Clinical Manifestation, Disease Burden and Management of Gorlin Syndrome

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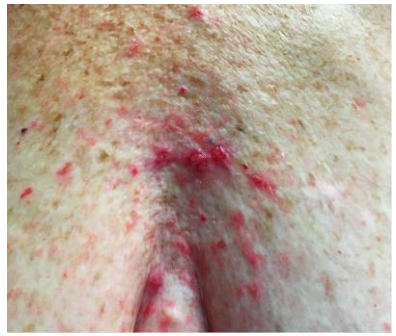
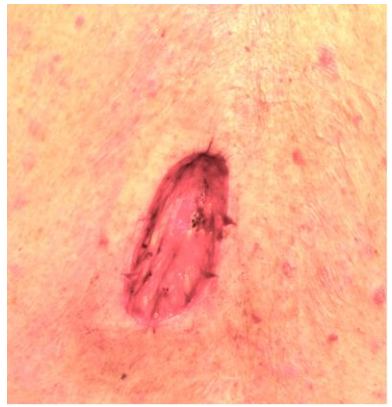
PI for GSA registry & Palvella Therapeutics sponsored clinical trial.

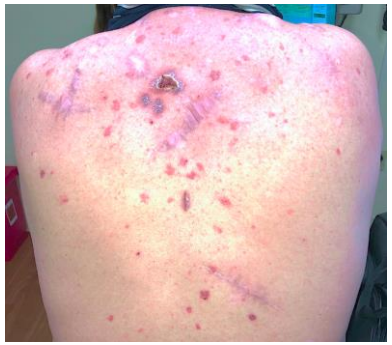
Gorlin Syndrome

-Urgent Unmet Medical Needs

- **Tremendous lifelong disease burden**





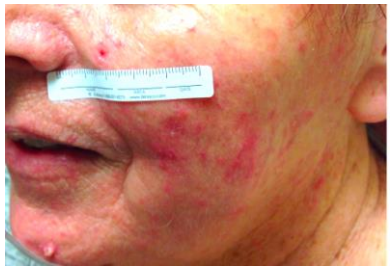


Cancer Development → Surgeries

Surgeries → Healing Recovery

Healing Recovery → Cancer Development

Pain, Scar, Disfigurement
Psychosocial impacts on work, family



Morbidity and Mortality

Need for safe & effective treatments

Background on Gorlin Syndrome

- AKA Basal Cell Nevus Syndrome (Omim) or Nevoid Basal Cell Carcinoma Syndrome (GeneReview)
- Initially described by Gorlin & Goltz in 1964

Epidemiology

- Minimum prevalence of GS is 1 per 57,000[1] to 1 per 30,827[2] (~6,000-10,000 in US)
- 1 in 200 patients with basal cell carcinomas had the syndrome, (more prevalent among pediatric patients with BCC)

1. Farndon, et al. **Location of gene for Gorlin syndrome.** Lancet 339: 581-582, 1992.
2. Evans DG, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A. 2010;152A:327–32.

Genetics and Diagnosis

- Autosomal Dominant mutation; 40% *de novo*
  - ***PTCH1* gene on chr 9q22**
  - *PTCH2* gene on chr 1p32
  - *SUFU* gene on chr 10q24-q25

Table 1 Gorlin syndrome diagnostic criteria[11]

Diagnosis of Gorlin syndrome is made in the presence of two major or one major and two minor criteria:

Major criteria

1. More than two BCC, or one in patients aged <20 years
2. Odontogenic keratocysts of the jaw on histology
3. Three or more palmar or plantar pits
4. Bilamellar calcification of the falx cerebri
5. Bifid, fused or markedly splayed ribs
6. First-degree relative with NBCC syndrome

Minor criteria

1. Macrocephaly determined after adjustment for height
2. Congenital malformations: cleft lip or palate, frontal bossing, "coarse face", moderate or severe hypertelorism
3. Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits
4. Radiological abnormalities: Bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defects of the hands and feet, or flame-shaped lucencies of the hands or feet
5. Ovarian fibroma
6. Medulloblastoma

