

Official Topic from UpToDate®, the clinical decision support resource accessed by 700,000+ clinicians worldwide. Available via the web and mobile devices, subscribe to UpToDate® at [www.uptodate.com/store](http://www.uptodate.com/store).

## Nevoid basal cell carcinoma syndrome

### Authors

Benjamin Barankin, MD, FRCPC  
Gary Goldenberg, MD

### Section Editors

Robert S Stern, MD  
June K Robinson, MD

### Deputy Editor

Rosamaria Corona, MD, DSc

All topics are updated as new evidence becomes available and our peer review process is complete.

**Literature review current through:** Jul 2014. | **This topic last updated:** May 28, 2014.

**INTRODUCTION** — Nevoid basal cell carcinoma syndrome (NBCCS) is a rare inherited multisystem disorder that is due to germline mutations in the human homolog of the patched (*PTCH*) gene. The estimated prevalence is between 1 in 57,000 and 1 in 164,000 persons [1-3].

First reported in 1894, the clinical manifestations of NBCCS were more clearly defined in 1960 by Gorlin and Goltz [4]. Affected patients have multiple developmental anomalies and the early onset of multiple nevoid basal cell carcinomas (BCCs) and medulloblastomas, usually by age 35 [5]. Other synonyms for NBCCS include the Gorlin or Gorlin-Goltz syndrome, basal cell nevus syndrome, bifid-rib basal-cell nevus syndrome, basal cell cancer syndrome, and multiple basal cell nevi.

**MOLECULAR GENETICS** — Nevoid basal cell carcinoma syndrome (NBCCS) is inherited as an autosomal dominant trait with a high degree of penetrance (approximately 97 percent), but variably expressed [6]. The cause is a germline inactivating mutation involving the human homolog of the *Drosophila PTCH1* (patched) gene, which is located on chromosome 9q22.3 [2,7-10]. In most cases, loss of function mutations in *PTCH1* result in premature termination of the PTCH protein [11-14]. Loss of heterozygosity at this site in both hereditary and sporadic basal cell carcinomas (BCCs) suggests that it functions as a tumor suppressor gene (see 'PTCH1 in sporadic basal cell carcinomas' below) [15]. In a manner similar to the retinoblastoma gene, two somatic "hits" in the same cell appear to be required for sporadic cases, while one somatic "hit" plus the inheritance of one defective allele underlies familial cases [16]. (See "Overview of retinoblastoma", section on 'Pathogenesis'.)

**Molecular pathogenesis** — The only known function of the PTCH protein is as a receptor for the hedgehog (HH) protein, a component of the sonic hedgehog (SHH) signaling pathway (figure 1).

This pathway is important in determining tissue patterning and cell fate in multiple structures within the developing embryo [17,18]. SHH signaling is activated when HH binds to its receptor, a complex that is formed by PTCH and a second protein, Smoothed (SMO), a transmembrane protein (figure 2) [19-23]. PTCH functions as a regulatory molecule for SMO, with PTCH-induced repression of SMO limiting the effect of the SHH signal [20,23].

According to this model, SMO repression is relieved following mutational inactivation of *PTCH1* in patients with NBCCS [24]. This results in constitutive overexpression of the SHH signal, which has been implicated in the development of BCC and other tumors, possibly via activation of the transcription factors Gli1 and/or Gli2 (figure 1) [18,20,25-28]. The evidence to support a link between overexpression of the SHH pathway and tumorigenesis is as follows:

- Transgenic mice overexpressing SMO or SHH in the skin spontaneously produce skin lesions resembling human BCCs [24,29].
- Owing to failure of negative feedback, the mutant *PTCH1* transcript is overexpressed in affected tissues. Such transcripts are found at high levels in the BCCs and odontogenic keratocysts from patients with NBCCS, but not in skin or other types of tumors [30-32].

**Influence of race** — Race appears to influence the incidence of NBCCS and also modulates its penetrance. Only about 5 percent of all NBCCS case reports involve blacks [33], and a similar low frequency is reported in Asians [34].

The expression of cutaneous BCCs as a component of the NBCCS appears to be blunted in individuals with dark skin as well as Asians [34,35]. Only about 30 to 38 percent of black persons with NBCCS have BCCs (compared to 75 to 80 percent in Caucasians, (see 'Clinical findings' below)), and fewer than 15 percent have more than two BCCs [36]. Because of this, most black patients with NBCCS are diagnosed by asymptomatic odontogenic cysts discovered during routine dental or facial radiography rather than by the appearance of BCCs [37].

**PTCH1 in sporadic basal cell carcinomas** — Support for the involvement of *PTCH1* in tumorigenesis is supported by the finding of acquired *PTCH1* mutations in approximately one-third of sporadic BCCs [38,39], in xeroderma pigmentosum-associated BCCs [40], as well as some sporadic meningiomas and medulloblastomas. In sporadic BCCs, inactivation of the *PTCH1* gene appears to be a necessary but insufficient step for tumor formation. (See "Epidemiology and clinical features of basal cell carcinoma" and "Histopathology and molecular pathogenesis of medulloblastoma" and "The genodermatoses", section on 'Xeroderma pigmentosum'.)

The mechanism responsible for *PTCH* mutations in sporadic BCCs is probably multifactorial. Exposure to ultraviolet (UV) light is an important risk factor for early onset BCCs, and the *PTCH* gene appears to be a target for UV-induced mutations. However, typical UV signature mutations are found in only 30 to 40 percent of *PTCH1*-mutated sporadic BCCs [14], while they are more prominent in the BCCs of patients with xeroderma pigmentosum [40]. Thus, mutational events other than UV irradiation may also cause *PTCH* inactivation and trigger tumorigenesis [40].

Other mutational events affecting the SHH pathway have also been implicated in the development of sporadic BCCs. These include activating mutations in the *SMO* gene, a reciprocal translocation between chromosomes 9q22.3 (the site of the *PTCH1* gene) and 16p, and mutations in a second *PTCH* gene, *PTCH2* [24,41-43].

**CLINICAL FINDINGS** — More than 100 clinical abnormalities have been reported in nevoid basal cell carcinoma syndrome (NBCCS). The major manifestations are [44-46]:

- Early development of multiple basal cell carcinomas (BCCs)
- Odontogenic (bone) keratocysts, especially in the mandible
- Palmar and plantar pitting (picture 1)
- Ectopic intracranial calcification, most often of the falx cerebri [47]
- Family history of NBCCS

Minor criteria include [46]:

- Craniofacial anomalies (macrocephaly, frontal bossing, hypertelorism)
- Bifid ribs
- Early onset medulloblastomas (3 to 5 percent)
- Cardiac or ovarian fibromas, often bilateral
- Lymphomesenteric cysts
- Congenital malformations (cleft lip/palate, polydactyly, eye abnormalities, colobomas, cataracts, glaucoma)

The frequency of the major clinical findings (BCCs, jaw cysts, macrocephaly, palmoplantar pits) is between 75 and 80 percent [3,45]. Although medulloblastomas (which are characteristically of the desmoplastic subtype) tend to develop at a young age, many of the classic features of NBCCS (ie, BCCs, palmar pits, calcified falx cerebri) may not be detected until the late teens or young adulthood [3]. (See "Histopathology and molecular pathogenesis of medulloblastoma".)

