentiated **E**xophytic **V**ulvar **I**ntraepithelial **L**esion[6]

1) Lesion with acanthotic/verruciform morphology
2) Abnormal keratinocyte differentiation
3) Absence of significant basal atypia
4) Absence of P53 abnormality

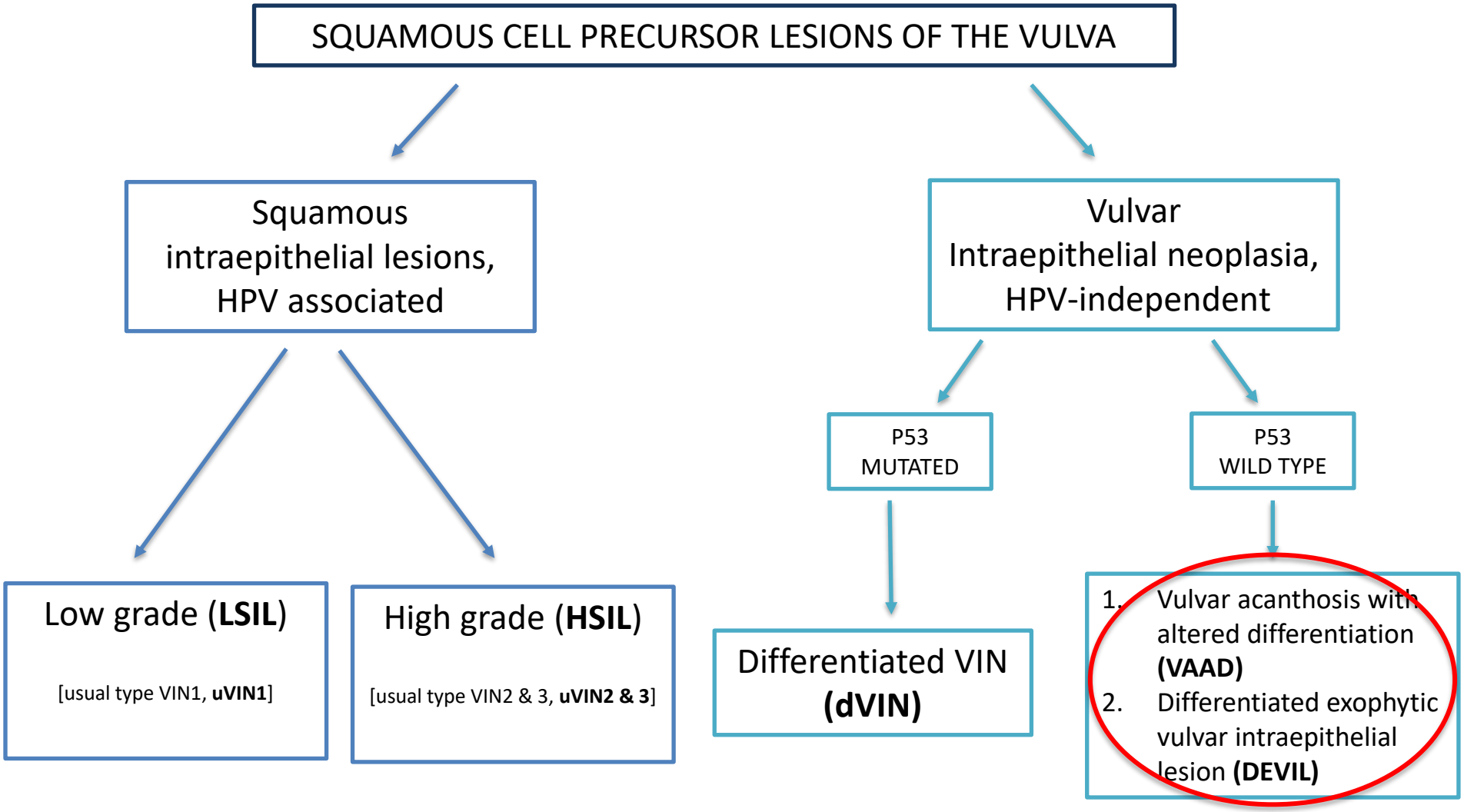
vLSC

Verruciform **L**ichen **S**implex **C**hronicus[7]