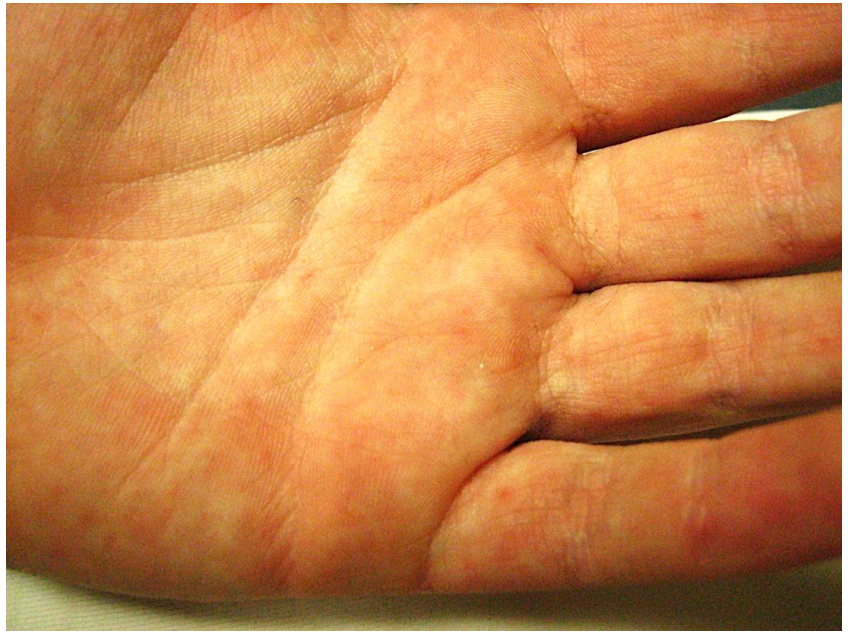
Major Criteria

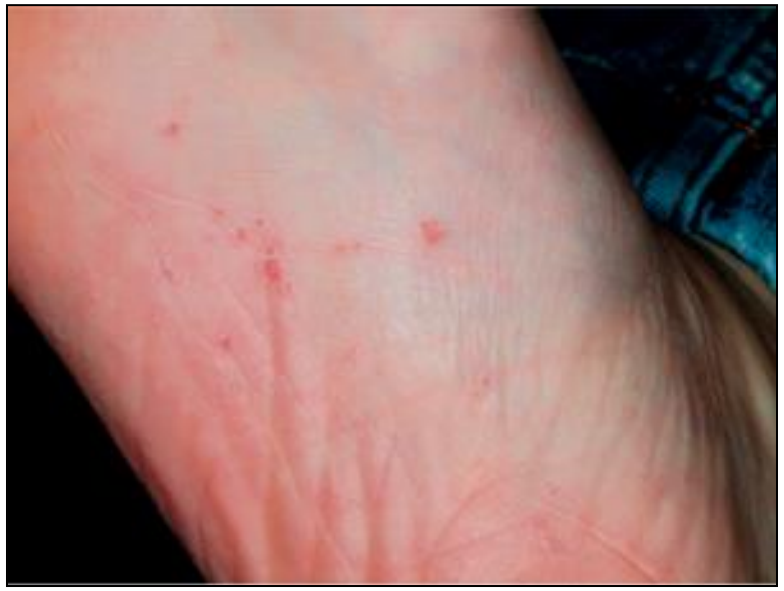
- **Lamellar (sheet-like) calcification of the falx**
- **Jaw keratocyst.** Odontogenic keratocyst
- **Palmar/plantar pits** (≥2); particularly useful in diagnosis and more pronounced when the hands and feet are soaked in warm water for up to ten minutes.
- **Multiple basal cell carcinomas (BCCs)** (>5 in a lifetime) or a BCC before age 30 years.
- **First-degree relative with NBCCS**

