A major section of the presentation is titled "Genodermatoses with predisposition toward internal malignancy." This section is authored by Jonathan A. Dyer, MD, an Associate Professor of Dermatology and Child Health at the University of Missouri – Columbia.

### Basal cell nevus (Gorlin’s) syndrome

- **Autosomal dominant**
  - 1:40,000 incidence
  - 20-30% de novo mutations
- **Mutations in patched gene**
  - Tumour suppressor gene
  - Receptor for signaling proteins in sonic hedgehog pathway
  - Suppressor of fused homolog (SUFU)
  - No jaw cysts; high medulloblastoma risk

### Gorlin’s syndrome

**Internal tumours**

- Medulloblastoma
  - 2nd most common malignancy
  - Average onset - 2 years
  - Frequency up to 5%
  - if <3 and/or desmoplastic histology consider NBCCS
  - SUFU mutations
- Ovarian fibromas

### Vismodegib

- Final results of trial
- Attrition noted
  - Hair loss; dysguesia; other SE
- Exploring intermittent dosing
- Rebound upon DC

Additionally, there are sections discussing disclosure of relationships with industry and more detailed notes on the genetic aspects of the conditions mentioned.

[Note: For a complete and accurate interpretation of the text, please refer to the presentation slides as they contain specific details and visual aids.]
Risk Factors for Basal Cell Carcinoma Among Patients With Basal Cell Nevus Syndrome

- Age/number of sunburns significantly associated with BCC severity

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Bazex-Cristol-Dupre syndrome

- X-linked dominant – OMIM# 301845
- Basal cell carcinomas
  - face
  - 15 to 26 years
- Follicular atrophoderma
  - "ice-pick marks"
  - dorsum of hands and elbows
- Milia
- Hypotrichosis
- Twisted and flattened hairs on scanning electron microscopy

Bazex-Cristol-Dupre syndrome

- ACTRT1 mutations (2/6 families)
  - Actin-related protein T1 (ARP-T1)
    - Germline mutations in noncoding sequences around ACTRT1 in other families
      - In transcribed sequences encoding enhancer RNAs (eRNAs)
      - Impair enhancer activity and ACTRT1 expression
      - ARP-T1 binds GLI1 promoter – inhibiting GLI1 expression
      - Loss of ARP-T1> activation of Hedgehog pathway

Muir-Torre syndrome

- Autosomal dominant; OMIM 158320
- MSH1 or MSH2 (90%) genes
  - DNA mismatch repair defect; HNPCC/ Lynch syndrome variant
  - 6-9% of HNPCC
- MSH6; PMS2 mutations
- Skin
  - Sebaceous neoplasms
  - Hyperplasia; adenoma; epithelioma; carcinoma
  - Prominent Fordyce spots - lips
  - Keratoacanthoma
- GI: Colon adenocA; proximal to splenic flexure
- Other GI, GU, breast, hematologic, lung CA

Gardner syndrome

- AD-APC gene; OMIM# 175100
- 1.8,300-16,000 incidence (FAP)
- Skin lesions: increased pigment
  - Epidermoid cysts: 50-65% of patients
  - Head, neck, and extremities; congenital
  - Multiple; pilomatricoma-like
  - Increase in number/size then stabilize
- Bone – Osteomas (79%): before skin
  - Membranous bones-face/head
- Thyroid CA – females
- Desmoid tumours

Gardner syndrome

- Ophthalmologic
  - RPE hamartoma (RPEH-FAP)
    - Not the same as Congenital hypertrophy of the retinal pigment epithelium (CHRPE)
    - Disorganization at one end; conical/fish tail
    - Some kindreds; May be earliest finding
- GI lesions – allelic to familial adenomatous polyposis
  - Premalignant adenomatous polyps – esp. colon
    - Rare before 10 yo; by 20 yo 50% of patients have polyps
    - High incidence of malignancy
Peutz-Jeghers syndrome
• AD - OMIM# 175200
• Serine-threonine kinase 11 (STK11)
  – ~40% spontaneous mutation
• Skin
  – Pigmented macules/ lentigines
    • First yrs of life
    • Lips and buccal mucosa
      – Any mucosal surface
  – Digits, nails, palms, soles
  – All but buccal fade with time

Peutz-Jeghers syndrome
• GI - Hamartomatous polyps
  • Small > large intestine
  • 30% undergo laparotomy for intussusception by 10
• Neoplasia
  – Increased breast, GI, ovarian, lung, endometrial, and pancreatic CA
  – Sex cord tumour with annular tubules
  – Calcifying Sertoli cell tumours of testes
  – Gynecomastia if estrogen secreted
  – Adenoma malignum
  – Rare aggressive cervical cancer

Cowden’s syndrome
• OMIM# 158350; PTEN hamartoma syndrome
• Incidence 1:300,000
  – 1:2 – Male:female
• Present in second-third decade