**Basal cell carcinomas** — BCCs are found in about three-fourths of all affected Caucasian patients with NBCCS, but are less frequent in affected blacks and Asians (see 'Influence of race' above). Age at first diagnosis ranges from 3 to 53 years old with an average age of 20 to 21 [36].

The number of BCCs can vary from only a few to thousands, and they range in size from 1 to 10 mm [48]. While BCCs frequently occur on sun-exposed areas such as the head, neck, back, chest, and upper limbs, they can occur in any location [3,49]. BCCs arising in NBCCS are histologically indistinguishable from sporadic BCCs. The term "nevoid" does not refer to an association of the BCC with nevi, but instead was coined because early lesions may have the appearance of nevi with a prominent vascular component.

BCCs tend to be more aggressive in patients with NBCCS. Despite this, only a small fraction become locally invasive, and they do so only after puberty [48]. Rarely, patients with NBCCS die as a result of local invasion into brain or lung, or distant metastatic spread [50].

### **Risk factors**

- Sun exposure — Sun exposure is the most important environmental cause of BCC in the general population. However, the relationship between sun exposure and the development of BCCs in patients with NBCCS is unclear. The anatomic site distribution of BCCs suggests that frequent sun exposure may not be essential for the development of BCCs in affected patients. However, the observation that there are more tumors on sun-exposed areas suggests that exposure promotes the development of BCCs in patients with NBCCS [51]. (See "Epidemiology and clinical features of basal cell carcinoma", section on 'Risk factors'.)
- Radiation therapy — Superficial therapeutic radiation, as for psoriasis, increases the risk of nonmelanoma skin cancers, including BCC (see "Epidemiology and clinical

features of basal cell carcinoma", section on 'Risk factors'). Patients with NBCCS are particularly sensitive to the effects of ionizing radiation, and the development of multiple BCCs within irradiated fields in affected patients is well described [49,52-55]. DNA synthesis is abnormally induced in irradiated NBCCS cells, and this abnormality may supply the subsequent mutation necessary for tumor development in NBCCS patients who have been exposed to ionizing radiation [56,57]. Because of this, radiation therapy is generally avoided in patients with NBCCS. (See "Treatment of basal cell carcinomas at high risk for recurrence", section on 'Radiation therapy'.)

**Odontogenic (jaw) keratocysts** — Odontogenic keratocysts are cystic lesions of the bone that are lined with keratinized epithelium and thought to originate from the dental lamina. Despite their bland histology, these lesions are locally destructive with heparanase expression, perhaps correlated with the neoplastic properties of NBCCS-associated odontogenic keratocysts [58]. They are neoplastic rather than developmental in origin [59] and are characterized by aggressive clinical behavior, including involvement of the teeth and a recurrence rate that is as high as 60 percent [60].

Recurrence can result from incomplete removal, remnants of dental lamina within the jaw, or the presence of satellite cysts. NBCCS keratocysts have a different immunophenotype from sporadic keratocysts [61]. A 10-year retrospective analysis of 83 patients with odontogenic keratocysts identified six patients (8 percent) with a total of 15 lesions who had NBCCS [62].

The cysts usually develop after the age of seven and peak during the second or third decades [44,48], but they have been reported in children as young as four [36]. The number of jaw cysts averages six (reported range, 1 to 28) [3,36], unlike with sporadic cases where they are typically solitary. Unlike BCCs, there is no racial predilection [33].

Three-fourths of odontogenic keratocysts present in the mandible [36,63]. The most common locations in decreasing frequency are the mandibular third molar region, maxillary third molar region, and mandibular first and second molar region [64]. Approximately one-third are asymptomatic and are detected on routine dental examination, while 50 percent present with jaw swelling, 25 percent with mild pain, and 15 percent with altered taste [65].

Treatment is discussed below. (See 'Odontogenic keratocysts' below.).

**Palmar-plantar pits** — Palmar and/or plantar pits are highly characteristic of NBCCS, occurring in approximately 80 percent of affected individuals [36,66]. They are asymptomatic nonpalpable shallow depressions (1 to 3 mm) in the skin of the palm and/or soles that are due to partial or complete absence of stratum corneum (figure 1). They may also be found on the sides, web spaces, and dorsum of the fingers and toes [67]. The differential diagnosis should consider punctate keratoderma, pitted keratolysis, and palmar pits of Darier's disease, but the clinical distinction is usually easy.

Pitting generally develops during the patient's 20s and later, but has been reported in much younger patients [49]. In contrast to BCC, there is no racial difference in the frequency of pitting in affected patients with NBCCS [33]. The number of pits is variable but can reach more than 500 in number, particularly in older individuals [67]. They are permanent, and do not wax and wane over time. Soaking the hands in water for 10 to 15 minutes can make their appearance more pronounced [3].

**Brain tumors** — Medulloblastomas characteristically arise in the midline in the area of the cerebellar vermis. Meningiomas are the next most common brain tumors developing in patients with NBCCS, although they are much less common than medulloblastoma [48,68]. Other tumors and cysts involving the brain have also been reported [48]. (See "Meningioma: Clinical presentation and diagnosis".)

The incidence of medulloblastoma in patients with NBCCS is 5 percent or less, and there is a male predominance of 3:1 [69,70]. In contrast to sporadic medulloblastomas, which most commonly present between the ages of 6 and 10, medulloblastomas characteristically present by age two in individuals with NBCCS. This syndrome should be considered in any atypically young child with medulloblastoma [48]. (See "Histopathology and molecular pathogenesis of medulloblastoma".)

**Myogenic tumors** — Tumors with myogenic differentiation, including fetal rhabdomyoma and rhabdomyosarcoma (RMS), have been reported in a small number of patients with NBCCS [71]. Fetal rhabdomyomas typically arise in children and younger adults, predominantly in the head and neck region, do not metastasize, and are cured by surgical resection alone [72]. RMS is the most common soft tissue sarcoma of childhood and adolescence. It can occur anywhere in the body, but the most common primary sites are the head and neck region and the genitourinary tract [73]. The tumor is locally invasive with high propensity for distant metastasis to lung, bone marrow, and bone. (See "Rhabdomyosarcoma in childhood and adolescence: Clinical presentation, diagnostic evaluation, and staging" and "Rhabdomyosarcoma and undifferentiated sarcoma in childhood and adolescence: Treatment".)

**Intracranial ectopic calcification** — Approximately 65 percent of affected persons have calcification of the falx cerebri, but this increases to 80 to 90 percent of those over the age of 40 [36,47]. Other areas of ectopic calcification include the diaphragma sellae in 60 to 80 percent (with complete or partial bridging of the sella turcica), the tentorium cerebelli in 40 percent, and the petroclinoid ligament in 20 percent [74].

**Characteristic facies and body habitus** — Many patients with NBCCS have a characteristic "coarse" facial appearance consisting of frontal bossing, macrocephaly (80 percent), hypertelorism (5 percent), high arched eyebrows (40 percent) and palate, widened nasal bridge (60 percent), and mandibular prognathism (35 percent) [3,5,36,48,75]. In 50 to 60 percent of affected individuals, there are milia scattered on the face among the BCCs. Approximately 15 percent of patients are very tall [75].