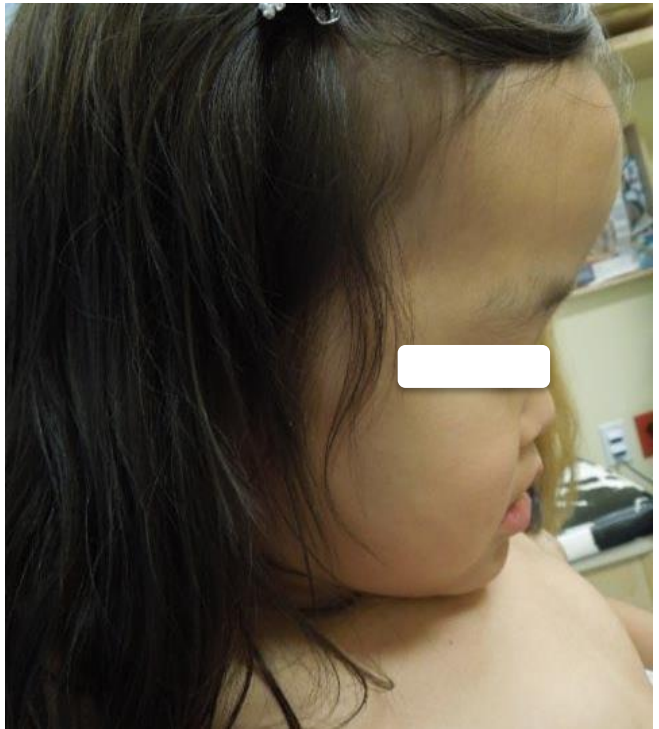
Minor Criteria

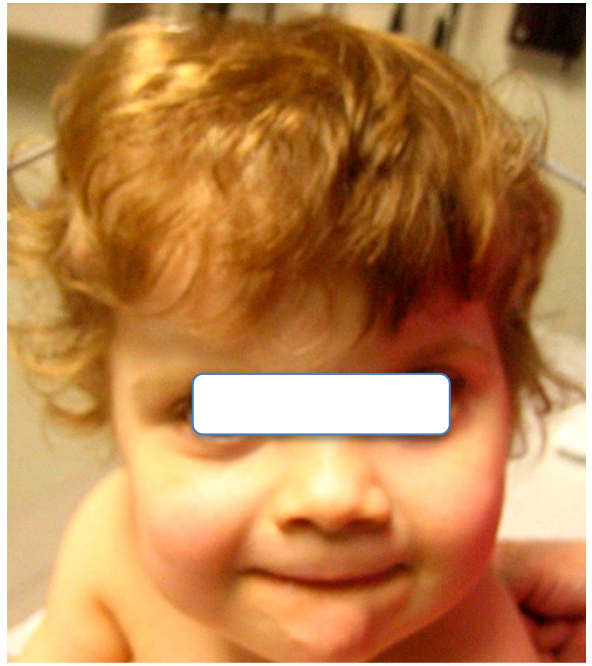
Lympho-mesenteric or pleural cysts
Macrocephaly (OFC >97th centile)
Cleft lip/palate
Vertebral/rib anomalies observed on chest x-ray and/or spinal x-ray (see **Notes regarding radiographs**): bifid/splayed/extra ribs; bifid vertebrae
Preaxial or postaxial polydactyly
Ovarian/cardiac fibromas
Ocular anomalies
Medulloblastoma

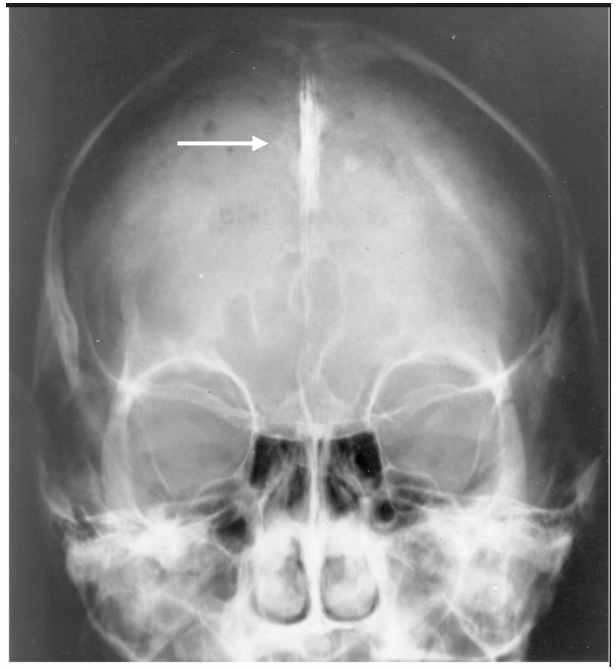
- 2 major + one minor diagnostic criterion or 1 major + three minor
- Identification of a heterozygous germline *PTCH1* or *SUFU* pathogenic variant on genetic testing

