Cervical Cytology and Vulvar Pathology

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Cervical Cancer Screening

• Most successful cancer screening program in the US
  – 70% reduction in cervical cancer deaths in past 60 years
  – 2012: 12,000 new cervical cancers; 4,200 deaths per year

• Earlier public health messages have impacted public attitudes and behaviors...but now they need to evolve!

• Advances in cervical cancer prevention since 1940s
  – Liquid-based cytology (LBC)...better test throughput
  – hrHPV-DNA testing...co-testing and triage of test results
  – HPV vaccination...primary prevention of cervical cancer
  – Evidence-based cytology screening guidelines

USPSTF Cervical Cytology Guidelines: 3/2012
Moyer VA; Ann Intern Med. 2012; 156(12):880-91

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology only, 21 to 65 years old</td>
<td>A</td>
<td>Every 3 years</td>
</tr>
<tr>
<td>HPV + cytology co-testing, 30-65 years old</td>
<td>A</td>
<td>Every 5 years</td>
</tr>
<tr>
<td>Women under 21 yrs old</td>
<td>D</td>
<td>Avoid screening</td>
</tr>
<tr>
<td>Age ≥65 with adequate prior screening and not high risk</td>
<td>D</td>
<td>Avoid screening</td>
</tr>
<tr>
<td>Total hysterectomy; benign disease</td>
<td>D</td>
<td>Avoid screening</td>
</tr>
<tr>
<td>HPV testing, alone or in combination, &lt; 30 years old</td>
<td>D</td>
<td>Avoid screening</td>
</tr>
</tbody>
</table>
**Triple A Guideline: ACS, ASCCP, Am Society for Clinical Pathology**

*CA CANCER J CLIN March 2012*

<table>
<thead>
<tr>
<th>Years of Age</th>
<th>Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;21</td>
<td>No screening</td>
</tr>
<tr>
<td>21-29</td>
<td>Cytology alone every 3 years</td>
</tr>
<tr>
<td>30-65</td>
<td>Preferred: HPV + cytology every 5 years* OR Acceptable: Cytology alone every 3 years*</td>
</tr>
<tr>
<td>&gt;65</td>
<td>No screening, following adequate neg prior screens</td>
</tr>
<tr>
<td>After total hysterectomy</td>
<td>No screening, if no history of CIN2+ in the past 20 years or cervical cancer ever</td>
</tr>
</tbody>
</table>

*If cytology result is negative or ASCUS + HPV negative

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**Management of Co-Testing Results**

<table>
<thead>
<tr>
<th>Cytology</th>
<th>HPV Positive</th>
<th>HPV Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>• Co-test in 12 months, or • Subtype for HPV 16/18</td>
<td>Co-test in 5 years</td>
</tr>
<tr>
<td>ASC-US</td>
<td>Colposcopy</td>
<td>Co-test in 5 years</td>
</tr>
</tbody>
</table>

ASC-US/HPV negative is managed as Pap negative/HPV negative

ACOG Practice Bulletin #131, Obstet Gynecol 2012;120:1222-38

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**Cervical Cytology in High Risk Women**

- Women with reduced immune surveillance have faster transit times from pre-invasive to invasive lesions
- Do not increase the screening interval **beyond annual testing** for women who are
  - HIV-positive
  - Immunosuppressed (transplant with anti-rejection drug)
  - Were exposed in utero to diethylstilbestrol
- Follow guidelines for women who have been treated for CIN 2 or 3 or adenocarcinoma in situ

ACOG Practice Bulletin No. 109, Dec 2009

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**Other Important Messages**

- Women at *any age* should not be screened annually by *any* screening method
- **For women 65 and older**
  - “Adequate screening” is defined as...
    - 3 consecutively negative results in prior 10 years, or
    - 2 negative co-tests, most recently within 5 years
  - If screening stopped, do not restart for any reason
- Women treated for CIN 2+ or AIS must be **regularly screened** for 20 years, even if 65 or older
  - With cytology alone Q 3 years or HPV+ cytology Q5 years
**USPSTF: Co-Testing Caveat**