**Cardiac fibromas** — Cardiac fibromas are increased in frequency in patients with NBCCS, developing in approximately 3 percent of affected individuals [46]. These are benign growths, and almost all develop within the ventricular myocardium. Although usually asymptomatic, cardiac fibromas can result in impaired left ventricular function and conduction defects, necessitating resection [76,77]. (See "Cardiac tumors".)

**Ovarian fibromas** — Ovarian fibromas develop in 15 to 25 percent of girls with NBCCS, and are often calcified and bilateral [3,36,46,78]. Other ovarian tumors including fibrosarcomas are rarely reported [79]. (See "Sex cord-stromal tumors of the ovary: Granulosa-stromal cell tumors", section on 'Fibroma'.)

**Bone abnormalities** — Occult skeletal abnormalities are frequent in patients with NBCCS. Between 38 to 60 percent have rib abnormalities including bifid ribs, marked widening of the anterior rib ends, and fusion and modeling defects of the ribs [36,48,80]. Occult spina bifida may be seen as a component of NBCCS [80], although it has not been documented in all series [36].

**Mesenteric cysts** — Single or multiple lymphomesenteric cysts may be seen as a component of NBCCS [78]. They tend to calcify and are usually asymptomatic.

**Skin tags** — The presence of skin tags in a child may be a clue as to the diagnosis of NBCCS [81]. Biopsy should be considered within the clinical context.

**Other anomalies** — Among the reported ocular anomalies in patients with NBCCS are congenital cataracts, colobomas (involving the choroids and optic nerve), nystagmus, strabismus, hypertelorism, and telecanthus (10 to 25 percent) [36,46,48]. Cleft palate is seen in approximately 5 percent of affected individuals.

Both pectus deformities and Sprengel deformity (narrow sloping shoulders) are more common in individuals with NBCCS [3,36] (see "Diseases of the chest wall"). Approximately 10 percent of patients have anosmia, which may be a sign of hypogonadotropic hypogonadism; other hypogonadal features include cryptorchidism, gynecomastia, and scanty facial or body hair [3,82].

Minor kidney abnormalities, often diagnosed incidentally or at autopsy, are seen in about 5 percent of patients with NBCCS [48]. Scattered case reports indicate the occasional association of other neoplasms with NBCCS including fetal rhabdomyoma [78,83], non-Hodgkin lymphoma, Hodgkin lymphoma, melanoma, chronic lymphoid leukemia, soft tissue leiomyosarcoma, breast and lung carcinoma, and sinonasal undifferentiated carcinoma (SNUC) [84].

**DIAGNOSIS** — The diagnosis of nevoid basal cell carcinoma syndrome (NBCCS) is a clinical one with the diagnosis being supported by finding either two major, or one major and two minor, criteria [46]. However, molecular findings (eg, high level of expression of PTCH1 transcripts on odontogenic keratocysts by reverse transcriptase polymerase chain reaction [RT-PCR]) can be used to support the diagnosis in questionable cases [30,31].

**DIAGNOSTIC WORKUP** — At a minimum, the following studies are indicated in patients suspected of having nevoid basal cell carcinoma syndrome (NBCCS):

- Skull radiograph or CT can demonstrate a calcified falx cerebri, complete or partial bridging of the sella turcica, or a broadened nasal root.
- Panoramic films are recommended to identify odontogenic keratocysts; MRI may be superior in demonstrating the internal composition and structure of the cysts [85].
- Chest x-ray to document rib abnormalities (eg, bifid ribs).
- Hand and foot x-rays will show flame-shaped lucencies (lytic bone lesions) in 30 percent of hand films and 17 percent of foot films [36].

Skin biopsy of a basal cell carcinoma will show nodules and/or strands of atypical basaloid cells which show nuclear palisading, cellular apoptosis, and scattered mitotic activity in the dermis (picture 2A-B). Artifactual cleft formation may be seen between the tumor lobules and the surrounding stroma, which may be mucinous. Solar elastosis is usually present in the dermis.

**MANAGEMENT** — Pertinent issues in the management of affected patients include surveillance for the development of syndrome-related complications, and specific treatment for postnatal tumors and odontogenic keratocysts. Most other abnormalities are either cosmetic, incidental, or managed as in patients without this syndrome.

**Surveillance** — For individuals diagnosed with nevoid basal cell carcinoma syndrome (NBCCS), regular visits to a dermatologist every two to three months is recommended, particularly during adolescence. Annual panoramic radiographs of the jaw are

recommended starting at the age of eight, and a cranial MRI to exclude medulloblastoma should be performed annually until the age of eight. Periodically, echocardiography to exclude cardiac fibroma should be performed.

For infants with a family history of NBCCS, early diagnosis may be achieved with the use of screening radiography to look for calcification of the falx, rib anomalies, or calcified ovarian fibromas [3]. Affected patients should be counseled to minimize exposure to ultraviolet light and avoid therapeutic ionizing irradiation (eg, MRI is preferred over CT), if at all possible [52].

**Treatment of basal cell carcinomas** — Because of the large number of lesions, treatment of basal cell carcinomas (BCCs) in these patients may be extremely difficult. Lesions that are growing or that become invasive should be excised, or curetted and electrodesiccated. More aggressive tumors or those in delicate or high-risk areas benefit from Mohs' micrographic surgery. (See "Treatment and prognosis of basal cell carcinoma" and "Treatment of basal cell carcinomas at high risk for recurrence".)

Multiple surgical procedures are often a source of discomfort, pain, and disfigurement for patients with NBCCS. Carbon dioxide laser therapy can be a useful modality in selected patients for tumors in low-risk areas and has shown efficacy in combination with microscopically controlled excision (Mohs micrographic surgery) [86-90].

**Topical tretinoin and 5-FU** — Although most of the BCCs are nodular, superficial lesions can be managed by topical application of 5 percent 5-fluorouracil (5-FU) with or without 0.1% tretinoin cream (to enhance penetration of 5-FU) applied twice daily [78]. Tretinoin should be avoided around the eyes.

**Topical imiquimod** — Case reports are also emerging that suggest a possible role for imiquimod cream as a less-invasive approach to managing and perhaps preventing development of new BCCs in patients with NBCCS. In several reports, imiquimod 5% cream applied three days per week has shown considerable efficacy for superficial BCCs in affected patients [91-95]. In one report, 13 of 17 superficial BCCs were successfully controlled (at least in the short run) after 8 to 14 weeks of three times weekly application [93]. The most common side effect of topical imiquimod is local erythema [96]. (See "Treatment and prognosis of basal cell carcinoma", section on 'Imiquimod'.)

However, the majority of BCCs are nodular in patients with NBCCS. Imiquimod is less successful for nodular BCCs [91], although it may be useful in conjunction with curettage [97].

**Other therapies** — There is increasing experience with photodynamic therapy (PDT) in patients with NBCCS [98]. As with sporadic BCCs, PDT appears most successful for flat lesions, rather than those that are raised or nodular [90]. (See "Treatment and prognosis of basal cell carcinoma", section on 'Photodynamic therapy'.)