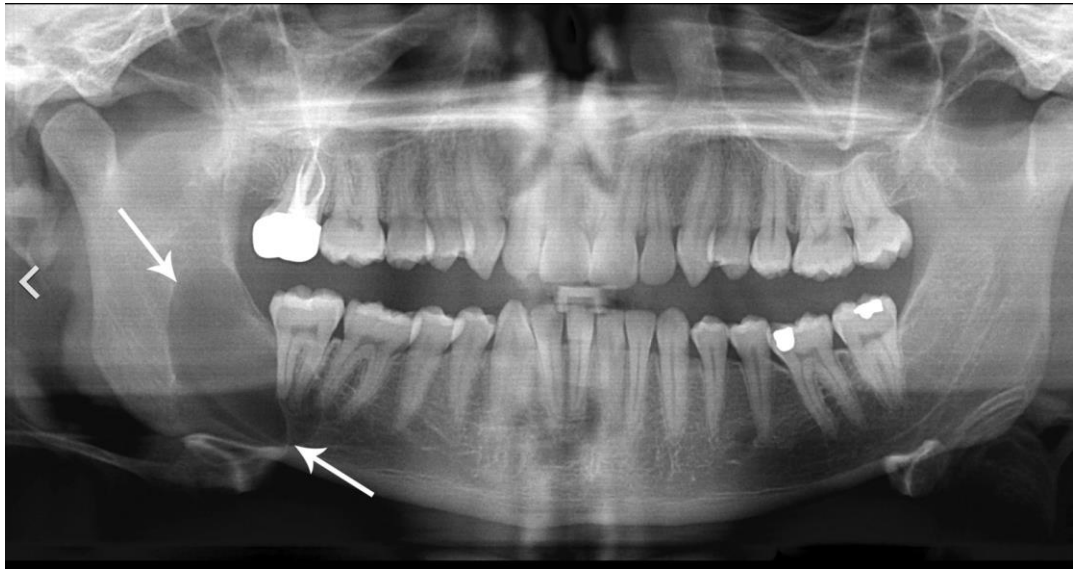


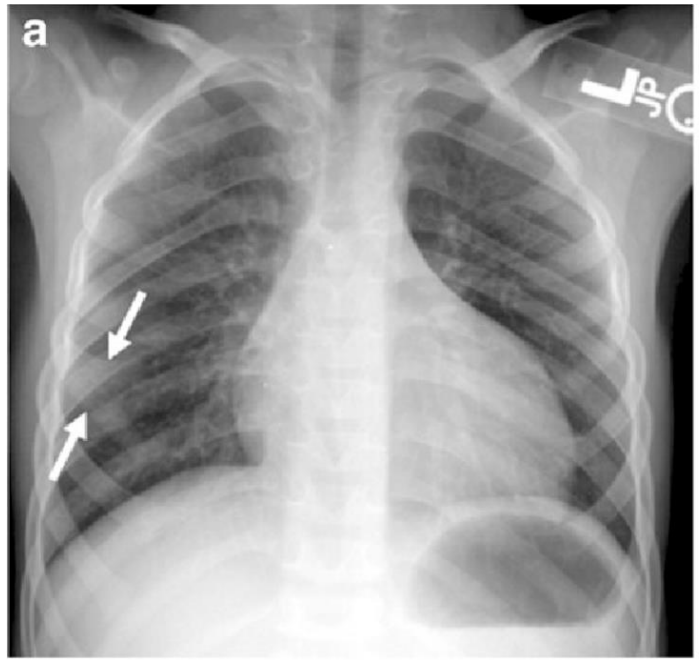








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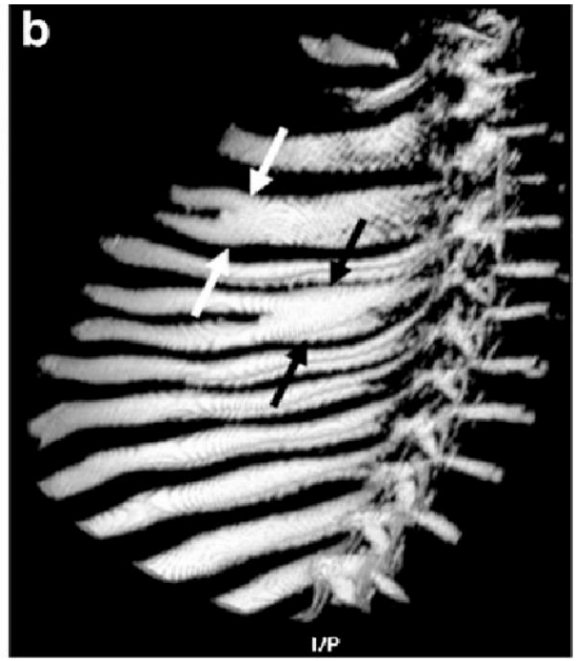
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2017

JAMA Dermatology | Brief Report

Risk Factors for Basal Cell Carcinoma Among Patients With Basal Cell Nevus Syndrome

Development of a Basal Cell Nevus Syndrome Patient Registry

Daniel C. Solis, BA; Gina P. Kwon, MD; Katherine J. Ransohoff, MD; Shufeng Li, MS; Harvind S. Chahal, BA; Mina S. Ally, MD; Marieke A. D. Peters, MD; Kristi Schmitt-Burr, BA; Joselyn Lindgren, MS; Irene Bailey-Healy, MLS; Joyce M. Teng, MD, PhD; Ervin H. Epstein Jr, MD; Jean Y. Tang, MD, PhD

Table. Frequency of Basal Cell Nevus Syndrome–Associated Characteristics in Our Registry Compared With Previous Studies

Characteristic	Evans et al,[9] 1993	Shanley et al,[10] 1994	Kimonis et al,[11] 1997	This Study
Country	United Kingdom	Australia	United States	United States
No. of cases	84	118	105	141
Age, mean (range), y	NR	35	34.5	53 (8-83)
Sex ratio, M:F	1:1.3	1:1.3	1:1.2	1:1.6
Age at first BCC, mean (range)	NR	20.3	21.4	18.2 (1-48)
Presence of jaw cysts, proportion (%)	46/70 (66)	85/113 (75)	78/105 (74)	57/141 (40)
Presence of any BCC, proportion (%)	33/70 (47)	90/118 (76)	71/90 (80)	135/141 (96)
Presence of pitting, proportion (%)	50/70 (71)	82/103 (80)	89/102 (87)	114/141 (81)
Medulloblastoma, proportion (%)	3/84 (4)	1/118 (1)	4/105 (4)	4/141 (2.8)
Ovarian fibromas, proportion (%)	6/25 (24)	9/63 (14)	9/52 (17)	31/85 (36)

Figure 1. Lifetime Basal Cell Carcinoma (BCC) Severity

Table 3 Clinical features in Japanese and Australian Gorlin syndrome patients[9,10]