- Co-testing is most appropriate for women who want to extend their screening interval to every 5 years

**But...**
- “Women choosing co-testing ... should be aware that positive screening results are more likely with HPV-based strategies... and that some women may require prolonged surveillance with additional frequent testing if they have persistently positive HPV results”

**Co-testing Strategy as Health Policy**

**Pros**
- Slightly more accurate than cytology alone
- Higher negative predictive value than cytology alone
- Longer screening interval available if desired by patient

**Cons**
- More false positives, esp. if done too frequently
- High cost/ year of life saved if done too frequently
- Many providers don’t have EMRs to prevent overuse

**Summary of Cervical Cancer Guidelines**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Age Group</th>
<th>Cytology</th>
<th>Co-test</th>
<th>Hyst, benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 21 years old</td>
<td>Every 3 y</td>
<td>Cytology: Q3</td>
<td>Co-test: Q5</td>
<td>None**</td>
</tr>
<tr>
<td>21-29 years old</td>
<td>Every 3 y</td>
<td>Cytology: Q3</td>
<td>Co-test: Q5*</td>
<td>None**</td>
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<td>Hyst, benign</td>
<td></td>
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</tbody>
</table>

* Preferred  ** If adequate prior screening with negative results

**When Is a Shorter Interval Justified?**

For women who...
- Are in a surveillance pathway
  - Previously abnormal cytology result
  - Post-treatment with cryotherapy, LEEP, or a cone biopsy for a pre-invasive cervical lesion
- Have had a result of “insufficient specimen adequacy” or an “unsatisfactory” result on her last cytology screen
- Have HIV infection, a major organ transplant with the use of an anti-rejection drug, or long term corticosteroid use
- Are newly enrolled in a practice and have no documented history of prior cytology results
Common Questions About Pap Intervals

- Do virginal women need Pap smears?
- Are the intervals any different for women
  - With multiple sexual partners?
  - Using hormonal contraceptives, menopausal hormone therapy?
  - Who only have female partners?
  - Who are pregnant?
- If a cytology is not scheduled or necessary, what about the need to perform a bimanual pelvic exam?
Pelvic Exam at the Well-Woman Visit

- **Women younger than 21 years**
  - Pelvic exam only when indicated by medical history
  - Screen for GC, chlamydia with vaginal swab or urine

- **Women aged 21 years or older**
  - “ACOG recommends an annual pelvic examination”
    - No evidence supports or refutes routine exam if low risk
    - If asymptomatic, pelvic exam should be a “shared decision”
      - Individual risk factors, patient expectations, and medico-legal concerns may influence these decisions
    - If TAH-BSO, decision “left to the patient” if asymptomatic

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial
Buys SS, Partridge E, et al. JAMA. 2011;305(22):2295-2303

- Randomized trial of 78,216 women aged 55-74
- Annual screening with CA-125 for 6 years + transvaginal U/S for 4 years (n=39,105) versus usual care (n=39,111)
- 10 US screening centers
- Followed a median of 12 years
- Bimanual examination originally part of the screening procedures but was discontinued

**Ovarian Cancers: PLCO Cancer Screening RCT**

**Is The “Screening Pelvic Exam” Outdated?**

<table>
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<th>Screen for</th>
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<td>GC, Ct</td>
<td>NAAT: vaginal swab or urine sample</td>
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<td>Not recommended until 21 years old</td>
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<tr>
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<td>None, if total hyst for benign disease</td>
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<td>Ovarian cancer</td>
<td>USPSTF rec. against bimanual exam</td>
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_JAMA. 2011;305(22):2295-2303_
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</tr>
<tr>
<td>Vulvar lesions</td>
<td>Unnecessary if asymptomatic</td>
</tr>
<tr>
<td>Vaginal infxn</td>
<td>Unnecessary if asymptomatic</td>
</tr>
<tr>
<td>Myomas</td>
<td>Unnecessary if asymptomatic</td>
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</table>

How Will These Changes Impact My Practice?

