PATHOLOGY (CANCERS AND BENIGN LESIONS)

- **Basal Cell Carcinoma (BCC)**
  - Risk Factors
    - Patient factors
      - Blonde/red hair
      - Green/blue eyes
      - **Fair Skin**
      - **Prior BCC**
        - 45% risk of subsequent BCC within 3 years

	BCC	SCC
UV Exposure History	Intermittent, intense UV	Cumulative UV
Sunburn History	Sunburns any age	Sunburns when young
Common Mutation	PTCH, P53	P53

    - **UV exposure** (intermittent, intense UV exposure vs. cumulative UV in SCC)
      - Direct DNA damage (UVB/UVC > UVA)
        - Create pyrimidine dimers by mutation from cytosine to thymine ("**UV Signature Mutation**" or "fingerprint")
        - Most common mutations = **PTCH and p53**
      - Indirect DNA damage
        - Reactive oxygen species (UVA > UVB)
      - Sunburns at any age (vs. SCC, more risk with childhood sunburns)
    - Ionizing radiation
      - Acne therapy when younger….shows up years later (20 years)
    - Occupational exposures
      - UV
      - Ionizing radiation (pilots)
      - Chemical exposures (arsenic….more common with SCC than BCC)
    - Immunosuppression Therapy Options:
      - Especially solid organ transplants > hematopoietic transplants
      - Options to <u>lower risk</u> of NMSC and AK's in immunosuppression:
        - Change to mTOR inhibitors (sirolimus) vs. calcineurin inhibitor (tacrolimus)
        - Oral nicotinamide
    - Medications
      - Photosensitivity and exacerbation of UV-damage
        - Hydrochlorothiazide, fluroquinolones, tacrolimus
      - Immunosuppression (loss of surveillance)
        - TNF-inhibitors (adalimumab, infliximab)
      - Direct molecular effect driving keratinocyte proliferation
        - Vemurafenib, Vismodegib
    - **<u>NOT</u>** a risk factor for BCC, as in SCC:

- Tobacco use
- HPV

- **Dermatoscopic** features of classic BCC:
  - Pearly, ulcerated papule
  - **Arborizing (or "tree-like") vessels**

- **Genetic syndromes with BCC's**
  - **Mohs Appropriate** for <u>any</u> type, location of BCC, when a genetic syndrome

  - Gorlin syndrome (Autosomal Dominant)
    - **PTCH1 mutation** (most common)
    - <u>Major criteria for Gorlin syndrome:</u>
      - Odontogenic keratocysts of jaw (<u>first presentation/sign</u>)
      - **BCCs** under age of 20
        - **Infundibulocystic BCC variant mainly**
      - **Palmoplantar pits**
      - Bifid ribs
      - 1st degree relative with Nevoid Basal Cell Carcinoma syndrome

    - Minor criteria:
      - **Medulloblastomas**/rhabdomyosarcomas
      - Calcification of falx cerebri

    - Risk of **ovarian fibromas** (often calcified and bilateral)

  - Rombo syndrome (Autosomal Dominant)
    - Think of:
      - *Rambo has BCC's, scars on cheeks & redness on extremities*

    - Clinical
      - **BCC**/trichoepithelioma
      - **Atrophoderma vermiculata**
        - Atrophy, scarring on cheeks at young age
      - Acral erythema

  - Bazex-Dupre-Christol syndrome (X-linked Dominant)
    - Clinical
      - **BCC**
      - Hypotrichosis/**fragile hair**
      - Follicular atrophoderma (scarring on hands, feet)
      - **Hypohidrosis**
      - Epidermal cysts/milia

- **<u>Non-BCC Genetic Syndromes with often basaloid skin lesions</u>**:
  - Schopf-Schulz-Passarge syndrome (WNT10A mutation):

        - Autosomal recessive, starts in teenage years and worsens
        - Clinical: Abnormalities in hair, teeth, nails, sweat glands, etc.
            - Multiple eyelid cysts (apocrine **hidradenomas**)
            - Hyperhidrosis
            - Hypotrichosis (sparse hair)
            - Malformed nails
            - Palmoplantar keratoderma/thickening of skin on hands/feet

    - **Brooke-Spiegler syndrome (CYLD mutation):**
        - Think "TC's"
            - T = Trichoepitheliomas
            - **C = Cylindromas**
            - S = Spiradenomas

    - PTEN Hamartoma Syndromes **(PTEN mutation):**
        - Cowden syndrome:
            - **Tricholemmomas**
            - Papillomas on gums/tongue (cobblestone appearance)
            - **Risk of breast cancer**, thyroid cancer, melanoma, etc.