≥50% in Japan	Japan (%)	Australia (%)	US
Keratocystic odontoid tumor	86.3	75	57/141 (40)
Falx calcification	79.4	92	
Palmar/plantar pits	69.2	80	114/141 (80)
Hypertelorism	68.8	6	
Broad nasal bridge	58.4	59	
15–49%			
Family history	48.4	NA	
Frontoparietal bossing	47.0	66	
Family members developing tumors	44.1	NA	
Highly arched eyebrows	44.0	NA	
Basal cell carcinoma	37.8	75	135/141 (90)
Rib anomalies	36.4	45	
Coarse face	27.9	NA	
Macrocephaly	26.5	80	
Prognathism	25.2	33	
Bridging of sella turcica	23.7	26	
Mental retardation	17.6	NA	
Hydrocephalus	16.2	NA	
Vertebral anomalies	15.1	35	
≤14%			
Ovarian fibroma	12.5	NA	31/58 (36)
Short 4th metacarpals	10.5	29	
Cleft lip/palate	9.0	4	
Epilepsy	9.0	NA	
Pectus deformity	6.1	23	
Medulloblastoma	3.3	NA	
Sprengel deformity	2.7	4	
Flame shaped lucencies of hands/feet	2.5	NA	
Cardiac fibroma	2.1	NA	
Syndactyly	2.1	NA	
Polydactyly	1.5	NA	
Modeling defects of hands/feet	0	NA	

NA, not available.

Early Diagnosis:

- Palmar/plantar pits, Craniofacial features, Radiologic manifestations

Pediatr Int. 2014 Oct;56(5):667-74.
JAMA Dermatol. 2017 Feb 1;153(2):189-192. Solis et al.
Genet. Med. 15: 79-83, 2013. Kimonis, et al.. **Clinical and radiological features in young individuals with nevoid basal cell carcinoma syndrome.**

Lifetime Disease Burden

Table 2 Tumor onset age in Gorlin syndrome

Tumor	Age of onset (mean)	Reference	
Cardiac fibroma	0–1 months	Evans *et al.*[8]	1993
Medulloblastoma	2–3 years	Evans *et al.*[8]	
Basal cell carcinoma	3–53 years (21.4 years)	Kimonis *et al.*[11]	1997
Keratocystic odontoid tumor	6–12 years (15.5 years)	Shanley *et al.*[9]	1994
Ovarian fibroma	16–45 years (30.6 years)	Kimonis *et al.*[11]	

The risk of developing **medulloblastoma** is substantially higher in individuals with an ***SUFU*** pathogenic variant (33%) than in those with a ***PTCH1*** pathogenic variant (<2%).

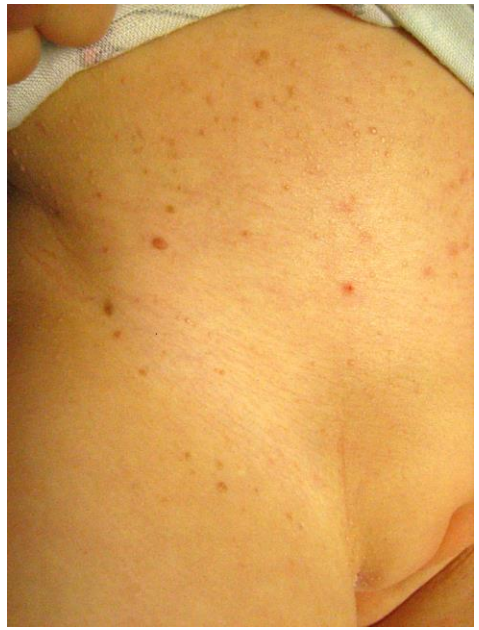
Peak incidence is at age 1-2 years.