- **The good news**
  - With ACA, *first dollar coverage* of well woman visits and cervical cytology screening
- **The bad news**
  - Since there is no national population-based educational campaign, *we* must explain changes to our patients
- **Systems issues**
  - Expect insurance benefit changes based on new guidelines
  - Quality indicators to measure under- and over-utilization

How Can My Practice Prepare?

- Ask every patient if she also sees another provider for screening....if so, avoid duplication of interventions
- Determine the screening policies for your practice
  - Make sure that all staff are aware of your policy
- Inform your patients of changes that apply to them
  - During transition, discuss these decisions with patients
  - Inform patients with a personal letter or newsletter
- Keep track of benefit changes made by your payers
  - Few have changed screening benefits yet...*but they will!*

Management of Abnormal Cytology Results

- On March 21, ASCCP released 2012 consensus guidelines for management of abnormal cervical cancer screening tests and CIN/AIS
- Comprehensively revised management strategies
- Guidance on co-testing for women 30 and older
- More conservative management for women 21-24 years old
- Builds on past guidelines but incorporates data on risk from 1.4 million women screened @ Kaiser N. California
Genital Skin Rashes

**Infectious**
- Candidiasis
- Tinea Cruris
- Tinea Versicolor
- Erythrasma

**Non-infectious**
- Intertrigo
- Psoriasis
- Atopic dermatitis (eczema)

Vulvar Candidiasis

**Symptoms:** vulva will be very itchy

**Presentation**
- Often excoriated
- Erythema ± satellite lesions
- Occasionally: thrush, LSC thickening if chronic

**Diagnosis:** skin scraping KOH, candidal culture

**Treatment**
- Topical antifungal therapy daily for 7-14 days, or fluconazole 150 mg PO repeat in 3 days
- Plus: TAC 0.1% or 0.5% ointment QD-BID

Take it Home

<table>
<thead>
<tr>
<th>Michael Pollan: Healthy eating</th>
<th>Healthy Cervical Cancer Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eat food</td>
<td>Start later, end sooner</td>
</tr>
<tr>
<td>Not too much</td>
<td>Not too often</td>
</tr>
<tr>
<td>Mostly plants</td>
<td>Every 3 or 5 years</td>
</tr>
</tbody>
</table>

What doesn’t matter for screening intervals
- Age of sexual debut
- Prior HPV vaccination
- New sexual partners or practices
- Hormonal contraceptives or hormone therapy
**Vulvar Candidiasis**

- Asymmetric lesions on proximal inner thighs
  - Plaque rarely involves scrotum; not penile shaft
- Well demarcated red plaques with accentuation of scale peripherally; no satellite lesions
- Fungal folliculitis: papules, nodules or pustules within area of plaque

**Treatment**
- Mild: topical azoles BID x 10-14d, terbinafine
- Severe: fluconazole 150 mg QW for 2-4 weeks
- If inflammatory, add TAC 0.1% on 1st 3 days

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**Tinea Cruris: “Jock Itch”**

- Asymmetric lesions on proximal inner thighs
  - Plaque rarely involves scrotum; not penile shaft
- Well demarcated red plaques with accentuation of scale peripherally; no satellite lesions
- Fungal folliculitis: papules, nodules or pustules within area of plaque

**Treatment**
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- Severe: fluconazole 150 mg QW for 2-4 weeks
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**Contact Dermatitis**

- **Irritant contact dermatitis (ICD)**
  - Elicited in most people with a high enough dose
  - Rapid onset vulvar itching (hours-days)
- **Allergic contact dermatitis (ACD)**
  - Delayed hypersensitivity
  - 10-14 days after 1st exposure; 1-7 d after repeat exposure

**ICD and ACD can present with**
- Itching, burning, swelling, redness
- Small vesicles or bullae more likely with ACD
### Contact Dermatitis

**Common contact irritants**
- Urine, feces, excessive sweating
- Saliva (receptive oral sex)
- Repetitive scratching, overwashing
- Detergents, fabric softeners
- Topical corticosteroids
- Toilet paper dyes and perfumes
- Hygiene pads (and liners), sprays, douches
- Lubricants, including condoms