        - Bannayan-Riley-Ruvalcaba syndrome
            - Lipomas
            - Macrocephaly
            - Freckling on genitals

- **BCC Mutations:**
    - Most common mutations = **PTCH then p53**
    - Sonic hedgehog pathway
        - Inactivating **PTCH gene** (tumor suppressor, "brake for SMO")
            - Prevents inhibition of SMO
                - BCC occurs with activating PTCH1 mutation that activates SMO then GLI pathway (proliferation)
        - **Itraconazole** – inhibits hedgehog pathway (inhibition of smoothened receptor)

- Higher risk BCCs (recurrence, metastasis, mortality)
    - Tumor > 2cm
    - Head and neck location
    - Depth beyond fat
    - Rarely, metastasis to visceral organs (usually lungs)

- Aggressive variants of BCC's
    - Micronodular
    - Morpheaform (1 to 2 cells thick form invading cords)
    - Infiltrating (3 or more cells forming infiltrating cords)
    - Sclerosing

- Basosquamous

- Non-aggressive variants of BCC
  - Nodular
  - Superficial
  - Infundibulocystic
  - Fibroepithelial of Pinkus (most common location = lower back)

- Imaging (CT or MRI) with BCC
  - Bone involvement
  - Perineural invasion
  - Deep soft tissue involvement

- BCC < 1% risk of metastasis
  - If occur, typically to lymph nodes, lungs or bone

- BCC Treatment
  - Mohs - Especially in H area ("Mask area")
  - Excision (typically, 4mm margins)
  - Topical therapy (5-FU, imiquimod) – Superficial BCC's
    - **Imiquimod** (Toll-like receptor 7 & 8 agonist) shown better results than 5-Fluoururacil (5-FU inhibits thymidylate synthetase that efects RNA/DNA) and other topical therapies
  - Radiation (long therapy period)
    - Consider with perineural involvement or positive margins after Mohs
  - ED&C (non-hair bearing sites)
  - Cryotherapy
    - Obtain **less than -50 degrees Celsius** to destroy malignant tissue
      - Freeze time of 45 seconds x 2 cycles may be required
    - Cryotherapy Trivia:
      - Benign lesions (5-7 seconds, obtain less than -20 degrees Celsius)
      - Melanocyte damage = **-5** degrees C
      - Keratinocyte damage = **-25** degrees C
      - Malignant lesion destruction = **-50** degrees C
      - LN2 temperature = **-196** degrees C
      - Optimum results/damage:
        - Rapid cooling followed by slow thawing

  - Systemic therapy
    - Hedgehog pathway inhibitors
      - Medications = Vismodegib and Sonidegib
        - **Vismodegib's most common side effect = Muscle spasms**
          - Amlodipine, L-carnitine supplement and magnesium may alleviate spasms

- Tumor resistance limits duration of benefit for medications
  - Usually due to novel smoothened mutations (50%)

- Side effects
  - **Muscle spasms** (*most common* side effect)…68%
  - Alopecia…63%
  - Loss of taste/dysgeusia…51%
  - Nausea/fatigue/weight loss

  - Trichodysplasia spinulosa (rare)
    - Trichohyaline debris in inner root sheath

  - Severely **teratogenic**
    - Avoid conception/breastfeeding for (vismodegib):
      - **24 months** (women)
      - **3 months** (men)

    - **Avoid donating blood:**
      - **24 months** (vismodegib)
      - 20 months (sonidegib)

BCC	Other Carcinomas
BerEP-4 (+)	SCC, MAC, Sebaceous carcinoma are Ber-EP4 (-)
BCL-2 (+)	SCC is BCL-2(-)
CD10 (+) in tumor cells	SCC is CD10 (-)
EMA (-)	Sebaceous Carcinoma is EMA (+)