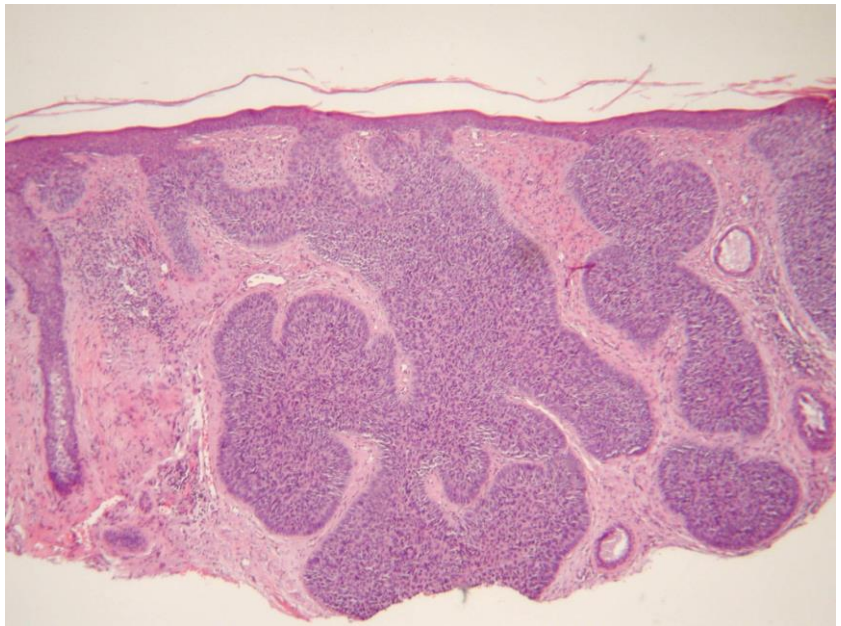
Gene review, 2018

Current Recommendations

- **Echocardiography** in the first year of life to evaluate for cardiac fibromas. Repeat if symptomatic.
- Baseline **brain MRI** to screen for medulloblastoma. Repeat yearly (or sooner) until 8 years old
- **Head circumference** should be followed throughout childhood to monitor for hydrocephalus
  Baseline **panorex of jaw** (digital if possible) as soon as tolerated. Repeat yearly until 1st jaw cyst. Then repeat every 6 mo until there are no jaw cysts x 2 yrs, or until age 21.
- Baseline **spine film** at 1-year-old or at the time of diagnosis (digital if possible). If abnormal, repeat per scoliosis protocol every 6 months.
- **Additional radiologic studies** if warranted, including chest X-ray for bifid ribs, PA and lateral skull for calcification of the falx, imaging of the long bones for bone cysts, and hand film.
- Annual **dermatologic examination** until first basal cell carcinoma. After 1st BCC, repeat every 6 months or more frequently as needed.
- Routine **developmental screening** with well child visits. If the child fails screening or is not meeting milestones, further developmental assessment and testing is warranted. If the child has difficulty learning in school, cognitive evaluation and testing is warranted.
- For females, **ultrasound examination of the ovaries** to evaluate for ovarian fibromas prior to pregnancy.
- **Ophthalmologic** evaluation for evidence of cataract, developmental defects, and pigmentary changes of the retinal epithelium. Repeat if symptomatic.

Gene review, 2018





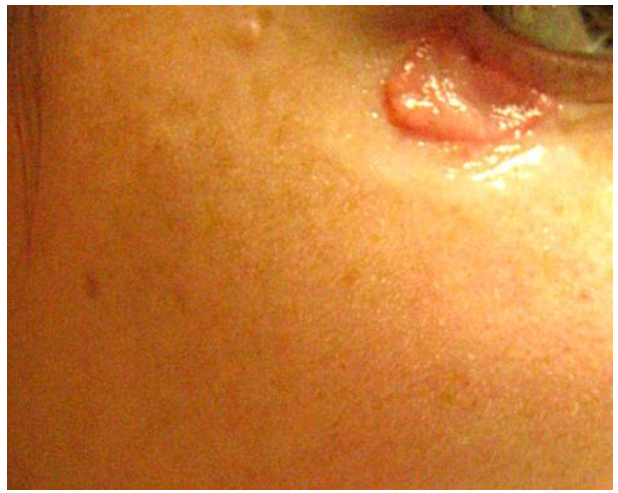
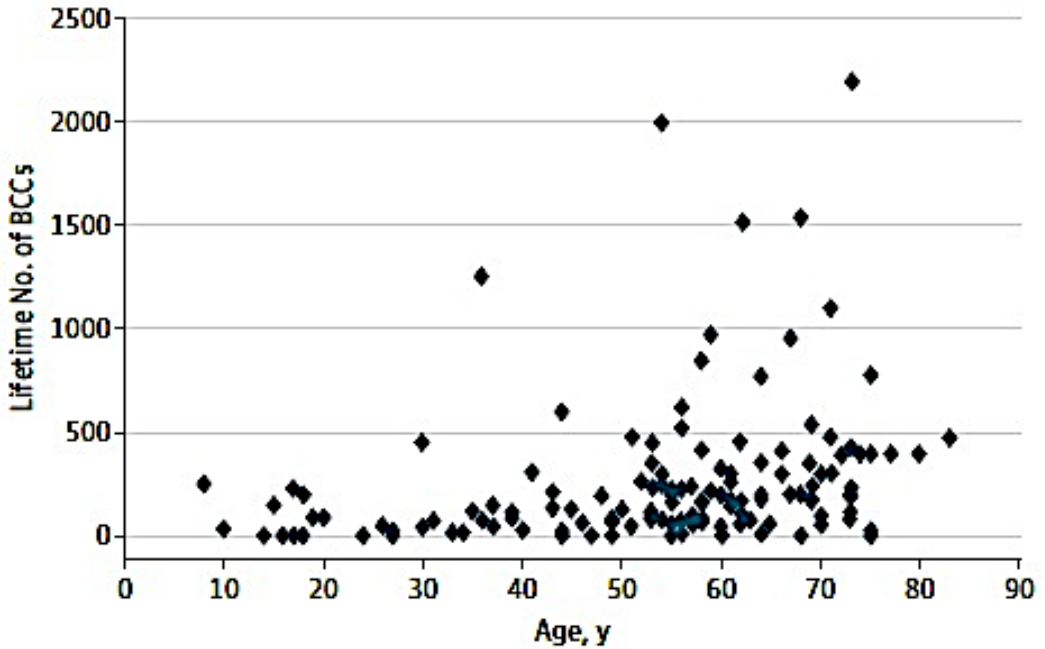