**Common contact allergens**
- Poison oak, poison ivy
- Topical antibiotics, esp neomycin, bacitracin
- Spermicides
- Latex (condoms, diaphragms)
- Vehicles of topical meds: propylene glycol
- Lidocaine, benzocaine
- Fragrances

### Contact Dermatitis: Treatment

- Exclude contact with possible irritants
- Restore skin barrier with sitz baths, compresses
- After hydration, apply a bland emollient
  - White petrolatum, mineral oil, olive oil
- Short term mild-moderate potency steroids
  - TAC 0.1% BID x10-14 days (or clobetasol 0.05%)
  - Fluconazole 150 mg PO weekly
- Cold packs: gel packs, peas in a “zip-lock” bag
- Doxypin or hydroxyzine (10-75 mg PO) at 6 pm
- If recurrent, refer for patch testing
Why Not Steroid-Antifungal Combination Drugs?

- Which products should be avoided?
  - Lotrisone: Clotrimazole and Betamethasone 0.5%
  - Mycolog II: Nystatin and Triamconolone acetonide
- Why avoid them?
  - Inflammation usually clears up before fungal infection
  - Steroid overshoot → skin atrophy
  - Local immunosuppression (from steroid) may blunt antifungal effect

Genital Skin Itching

- Infections
  - Candidiasis
  - *Tinea cruris*
- Dermatitis
  - Psoriasis
  - Seborrheic dermatitis
  - Eczema

Dermatoses

- Lichen sclerosus
- Lichen simplex chronicus (LSC)
- LS + LSC

Neoplasms

- Paget’s Disease (women)
- Vulvar Intraepithelial neoplasia (VIN)
- Penile Intraepithelial neoplasia (PIN)

ISSVD 1987: Vulvar Dermatoses

<table>
<thead>
<tr>
<th>Type</th>
<th>ISSVD Term</th>
<th>Old Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophic</td>
<td>Lichen sclerosus</td>
<td>• Lichen sclerosus et atrophicus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Kraurosis vulvae</td>
</tr>
<tr>
<td>Hyper-plastic</td>
<td>Squamous cell hyperplasia</td>
<td>• Hyperplastic dystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Neurodermatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lichen simplex chronicus</td>
</tr>
<tr>
<td>Systemic</td>
<td>Other dermatoses</td>
<td>• Lichen planus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Psoriasis</td>
</tr>
<tr>
<td>Premalignant</td>
<td>VIN</td>
<td>• Hyperplastic dystrophy/atrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bowen’s disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bowenoid papulosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Vulvar CIS</td>
</tr>
</tbody>
</table>

ISSVD: International Society for the Study of Vulvar Disease

2006 ISSVD Classification of Vulvar Dermatoses

- No consensus agreement on a system based upon clinical morphology, path physiology, or etiology
- Include only non-Neoplastic, non-infectious entities
- Agreed upon a *microscopic morphology* based system
- **Rationale of ISSVD Committee**
  - Clinical diagnosis → no classification needed
  - Unclear clinical diagnosis → seek biopsy diagnosis
  - Unclear biopsy diagnosis → seek clinic pathologic correlation
2006 ISSVD Classification of Vulvar Dermatoses

<table>
<thead>
<tr>
<th>Path pattern</th>
<th>Clinical Correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spongiotic</td>
<td>Atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis</td>
</tr>
<tr>
<td>Acanthotic</td>
<td>Psoriasis, LSC (primary or superimposed), (VIN)</td>
</tr>
<tr>
<td>Lichenoid</td>
<td>Lichen sclerosus, lichen planus</td>
</tr>
<tr>
<td>Dermal homogenization</td>
<td>Lichen sclerosus</td>
</tr>
<tr>
<td>Vesiculobullous</td>
<td>Pemphigoid, linear IgA disease</td>
</tr>
<tr>
<td>Acantholytic</td>
<td>Hailey-Hailey disease, Darier disease, papular genitocrural acantholysis</td>
</tr>
<tr>
<td>Granulomatous</td>
<td>Crohn disease</td>
</tr>
<tr>
<td>Vasculopathic</td>
<td>Apthous ulcers, Behcet disease, plasma c. vulvitis</td>
</tr>
</tbody>
</table>