**Chemoprevention with oral retinoids** — Oral retinoids are not useful therapeutically; few lesions objectively regress [99,100]. They are used more often for chemoprevention rather than treatment of existing BCCs. However, large trials of systemic retinoids as chemopreventive agents have not been conducted in patients with NBCCS. At least one report suggests that low dose isotretinoin (10 mg daily) is ineffective in preventing additional BCCs in patients who have had two or more sporadic BCCs [101]. Because of the need for moderate to high doses and the limited degree of benefit, oral retinoids are seldom to uncommonly used.

**Locally advanced and metastatic BCCs** — Vismodegib, an agent targeting the sonic hedgehog pathway, offers a new approach for patients with metastatic disease or no longer amenable to local therapy [102]. This approach is discussed separately. (See "Systemic treatment of advanced cutaneous squamous and basal cell carcinomas", section on 'Vismodegib'.)

**Odontogenic keratocysts** — As noted previously, odontogenic cysts frequently recur following surgery. The treatment of choice is wide surgical excision and curettage with extraction of associated teeth by an experienced oral-maxillofacial surgeon or otolaryngologist [3,48]. Bone and alveolar nerve grafting may be required in some instances. A 10-year retrospective review of 83 cases of odontogenic keratocysts suggests that marsupialization followed by enucleation results in the lowest recurrence rate [62]. Histopathologic examination of tissue is important because several cases of malignant transformation to squamous cell carcinoma have been reported [103-105].

Reduction in size or resolution of odontogenic keratocysts has been reported in some patients treated with vismodegib, an oral inhibitor of the hedgehog pathway that has been used for the treatment of BCC in patients with NBCCS [106]. (See 'Future directions' below and "Systemic treatment of advanced cutaneous squamous and basal cell carcinomas", section on 'Vismodegib'.)

A series of six patients with nine odontogenic keratocysts for whom baseline magnetic resonance imaging (MRI) was available were treated with vismodegib 150 mg per day for 11 to 24 months [107]. Posttreatment MRI showed a 50 percent reduction of the longest diameter of keratocysts in four of six patients. In one patient with complete resolution of one lesion, there was no recurrence nine months after drug cessation. All patients experienced mild to moderate adverse effects of taste loss, muscle cramps, and hair loss; three patients required a brief drug break.

However, additional studies are necessary to determine the role, long-term efficacy, and maintenance regimen of vismodegib for the treatment of odontogenic keratocysts. (See 'Future directions' below and "Systemic treatment of advanced cutaneous squamous and basal cell carcinomas", section on 'Vismodegib'.)

**Medulloblastomas** — In patients with NBCCS, radiation therapy for medulloblastomas induces hundreds of difficult to manage BCCs; it should be avoided. Often these BCCs are preceded by a "rash" from 6 to 36 months following radiation which represents activated BCCs. A sinonasal tumor developing 17 years after initial irradiation of a medulloblastoma has been reported [108]. Medulloblastomas may also be treated by surgery and chemotherapy. (See "Clinical presentation, diagnosis, and risk stratification of medulloblastoma".)

**Vitamin D deficiency** — Synthesis of vitamin D in the skin is inhibited by photoprotective measures, and patients with photosensitive disorders such as NBCCS may have an increased risk for vitamin D deficiency. In a retrospective cohort study of 41 patients with NBCCS, the prevalence of vitamin D deficiency (25[OH]D level  $\leq$ 20 ng/mL) was significantly greater than the prevalence reported in the general population (56 versus 18 percent) [109]. Thus, clinicians should be aware of the potential for vitamin D deficiency in patients with NBCCS. (See "Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment" and "Vitamin D and extraskeletal health".)

Additional studies are necessary to evaluate whether disease-specific factors other than photoprotection contribute to vitamin D deficiency in NBCCS.

**Future directions** — A placebo-controlled randomized trial found that vismodegib, an oral hedgehog antagonist approved for the treatment of locally advanced or metastatic



BCC, was beneficial for slowing the rate of BCC development and reducing tumor burden in NBCCS [110]. In the trial, patients with NBCCS were treated with either 150 mg per day of vismodegib (n = 26) or placebo (n = 15) for 1 to 15 months (mean, 8 months). At three months, a significantly lower mean per-patient incidence of new, surgically eligible BCCs (diameter >3 mm on nose or periorbital skin, >5 mm on other facial sites, or >9 mm on the trunk or limbs) was detected in the active treatment group than in the placebo group (2 versus 29 BCCs per year). In addition, tumor size decreased to a greater extent in patients who received vismodegib than in those who received placebo, with a few patients achieving complete remission.

Although these findings are promising, adverse effects, such as loss of taste, muscle cramps, hair loss, and weight loss limited the use of vismodegib; 14 of 26 patients (54 percent) discontinued treatment for this reason. In addition, tumors regrew following drug discontinuation. More studies are required to determine whether vismodegib has the potential to truly cure individual BCCs in NBCCS, as well as to clarify the optimal treatment regimen for vismodegib in this setting. (See "Systemic treatment of advanced cutaneous squamous and basal cell carcinomas", section on 'Vismodegib'.)

Some patients with tumors that appear to respond well to vismodegib eventually experience regrowth of tumors despite continued therapy [111,112]. In a series of 28 patients with a total of 230 advanced and nonadvanced BCCs (including five patients with NBCCS), tumor regrowth during treatment was detected in six patients (21 percent) and affected 5 percent of all tumors [111]. The mean time to tumor regrowth was 56 weeks. The reason for this occurrence is unknown.

The topical administration of an inhibitor of the hedgehog pathway may be a future option for the management of patients with NBCCS. In a randomized trial in which 27 BCCs in eight patients with NBCCS were treated with a topical inhibitor of Smoothed or a placebo agent twice daily for four weeks, complete or partial responses were observed in 12 out of 13 lesions treated with the Smoothed inhibitor compared with 1 out of 14 lesions treated with the placebo agent [113]. The effect of this treatment on BCCs in patients without NBCCS is unknown.

## SUMMARY

- Nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant, multisystem disorder, due to mutations in the PTCH1 tumor suppressor gene. (See 'Molecular genetics' above.)
- The primary manifestation of NBCCS is the development of multiple basal cell carcinomas (BCCs), which are histologically identical to sporadic BCCs. While BCCs frequently occur on sun-exposed areas, they can occur in any location and tend to be more aggressive in patients with NBCCS. Important risk factors for the development of BCCs include sun exposure and radiation. (See 'Basal cell carcinomas' above.)
- Individuals diagnosed with NBCCS should undergo frequent surveillance by a dermatologist to facilitate early diagnosis of new nevi. The management of BCCs that are diagnosed can be difficult because of the multiplicity of lesions and the need for multiple procedures. (See 'Surveillance' above and 'Treatment of basal cell carcinomas' above.)
- In addition to BCCs, NBCCS is associated with a variety of other cysts and tumors, including odontogenic keratocysts and medulloblastomas. Therapeutic radiation therapy needs to be avoided in such patients, since this can precipitate the development of numerous, aggressive BCCs. (See 'Clinical findings' above.)

Use of UpToDate is subject to the [Subscription and License Agreement](#).