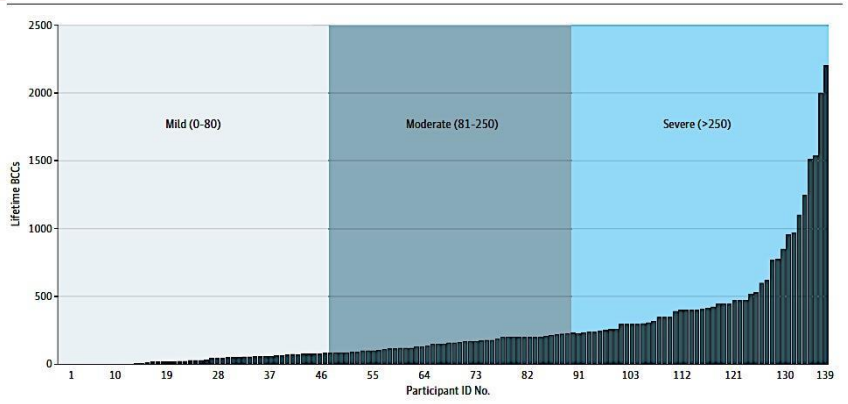
Figure 2. Number of Lifetime Basal Cell Carcinomas (BCCs) by Age



Scatterplot showing correlation between age and lifetime BCC number (Spearman correlation, 0.41). Symbols indicate individual patients.

JAMA Dermatol. 2017 Feb 1;153(2):189-192. Solis et al.

Skin Tumors (BCCs)
Previous 2 years: mean = 36 BCCs (median 16)
Moderate to severe disease of BCNS patients (> 10 new BCCs/past 2 years) = 70%
BCCs per lifetime: mean = 312 (median 226; range 30-2200) per subject
Surgical excisions per lifetime: mean = 202
Location BCCs: 93.5% of tumors were on **sun-exposed areas**
Advanced BCCs: 10%
Tried Vismodegib: 57% but 42% of that total discontinued because of side effects

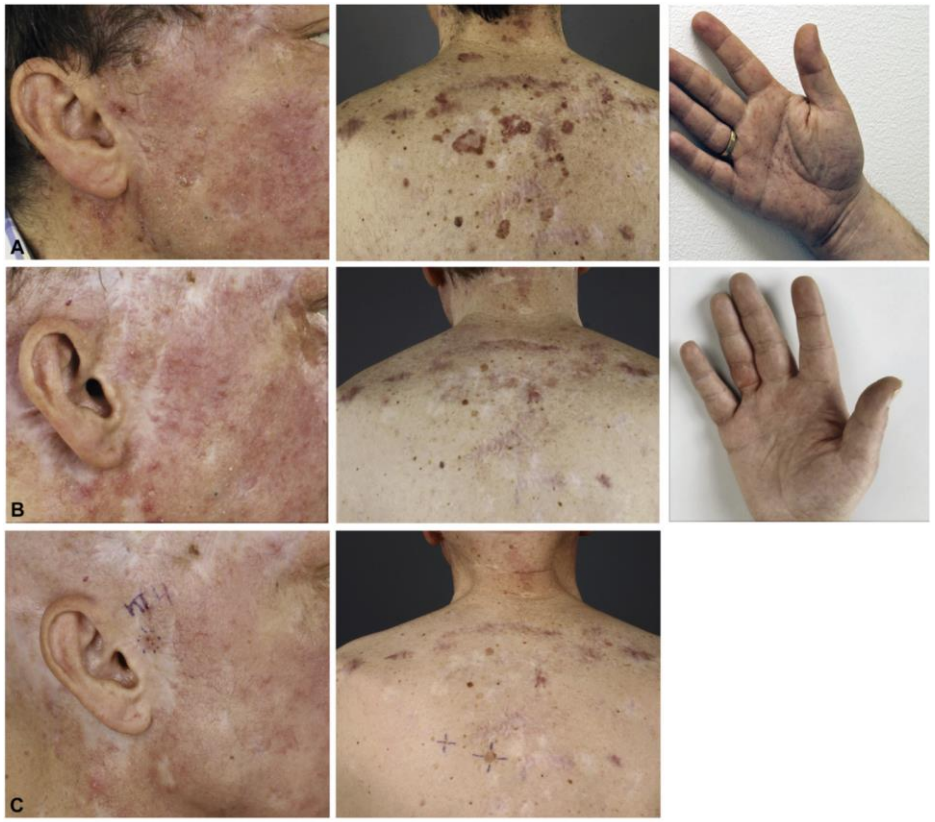


Histogram showing number of lifetime BCCs divided into tertiles to define relatively mild (0-80 BCCs), moderate (81-250 BCCs), and severe (>250 BCCs) BCC disease burden.