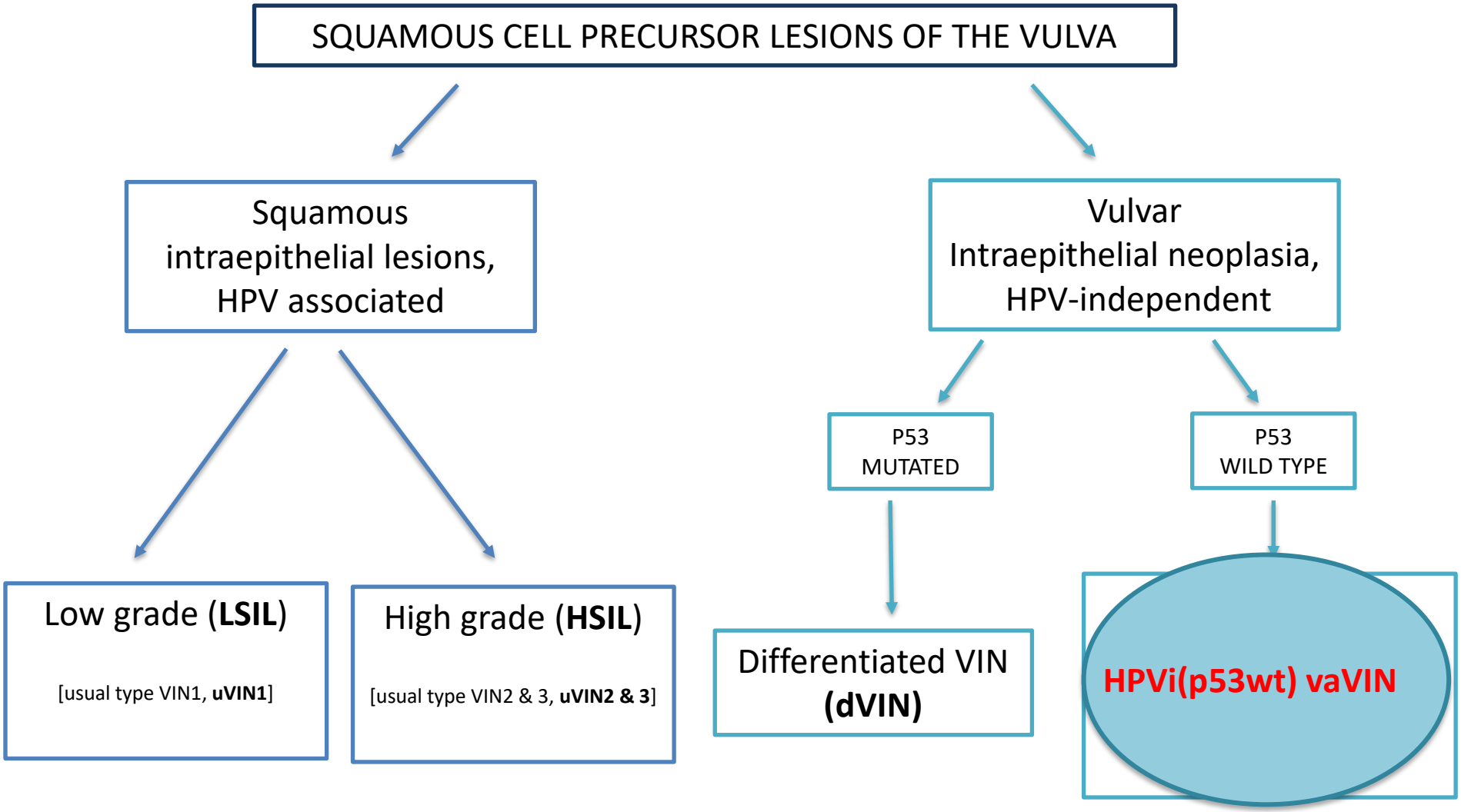
1) Verruciform architecture
2) Hy**per**granulosis
3) Lack of epithelial pallor