## REFERENCES

- 1 [Cohen MM Jr. Nevoid basal cell carcinoma syndrome: molecular biology and new hypotheses. Int J Oral Maxillofac Surg 1999; 28:216.](#)
- 2 [Farndon PA, Del Mastro RG, Evans DG, Kilpatrick MW. Location of gene for Gorlin syndrome. Lancet 1992; 339:581.](#)
- 3 [Shanley S, Ratcliffe J, Hockey A, et al. Nevoid basal cell carcinoma syndrome: review of 118 affected individuals. Am J Med Genet 1994; 50:282.](#)
- 4 [GORLIN RJ, GOLTZ RW. Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib. A syndrome. N Engl J Med 1960; 262:908.](#)
- 5 [Rahbari H, Mehregan AH. Basal cell epithelioma \(carcinoma\) in children and teenagers. Cancer 1982; 49:350.](#)
- 6 [Anderson DE, Taylor WB, Falls HF, Davidson RT. The nevoid basal cell carcinoma syndrome. Am J Hum Genet 1967; 19:12.](#)
- 7 [Hahn H, Wicking C, Zaphiropoulos PG, et al. Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. Cell 1996; 85:841.](#)
- 8 [Johnson RL, Rothman AL, Xie J, et al. Human homolog of patched, a candidate gene for the basal cell nevus syndrome. Science 1996; 272:1668.](#)
- 9 [Unden AB, Holmberg E, Lundh-Rozell B, et al. Mutations in the human homologue of Drosophila patched \(PTCH\) in basal cell carcinomas and the Gorlin syndrome: different in vivo mechanisms of PTCH inactivation. Cancer Res 1996; 56:4562.](#)
- 10 [Goldstein AM, Stewart C, Bale AE, et al. Localization of the gene for the nevoid basal cell carcinoma syndrome. Am J Hum Genet 1994; 54:765.](#)
- 11 [Lam CW, Leung CY, Lee KC, et al. Novel mutations in the PATCHED gene in basal cell nevus syndrome. Mol Genet Metab 2002; 76:57.](#)
- 12 [Aszterbaum M, Rothman A, Johnson RL, et al. Identification of mutations in the human PATCHED gene in sporadic basal cell carcinomas and in patients with the basal cell nevus syndrome. J Invest Dermatol 1998; 110:885.](#)
- 13 [Wicking C, Shanley S, Smyth I, et al. Most germ-line mutations in the nevoid basal cell carcinoma syndrome lead to a premature termination of the PATCHED protein, and no genotype-phenotype correlations are evident. Am J Hum Genet 1997; 60:21.](#)
- 14 [Zhang H, Ping XL, Lee PK, et al. Role of PTCH and p53 genes in early-onset basal cell carcinoma. Am J Pathol 2001; 158:381.](#)
- 15 [Teh MT, Blaydon D, Chaplin T, et al. Genomewide single nucleotide polymorphism microarray mapping in basal cell carcinomas unveils uniparental disomy as a key somatic event. Cancer Res 2005; 65:8597.](#)
- 16 [Levanat S, Gorlin RJ, Fallet S, et al. A two-hit model for developmental defects in Gorlin syndrome. Nat Genet 1996; 12:85.](#)
- 17 [Gailani MR, Bale AE. Developmental genes and cancer: role of patched in basal cell carcinoma of the skin. J Natl Cancer Inst 1997; 89:1103.](#)
- 18 [Booth DR. The hedgehog signalling pathway and its role in basal cell carcinoma. Cancer Metastasis Rev 1999; 18:261.](#)
- 19 [Grachtchouk V, Grachtchouk M, Lowe L, et al. The magnitude of hedgehog signaling activity defines skin tumor phenotype. EMBO J 2003; 22:2741.](#)
- 20 [Dahmane N, Lee J, Robins P, et al. Activation of the transcription factor Gli1 and the Sonic hedgehog signalling pathway in skin tumours. Nature 1997; 389:876.](#)
- 21 [Ruiz i Altaba A, Sánchez P, Dahmane N. Gli and hedgehog in cancer: tumours, embryos and stem cells. Nat Rev Cancer 2002; 2:361.](#)
- 22 [Ghali L, Wong ST, Green J, et al. Gli1 protein is expressed in basal cell carcinomas, outer root sheath keratinocytes and a subpopulation of mesenchymal cells in normal human skin. J Invest Dermatol 1999; 113:595.](#)

- 23 [Alcedo J, Ayzenzon M, Von Ohlen T, et al. The Drosophila smoothed gene encodes a seven-pass membrane protein, a putative receptor for the hedgehog signal. Cell 1996; 86:221.](#)
- 24 [Xie J, Murone M, Luoh SM, et al. Activating Smoothed mutations in sporadic basal-cell carcinoma. Nature 1998; 391:90.](#)
- 25 [Eichberger T, Regl G, Ikram MS, et al. FOXE1, a new transcriptional target of GLI2 is expressed in human epidermis and basal cell carcinoma. J Invest Dermatol 2004; 122:1180.](#)
- 26 [Green J, Leigh IM, Poulosom R, Quinn AG. Basal cell carcinoma development is associated with induction of the expression of the transcription factor Gli-1. Br J Dermatol 1998; 139:911.](#)
- 27 [Wicking C, Smyth I, Bale A. The hedgehog signalling pathway in tumorigenesis and development. Oncogene 1999; 18:7844.](#)
- 28 [Duman-Scheel M, Weng L, Xin S, Du W. Hedgehog regulates cell growth and proliferation by inducing Cyclin D and Cyclin E. Nature 2002; 417:299.](#)
- 29 [Oro AE, Higgins KM, Hu Z, et al. Basal cell carcinomas in mice overexpressing sonic hedgehog. Science 1997; 276:817.](#)
- 30 [Nagano T, Bito T, Kallassy M, et al. Overexpression of the human homologue of Drosophila patched \(PTCH\) in skin tumours: specificity for basal cell carcinoma. Br J Dermatol 1999; 140:287.](#)
- 31 [Zedan W, Robinson PA, Markham AF, High AS. Expression of the Sonic Hedgehog receptor "PATCHED" in basal cell carcinomas and odontogenic keratocysts. J Pathol 2001; 194:473.](#)
- 32 [Ohki K, Kumamoto H, Ichinohasama R, et al. PTC gene mutations and expression of SHH, PTC, SMO, and GLI-1 in odontogenic keratocysts. Int J Oral Maxillofac Surg 2004; 33:584.](#)
- 33 [Goldstein AM, Pastakia B, DiGiovanna JJ, et al. Clinical findings in two African-American families with the nevoid basal cell carcinoma syndrome \(NBCC\). Am J Med Genet 1994; 50:272.](#)
- 34 [Ahn SG, Lim YS, Kim DK, et al. Nevoid basal cell carcinoma syndrome: a retrospective analysis of 33 affected Korean individuals. Int J Oral Maxillofac Surg 2004; 33:458.](#)
- 35 [Kulkarni P, Brashear R, Chuang TY. Nevoid basal cell carcinoma syndrome in a person with dark skin. J Am Acad Dermatol 2003; 49:332.](#)
- 36 [Kimonis VE, Goldstein AM, Pastakia B, et al. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. Am J Med Genet 1997; 69:299.](#)
- 37 [Hall J, Johnston KA, McPhillips JP, et al. Nevoid basal cell carcinoma syndrome in a black child. J Am Acad Dermatol 1998; 38:363.](#)
- 38 [Gailani MR, Stähle-Bäckdahl M, Leffell DJ, et al. The role of the human homologue of Drosophila patched in sporadic basal cell carcinomas. Nat Genet 1996; 14:78.](#)
- 39 [Wolter M, Reifenberger J, Sommer C, et al. Mutations in the human homologue of the Drosophila segment polarity gene patched \(PTCH\) in sporadic basal cell carcinomas of the skin and primitive neuroectodermal tumors of the central nervous system. Cancer Res 1997; 57:2581.](#)
- 40 [Bodak N, Queille S, Avril MF, et al. High levels of patched gene mutations in basal-cell carcinomas from patients with xeroderma pigmentosum. Proc Natl Acad Sci U S A 1999; 96:5117.](#)
- 41 [Jin Y, Merterns F, Persson B, et al. The reciprocal translocation t\(9;16\)\(q22;p13\) is a primary chromosome abnormality in basal cell carcinomas. Cancer Res 1997; 57:404.](#)
- 42 [Smyth I, Narang MA, Evans T, et al. Isolation and characterization of human patched 2 \(PTCH2\), a putative tumour suppressor gene in basal cell carcinoma and](#)