Cowden’s syndrome
• Skin
  – Trichilemmomas
• Mucosa
  – Papillomas

Cowden’s syndrome
• Skin
  – Acral keratotic papules
  – Lipoma, angioma
  – Fibromas
    • Sclerotic fibromas
      – characteristic
    • J Cutan Pathol. 1991;19:346-351
• Breast
  – Virginal hypertrophy
  – Fibrocystic disease
  – Fibroadenoma
  – Adenocarcinoma
  – Gynecomastia (males)
• Thyroid
  – Goiter
  – Adenoma
  – Follicular adenocA
• GI
  – Hamartomatous polyps
  – Colon / Usually benign
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)

- OMIM# 605839: AD
- Skin - Variable phenotype
  - Leiomyomas - Typically sensitive to 5% lidocaine patch
  - Uterine leiomyomas
  - Fibroids
  - Leptomeningeal hamartoma
  - All races
  - Fumarate hydratase mutations
  - Krebs cycle enzyme
  - Converts fumarate to malate
  - No clear genotype/phenotype correlation

Birt-Hogg-Dube syndrome

- Autosomal dominant - OMIM# 135150
- Clinical
  - Fibrofolliculomas
  - Trichodiscomas
  - Acrocordons
  - Thyroid disease
  - Renal cell carcinoma
  - Systemic:
    - Lung cyst
    - Pneumothorax
  - Skin
    - Skin cysts
  - Ocular changes
  - Renal ultrasound

Multiple endocrine neoplasia-Type 1

- AD - Menin gene
- GI
  - Zollinger-Ellison syndrome
  - Endocrine:
    - Pancreatic islet cell adenoma
    - VIPoma; Gastrinoma
    - Parathyroid adenoma
    - Pituitary adenoma
    - Adrenocortical adenomas; Cushing syndrome
    - Pheochromocytoma, Acromegaly
- Endocrine:
  - Thyroid disease
  - Carcinoid tumors

Multiple endocrine neoplasia-type IIb

- AD - RET proto-oncogene mutations
  - 50% spontaneous
  - First lesions noted from birth to first years of life
- Mucocutaneous
  - Mucosal neuromas
    - Tongue and lips
    - Thickened lips - Often earliest finding
    - Marfanoid habitus
- Management
  - Endocrine
    - Thyroid:
      - Early thyroid resection? (first 6 months of life)
    - Ophthalmology
    - Gastroenterology
    - Dermatology
Carney complex

- AD - Mutations in the cAMP-dependent protein kinase, regulatory, type I, alpha gene (PRKAR1A)

- SKIN
  - Profuse pigmented skin lesions
  - Most common presenting feature
  - Increase at puberty
  - Nevi, Blue nevi
  - Ephelides
  - Centrifugal/mucosal lentigines
  - Red Hair
  - Myxoma – Cardiac
    - Skin; Breast; Oropharynx; Female genital tract

- Endocrine
  - Primary pigmented nodular adrenocortical disease (PPNAD)
    - Causes Cushing syndrome
    - Most frequent endocrine tumor
      - ~ 25% of patients
  - Large cell calcifying Sertoli cell tumors (LCCSCT)
    - 1/3 of affected males in first decade
      - Eventually almost all males
      - Multiple thyroid nodules
        - Up to 75% of patients
        - Most are thyroid follicular adenomas
      - Growth hormone-producing adenoma
        - Resulting in acromegaly
        - 10% of adults

- Other:
  - Mammary ductal fibroadenoma
  - Psammomatous melanotic schwannoma (PMS) - 50%
    - 1/3 of affected males in first decade
    - Eventually almost all males
  - Multiple thyroid nodules
    - Up to 75% of patients
    - Most are thyroid follicular adenomas
  - Growth hormone-producing adenoma
    - Resulting in acromegaly
    - 10% of adults
  - Pheochromocytoma

Dyskeratosis congenita

- XLR
  - AD and AR forms
  - Multisystem disorder of telomere maintenance
  - Reticulate skin pigmentation
  - Nail dystrophy
  - Leukoplakia
  - Hematologic abnormalities

- Malignancy
  - 10% of patients
    - Squamous cell carcinoma
    - Hodgkin’s disease; GI adenocarcinoma; bronchial or laryngeal carcinoma
    - Leukoplakia is premalignant

- Hematologic
  - Bone marrow failure
    - 50% of X-linked and AR patients develop marrow failure in 2nd decade
    - Panmyelopenia
      - Rare in AR forms
    - Infections
    - Respiratory
    - Main cause of death
  - No reported endocrine abnormalities

Hematological abnormality % of patients
Panmyelopenia 74.3%
Thrombocytopenia only 6.6%
Leukopenia only 2.6%
No-anemia 14.5%

Thank you for attending!
Please contact me should you have any questions.

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Schachner and Hansen; Pediatric Dermatology, 3rd edition