Lichen Sclerosus: Natural History

- Most common vulvar dermatosis
- Prevalence: 1.7% in a general GYN practice
- Cause: autoimmune condition
- Bimodal age distribution: older women and children, but may be present at any age
- Chronic, progressive, lifelong condition

Lichen Sclerosus: Findings

- Symptoms
  - Most commonly, itching
  - Often irritation, burning, dyspareunia, tearing
  - 58% of newly-diagnosed patients are asymptomatic
- Signs
  - Thin white “parchment paper” epithelium
  - Fissures, ulcers, bruises, or submucosal hemorrhage
  - Changes in vulvar architecture: loss of labia minora, fusion of labia, phimosis of clitoral hood
  - Depigmentation (white) or hyperpigmentation in “keyhole” distribution: vulva and anus
  - Introital stenosis

Lichen Sclerosus: Natural History

- Most common in Caucasian women
- Can affect non-vulvar areas
- Part (or all) of lesion can progress to VIN-d type
- Predisposition to vulvar squamous cell carcinoma
  - 1-5% lifetime risk (vs. < 0.01% without LS)
  - LS in 30-40% women with vulvar squamous cancers
“Early” Lichen Sclerosus

- Hyperpigmentation due to scarring
- Loss of labia minora

“Late” Lichen Sclerosus

- Agglutination of clitoral hood
- Loss of labia minora
- Introital narrowing
- Parchment paper epithelium

68 year old woman with urinary obstruction

- Labial agglutination over urethral meatus
Lichen Sclerosus: Treatment

• Biopsy mandatory for diagnosis, unless classic findings
• Preferred treatment
  – Clobetasol 0.05% ointment QD x4 weeks, then QOD x4 weeks, then twice-weekly for 4 weeks
  – Taper to med potency steroid (or clobetasol) 2-4 times per month for life
  – Explain “titration” regimen to patient, including management of flares and recurrent symptoms
  – 30 gm tube of ultrapotent steroid lasts 3-6 mo
  – Monitor every 3 months twice, then annually

Second line therapy
– Pimecrolimus, tacrolimus
– Retinoids, potassium para-aminobenzoate
• Testosterone (and estrogen or progesterone) ointment or cream no longer recommended
• Explain chronicity and need for life-long treatment
• Adjunctive therapy: anti-pruritic therapy
  – Antihistamines, especially at bedtime
  – Doxypin, at bedtime or topically
  – If not effective: amitriptyline, desipramine PO
• Perineoplasty may help dyspareunia, fissuring

Lichen Simplex Chronicus = Squamous Cell Hyperplasia

• Cause: an irritant initiates a “scratch-itch” cycle
• LSC classified as
  – Primary (idiopathic)
  – Secondary (superimposed upon lichen sclerosus, candida vulvitis; vulvar contact dermatitis)
• Presentation: always itching; burning, pain, tenderness
• Signs: Thickened red (white if moisture) raised lesion
• In absence of atypia, no malignant potential
  – If atypia present, classified as VIN

Lichen Simplex Chronicus
L. Simplex Chronicus: Treatment

- Removal of irritants or allergens
- Treatment
  - Triamcinolone acetonide (TAC) 0.1% ointment BID x4-6 weeks, then QD
  - Other moderate strength steroid ointments
  - Intralesional TAC once every 3-6 months
- Anti-pruritics
  - Hydroxyzine (Atarax) 25-75 mg QHS
  - Doxepin 25-75 mg PO QHS
  - Doxepin (Zonalon) 5% cream; start QD, work up

Lichen Sclerosus + LSC

- “Mixed dystrophy” deleted in 1987 ISSVD System
- 15% all vulvar dermatoses
- LS is irritant; scratching → LSC
- Consider: LS with plaque, VIN, squamous cell cancer of vulva
- Treatment
  - Clobetasol x12 weeks, then steroid maintenance
  - Stop the itch!!