- medulloblastoma on chromosome 1p32. Hum Mol Genet 1999; 8:291.
- 43 Motoyama J, Takabatake T, Takeshima K, Hui C. Ptch2, a second mouse Patched gene is co-expressed with Sonic hedgehog. Nat Genet 1998; 18:104.
- 44 Howell JB, Anderson DE. "The basal-cell nevus" by Howell and Caro, January 1959. Commentary: The nevoid basal cell carcinoma syndrome. Arch Dermatol 1982; 118:813.
- 45 Lo Muzio L, Nocini PF, Savoia A, et al. Nevoid basal cell carcinoma syndrome. Clinical findings in 37 Italian affected individuals. Clin Genet 1999; 55:34.
- 46 Evans DG, Ladusans EJ, Rimmer S, et al. Complications of the naevoid basal cell carcinoma syndrome: results of a population based study. J Med Genet 1993; 30:460.
- 47 Ratcliffe JF, Shanley S, Ferguson J, Chenevix-Trench G. The diagnostic implication of falcine calcification on plain skull radiographs of patients with basal cell naevus syndrome and the incidence of falcine calcification in their relatives and two control groups. Br J Radiol 1995; 68:361.
- 48 Gorlin RJ. Nevoid basal-cell carcinoma syndrome. Medicine (Baltimore) 1987; 66:98.
- 49 Howell JB. Nevoid basal cell carcinoma syndrome. Profile of genetic and environmental factors in oncogenesis. J Am Acad Dermatol 1984; 11:98.
- 50 Winkler PA, Guyuron B. Multiple metastases from basal cell naevus syndrome. Br J Plast Surg 1987; 40:528.
- 51 Goldstein AM, Bale SJ, Peck GL, DiGiovanna JJ. Sun exposure and basal cell carcinomas in the nevoid basal cell carcinoma syndrome. J Am Acad Dermatol 1993; 29:34.
- 52 Frentz G, Munch-Petersen B, Wulf HC, et al. The nevoid basal cell carcinoma syndrome: sensitivity to ultraviolet and x-ray irradiation. J Am Acad Dermatol 1987; 17:637.
- 53 O'Malley S, Weitman D, Olding M, Sekhar L. Multiple neoplasms following craniospinal irradiation for medulloblastoma in a patient with nevoid basal cell carcinoma syndrome. Case report. J Neurosurg 1997; 86:286.
- 54 Wollenberg A, Peter RU, Przybilla B. Multiple superficial basal cell carcinomas (basalomatosis) following cobalt irradiation. Br J Dermatol 1995; 133:644.
- 55 Stavrou T, Bromley CM, Nicholson HS, et al. Prognostic factors and secondary malignancies in childhood medulloblastoma. J Pediatr Hematol Oncol 2001; 23:431.
- 56 Fujii K, Suzuki N, Ishijima S, et al. Abnormal DNA synthesis activity induced by X-rays in nevoid basal cell carcinoma syndrome cells. Biochem Biophys Res Commun 1997; 240:269.
- 57 Mancuso M, Pazzaglia S, Tanori M, et al. Basal cell carcinoma and its development: insights from radiation-induced tumors in Ptch1-deficient mice. Cancer Res 2004; 64:934.
- 58 Katase N, Nagatsuka H, Tsujigiwa H, et al. Analysis of the neoplastic nature and biological potential of sporadic and nevoid basal cell carcinoma syndrome-associated keratocystic odontogenic tumor. J Oral Pathol Med 2007; 36:550.
- 59 Agaram NP, Collins BM, Barnes L, et al. Molecular analysis to demonstrate that odontogenic keratocysts are neoplastic. Arch Pathol Lab Med 2004; 128:313.
- 60 Meara JG, Shah S, Li KK, Cunningham MJ. The odontogenic keratocyst: a 20-year clinicopathologic review. Laryngoscope 1998; 108:280.
- 61 Kolár Z, Geierová M, Bouchal J, et al. Immunohistochemical analysis of the biological potential of odontogenic keratocysts. J Oral Pathol Med 2006; 35:75.
- 62 Habibi A, Saghravanian N, Habibi M, et al. Keratocystic odontogenic tumor: a 10-year retrospective study of 83 cases in an Iranian population. J Oral Sci 2007; 49:229.
- 63 Myoung H, Hong SP, Hong SD, et al. Odontogenic keratocyst: Review of 256 cases