Frequent alterations in PIK3CA (73%), ARID2 (55%) and HRAS (18%)[7]

Brief overview of terminology



Brief overview of terminology



VAM

- **V**ulvar **A**berrant **M**aturation
  - The International Society of the Study of Vulvovaginal Diseases[8]
  - "Umbrella term for HPV-independent lesions combining aberrant maturation with minimal nuclear atypia"
    - VAAD
    - DEVIL
    - vLSC
    - Lichen sclerosus with acanthosis or hyperplasia
    - Squamous cell hyperplasia

Clinical Implications

- Rare lesions
- Close temporal and spatial associations with verrucous carcinoma[4,9]
- 37% rate of progression to invasive SCC[7]
- Excision with negative margins
  - Close surveillance with follow-up biopsies if surgery not suitable

Differential Diagnoses for vaVIN

Differential Diagnoses[1]: Neoplastic

Diagnosis	Similarities with vaVIN	Differentiating features from vaVIN
dVIN	• Can be acanthotic & exophytic with hyper/parakeratosis	• Cytological atypia • P53 mutated
uVIN	• Can be acanthotic with superimposed LSC-like changes	• Cytological atypia • Loss of maturation • P16 positivity
SCC	• Verrucous SCC lacks cytological atypia	• Conventional SCC – cytological atypia & infiltration • Verrucous SCC – endophytic growth beyond the DEJ (requires good orientation)
Vulvar exophytic condyloma	• Warty/verrucous appearance • Acanthotic • Variable granular cell layer • Can have parakeratosis	• Viral cytopathic effect • Low risk HPV on genotyping (if available)

Differential Diagnoses: Non-neoplastic

Diagnosis	Similarities with vaVIN	Differentiating features from vaVIN
Lichen simplex chronicus	• Acanthosis • Thick hyperkeratosis	• Hypergranulosis (less common in vaVIN but can be seen) • Lichenoid inflammation ***If florid acanthosis and/or verruciform architecture consider verruciform LSC**
(Hypertrophic) Lichen sclerosus	• Epithelial hyperplasia • Diminished granular cell layer • Parakeratosis	• Lichenoid inflammation with basal vacuolar damage • Dyskeratotic keratinocytes • Homogenised dermal stroma & oedema
Psoriasis	• Verruciform acanthosis • Hypogranulosis	• Vulva is an uncommon site • Younger patients (average age 30) • More widespread rash (other sites) • Thinning of dermal papillae • Neutrophilic micro-abscesses

Differential Diagnoses: Non-neoplastic

Diagnosis	Similarities with vaVIN	Differentiating features from vaVIN
Verruciform xanthoma	• Verruciform acanthosis	• Younger (pre-menopausal) • Foamy histiocytes in superficial dermis
Keratoacanthoma	• Raised lesion • Acanthotic	• Rapid growth (with subsequent regression) • Crateriform with dense keratin plug
Pseudo-epitheliomatous hyperplasia	• Raised lesion • Acanthotic	• Convoluted stromal interface • May have associated lesion (e.g. granular cell tumour)
Syphilis	• Mass lesion • Acanthosis and psoriasiform hyperplasia with loss of granular cell layer	• Inflammation (plasma cells) • Spirochetes on special stains/IHC

Conclusion

- Relatively new diagnostic category
- Rare lesions
- Diagnosis can be challenging!
- Further observations are required over time to build the full clinicopathological picture
  - Central review of cases may be beneficial

References & Recommended Resources

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8) Heller, DS. et al. Diagnostic criteria for differentiated vulvar intraepithelial neoplasia and vulvar aberrant maturation. J. Low Genit Tract Dis. 2021 Jan; 25(1):57-70
9) Akbari A. et al. Differentiated exophytic vulvar intraepithelial lesion: clinicopathologic and molecular analysis documenting its relationship with verrucous carcinoma of the vulva. Mod Pathol. 2020; 33:2011-2018

Thank you for listening