Treatment of BCC

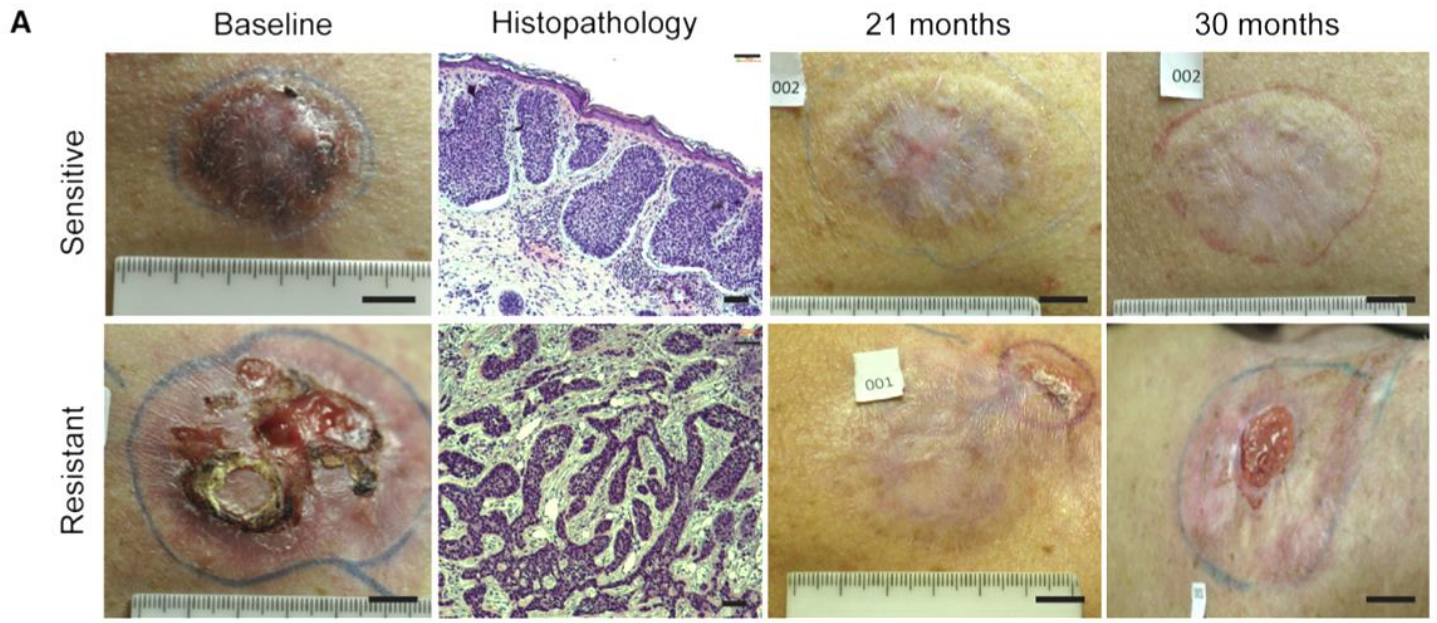
- **Surgical**
  - Cryo
  - Photodynamic
  - Electrodessication
  - Excision
  - Mohs micrographic surgery
- **Medical**
  - Retinoids (topical & systemic)
  - Imiquimod/5-FU/Itraconazole/Ingenol mebutate
  - Hedgehog inhibitors (vismotigib, sonidegib)

Response & Recurrence



Sinx et al. JAAD Case Reports. 2021 Vol 4. 408-411
Atwood et al. Cancer Cell. 2015;27(3):327-341

Response & Recurrence



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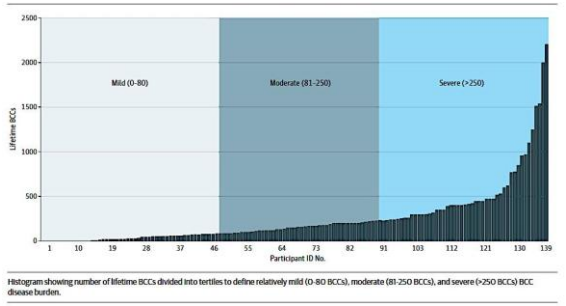
Knowledge Gap



Histogram showing number of lifetime BCCs divided into tertiles to define relatively mild (0-80 BCCs), moderate (81-250 BCCs), and severe (>250 BCCs) BCC disease burden.

Natural History

- What is the natural course of BCC and other extracutaneous disease manifestation?
- What are predictors of disease progression and poor outcomes?

Intervention & Treatment

- What is the safety and efficacy of a specific therapy?
- Does a treatment lead to long-term benefits, including delayed complications?
- How is disease progression affected by available therapies? What is the recurrence?

Care Delivery

- How do clinical practices vary, and what are the best predictors of treatment practices?
- What characteristics or practices enhance compliance and adherence?
- Do quality improvement programs affect patient outcomes, and, if so, how?
- What process/outcome metrics should be incorporated to track quality of patient care?

Access to care

- Should a particular procedure or product be a covered benefit?
- Was an intervention program or risk-management activity successful?
- What are the resources used/economic parameters of actual use in typical patients

Summary: Addressing GS Disease Burden & Meet Clinical Needs

Safe, Effective Therapies