- for recurrence and clinicopathologic parameters. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001; 91:328.
- 64 Brannon RB. The odontogenic keratocyst. A clinicopathologic study of 312 cases. Part I. Clinical features. Oral Surg Oral Med Oral Pathol 1976; 42:54.
- 65 Chenevix-Trench G, Wicking C, Berkman J, et al. Further localization of the gene for nevoid basal cell carcinoma syndrome (NBCCS) in 15 Australasian families: linkage and loss of heterozygosity. Am J Hum Genet 1993; 53:760.
- 66 Gutierrez MM, Mora RG. Nevoid basal cell carcinoma syndrome. A review and case report of a patient with unilateral basal cell nevus syndrome. J Am Acad Dermatol 1986; 15:1023.
- 67 Howell JB, Mehregan AH. Pursuit of the pits in the nevoid basal cell carcinoma syndrome. Arch Dermatol 1970; 102:586.
- 68 Mortimer PS, Geaney DP, Liddell K, Dawber RP. Basal cell naevus syndrome and intracranial meningioma. J Neurol Neurosurg Psychiatry 1984; 47:210.
- 69 Evans DG, Farndon PA, Burnell LD, et al. The incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma. Br J Cancer 1991; 64:959.
- 70 Lacombe D, Chateil JF, Fontan D, Battin J. Medulloblastoma in the nevoid basal-cell carcinoma syndrome: case reports and review of the literature. Genet Couns 1990; 1:273.
- 71 Hettmer S, Teot LA, Kozakewich H, et al. Myogenic Tumors in Nevoid Basal Cell Carcinoma Syndrome. J Pediatr Hematol Oncol 2014.
- 72 Walsh SN, Hurt MA. Cutaneous fetal rhabdomyoma: a case report and historical review of the literature. Am J Surg Pathol 2008; 32:485.
- 73 Wang C. Childhood rhabdomyosarcoma: recent advances and prospective views. J Dent Res 2012; 91:341.
- 74 Dunnick NR, Head GL, Peck GL, Yoder FW. Nevoid basal cell carcinoma syndrome: radiographic manifestations including cystlike lesions of the phalanges. Radiology 1978; 127:331.
- 75 Southwick GJ, Schwartz RA. The basal cell nevus syndrome: disasters occurring among a series of 36 patients. Cancer 1979; 44:2294.
- 76 Jones KL, Wolf PL, Jensen P, et al. The Gorlin syndrome: a genetically determined disorder associated with cardiac tumor. Am Heart J 1986; 111:1013.
- 77 Cho JM, Danielson GK, Puga FJ, et al. Surgical resection of ventricular cardiac fibromas: early and late results. Ann Thorac Surg 2003; 76:1929.
- 78 Gorlin RJ. Nevoid basal cell carcinoma syndrome. Dermatol Clin 1995; 13:113.
- 79 Kraemer BB, Silva EG, Sneige N. Fibrosarcoma of ovary. A new component in the nevoid basal-cell carcinoma syndrome. Am J Surg Pathol 1984; 8:231.
- 80 Ratcliffe JF, Shanley S, Chenevix-Trench G. The prevalence of cervical and thoracic congenital skeletal abnormalities in basal cell naevus syndrome; a review of cervical and chest radiographs in 80 patients with BCNS. Br J Radiol 1995; 68:596.
- 81 Chiritescu E, Maloney ME. Acrochordons as a presenting sign of nevoid basal cell carcinoma syndrome. J Am Acad Dermatol 2001; 44:789.
- 82 Wallace DC, Murphy KJ, Kelly L, Ward WH. The basal cell naevus syndrome. Report of a family with anosmia and a case of hypogonadotrophic hypopituitarism. J Med Genet 1973; 10:30.
- 83 DiSanto S, Abt AB, Boal DK, Krummel TM. Fetal rhabdomyoma and nevoid basal cell carcinoma syndrome. Pediatr Pathol 1992; 12:441.
- 84 Sobota A, Pena M, Santi M, Ali Ahmed A. Undifferentiated sinonasal carcinoma in a patient with nevoid basal cell carcinoma syndrome. Int J Surg Pathol 2007; 15:303.
- 85 Palacios E, Serou M, Restrepo S, Rojas R. Odontogenic keratocysts in nevoid basal cell carcinoma (Gorlin's) syndrome: CT and MRI evaluation. Ear Nose Throat J 2004;

83:40.

- 86 [Doctoroff A, Oberlender SA, Purcell SM. Full-face carbon dioxide laser resurfacing in the management of a patient with the nevoid basal cell carcinoma syndrome. Dermatol Surg 2003; 29:1236.](#)
- 87 [Nouri K, Chang A, Trent JT, Jiménez GP. Ultrapulse CO2 used for the successful treatment of basal cell carcinomas found in patients with basal cell nevus syndrome. Dermatol Surg 2002; 28:287.](#)
- 88 [Grobbelaar AO, Horlock N, Gault DT. Gorlin's syndrome: the role of the carbon dioxide laser in patient management. Ann Plast Surg 1997; 39:366.](#)
- 89 [Kronic AL, Viehman GE, Madani S, Clark RE. Microscopically controlled surgical excision combined with ultrapulse CO2 vaporization in the management of a patient with the nevoid basal cell carcinoma syndrome. J Dermatol 1998; 25:10.](#)
- 90 [Kopera D, Cerroni L, Fink-Puches R, Kerl H. Different treatment modalities for the management of a patient with the nevoid basal cell carcinoma syndrome. J Am Acad Dermatol 1996; 34:937.](#)
- 91 [Micali G, De Pasquale R, Caltabiano R, et al. Topical imiquimod treatment of superficial and nodular basal cell carcinomas in patients affected by basal cell nevus syndrome: a preliminary report. J Dermatolog Treat 2002; 13:123.](#)
- 92 [Stockfleth E, Ulrich C, Hauschild A, et al. Successful treatment of basal cell carcinomas in a nevoid basal cell carcinoma syndrome with topical 5% imiquimod. Eur J Dermatol 2002; 12:569.](#)
- 93 [Micali G, Lacarrubba F, Nasca MR, De Pasquale R. The use of imiquimod 5% cream for the treatment of basal cell carcinoma as observed in Gorlin's syndrome. Clin Exp Dermatol 2003; 28 Suppl 1:19.](#)
- 94 [Kagy MK, Amonette R. The use of imiquimod 5% cream for the treatment of superficial basal cell carcinomas in a basal cell nevus syndrome patient. Dermatol Surg 2000; 26:577.](#)
- 95 [Vereecken P, Monsieur E, Petein M, Heenen M. Topical application of imiquimod for the treatment of high-risk facial basal cell carcinoma in Gorlin syndrome. J Dermatolog Treat 2004; 15:120.](#)
- 96 [Sterry W, Ruzicka T, Herrera E, et al. Imiquimod 5% cream for the treatment of superficial and nodular basal cell carcinoma: randomized studies comparing low-frequency dosing with and without occlusion. Br J Dermatol 2002; 147:1227.](#)
- 97 [Neville JA, Williford PM, Jorizzo JL. Pilot study using topical imiquimod 5% cream in the treatment of nodular basal cell carcinoma after initial treatment with curettage. J Drugs Dermatol 2007; 6:910.](#)
- 98 [Chapas AM, Gilchrest BA. Broad area photodynamic therapy for treatment of multiple basal cell carcinomas in a patient with nevoid basal cell carcinoma syndrome. J Drugs Dermatol 2006; 5:3.](#)
- 99 [Peck GL, DiGiovanna JJ, Sarnoff DS, et al. Treatment and prevention of basal cell carcinoma with oral isotretinoin. J Am Acad Dermatol 1988; 19:176.](#)
- 100 [Sanchez-Conejo-Mir J, Camacho F. Nevoid basal cell carcinoma syndrome: combined etretinate and surgical treatment. J Dermatol Surg Oncol 1989; 15:868.](#)
- 101 [Tangrea JA, Edwards BK, Taylor PR, et al. Long-term therapy with low-dose isotretinoin for prevention of basal cell carcinoma: a multicenter clinical trial. Isotretinoin-Basal Cell Carcinoma Study Group. J Natl Cancer Inst 1992; 84:328.](#)
- 102 [Goldberg LH, Firoz BF, Weiss GJ, et al. Basal cell nevus syndrome: a brave new world. Arch Dermatol 2010; 146:17.](#)
- 103 [Anand VK, Arrowood JP Jr, Krolls SO. Malignant potential of the odontogenic keratocyst. Otolaryngol Head Neck Surg 1994; 111:124.](#)
- 104 [Goldenberg D, Sciubba J, Koch W, Tufano RP. Malignant odontogenic tumors: a 22-year experience. Laryngoscope 2004; 114:1770.](#)