Vulvar Intraepithelial Neoplasia (VIN):

Prior to 2004

- Grading of VIN-1 through VIN-3, based upon degree of epithelial involvement
- The mnemonic of the 4 P’s
  - Papule: formation: raised lesion (erosion also possible, but much less common)
  - Pruritic: itching is prominent
  - Patriotic: red, white, or blue (hyperpigmented)
  - Parakeratosis on microscopy

ISSVD Classification of VIN (2004)

- Since VIN 1 is not a cancer precursor, abandon use of term
  - Instead, use “condycoma” or “flat wart”
- Combine VIN-2 and VIN-3 into single “VIN” diagnosis
- Two distinct variants of VIN

<table>
<thead>
<tr>
<th>ISSVD 1986</th>
<th>ISSVD 2004</th>
<th>VIN-u</th>
</tr>
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<tbody>
<tr>
<td>VIN 1</td>
<td>Flat condyoma</td>
<td>VIN-u</td>
</tr>
<tr>
<td>VIN 2</td>
<td>VIN-usual (VIN-u)</td>
<td>Warty</td>
</tr>
<tr>
<td>VIN 3</td>
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<td>Basaloid</td>
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<tr>
<td>Differentiated</td>
<td>VIN-differentiated (VIN-d)</td>
<td>Mixed</td>
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ISSVD: VIN, Usual Type (VIN-u)

- Usually HPV-related (mainly type 16)
- More common in younger women (30s-40s)
- Often asymptomatic
- Lesions usually elevated and have a rough surface, although flat lesions can be seen
- Often multifocal (incl periurethral and perianal areas) and multicentric in 50%
- Strongly associated with immunocompromise, smoking
- Low malignant potential (5-20%)
  - Progression more likely with the basaloid type

VIN, usual (basaloid) type

White VIN, Usual (warty) type

FIGURE 3. Vulvar intraepithelial neoplasia, usual type, with white-gray color changes and irregular borders.
VIN: warty-basaloid type

VIN-d: Differentiated Type
- Usually in older women with LS, LSC, or LP
- Not HPV related
- Far less common than VIN-usual type
- **Symptoms**: long history of pruritus and burning
- **Findings**
  - Red, pink, or white papule; rough or eroded surfaces
  - A persistent, non-healing ulcer
  - Unifocal, unicentric
- More likely to progress to SCC of vulva than VIN-u (90%)

Vulvar Intraepithelial Neoplasia
- **Risk of invasion**: greater if immunocompromised (steroids, HIV), >40 years old, previous lower genital tract neoplasia
- **Treatment**
  - Wide local excision: highest cure rate, esp hair-bearing
  - CO₂ laser ablation: best cosmetic result
  - Topical agents: imiquimod
  - Skinning or simple vulvectomy rarely used
- **Recurrence** is common (48% at 15 years)
  - Monitor @ 6,12 months, then annually
  - Smoking cessation may reduce recurrence rate
- **Prevention**: HPV-4 vaccine

Genital Skin: Dark Lesions (% are in women only)
- 36% Lentigo, benign genital melanosis
- 22% VIN
- 21% Nevi (mole)
- 10% Reactive hyperpigmentation (scarring)
- 5% Seborrheic keratosis
- 2% Malignant melanoma
- 1% Basal cell or squamous cell carcinoma
Vulvar Intraepithelial Neoplasia

Hyperpigmented VIN, usual type

Lichen Sclerosus with Scarring

Vulvar Melanoma: ABCDE Rule

A: Asymmetry
B: Border Irregularities
C: Color black or multicolored
D: Diameter larger than 6 mm
E: Evolution
   – Any change in mole should arouse suspicion
   – Biopsy mandatory when melanoma is a possibility
Indications for Vulvar Biopsy

- Papular or exophytic lesions, except obvious condylomata
- Thickened lesions (biopsy thickest region) to differentiate VIN vs. LSC
- Hyperpigmented lesions (biopsy darkest area), unless obvious nevus or lentigo
- Ulcerative lesions (biopsy at edge), unless obvious herpes, syphilis or chancroid
- Lesions that do not respond or worsen during treatment
- In summary: biopsy whenever diagnosis is uncertain