- 105 [Scheer M, Koch AM, Drebber U, Kübler AC. Primary intraosseous carcinoma of the jaws arising from an odontogenic cyst--a case report. J Craniomaxillofac Surg 2004; 32:166.](#)
- 106 [Goldberg LH, Landau JM, Moody MN, et al. Resolution of odontogenic keratocysts of the jaw in basal cell nevus syndrome with GDC-0449. Arch Dermatol 2011; 147:839.](#)
- 107 [Ally MS, Tang JY, Joseph T, et al. The use of vismodegib to shrink keratocystic odontogenic tumors in patients with Basal cell nevus syndrome. JAMA Dermatol 2014; 150:542.](#)
- 108 [Wallin JL, Tanna N, Misra S, et al. Sinonasal carcinoma after irradiation for medulloblastoma in nevoid basal cell carcinoma syndrome. Am J Otolaryngol 2007; 28:360.](#)
- 109 [Tang JY, Wu A, Linos E, et al. High prevalence of vitamin D deficiency in patients with basal cell nevus syndrome. Arch Dermatol 2010; 146:1105.](#)
- 110 [Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. N Engl J Med 2012; 366:2180.](#)
- 111 [Chang AL, Oro AE. Initial assessment of tumor regrowth after vismodegib in advanced Basal cell carcinoma. Arch Dermatol 2012; 148:1324.](#)
- 112 [Chang AL, Atwood SX, Tartar DM, Oro AE. Surgical excision after neoadjuvant therapy with vismodegib for a locally advanced basal cell carcinoma and resistant basal carcinomas in Gorlin syndrome. JAMA Dermatol 2013; 149:639.](#)
- 113 [Skvara H, Kalthoff F, Meingassner JG, et al. Topical treatment of Basal cell carcinomas in nevoid Basal cell carcinoma syndrome with a smoothed inhibitor. J Invest Dermatol 2011; 131:1735.](#)

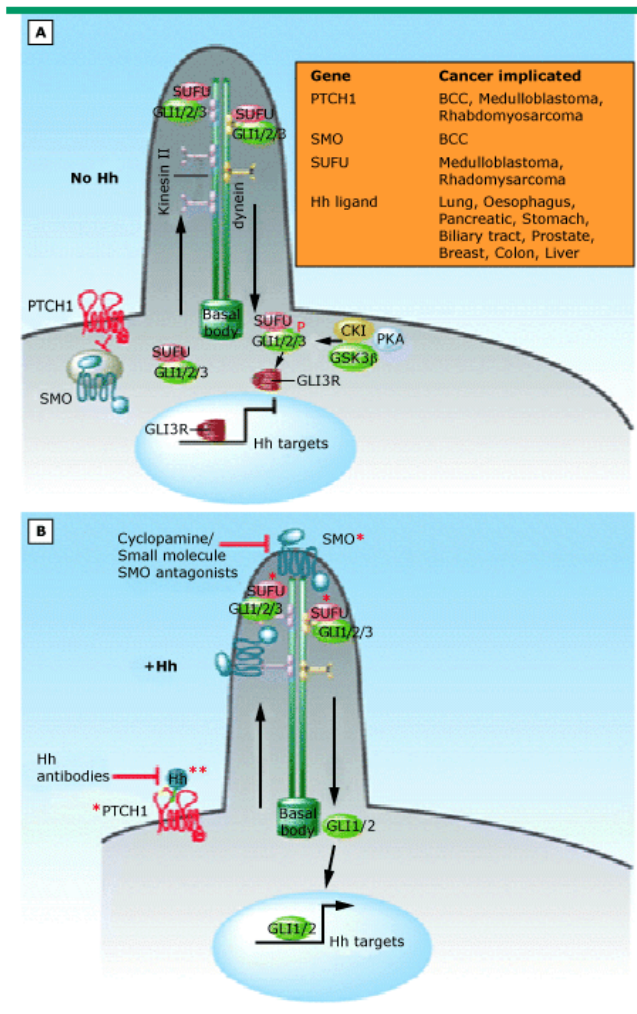
Topic 5340 Version 17.0

- All rights reserved. •



Figure 1.

**Hedgehog signaling pathway in cancer**

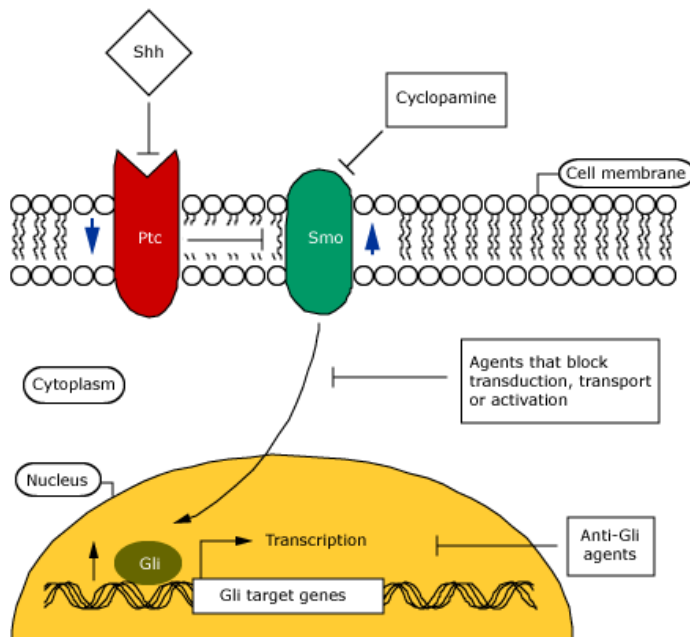


A) In the absence of Hh ligand, Ptc1 inhibits surface localization of Smo and protein kinases phosphorylate Gli proteins, leading to an NH-terminal truncated form, which acts as a repressor of Hh target gene expression. Gli3 is the predominant repressor. SuFu also regulates the pathway by binding to Gli, both in the cytoplasm and in the nucleus, to prevent it from activating Hh target genes. Table, summary of genes implicated in cancer and potential treatment using Hh antagonists or Hh antibodies. B) Hh-mediated (Sonic, Indian, or Desert) inactivation of Ptc1 allows relocation of Smo to the tip of cilia, leading to downstream signaling events and the activation of the Gli proteins. Mutations in the pathway (\*) or overexpression of the Hh ligand are highlighted (\*\*) in (A) and (B) along with possible avenues of treatment using antibodies or small molecules (red arrows).

Reproduced with permission from: Evangelista, M, Tian, H, de Sauvage, FJ. The hedgehog signaling pathway in cancer. *Clin Cancer Res* 2006; 12:5924. Copyright ©2006 The American Association for Cancer Research.

Figure 2.

### The Shh-Gli pathway and potential sites for blocking it with therapeutic agents



Sonic hedgehog (Shh) acts on the membrane receptor complex formed by Patched (Ptc) and Smoothened (Smo) to inhibit the repression of Smo by Ptc. Smo is then thought to send the signal intracellularly through several cytoplasmic transduction steps (not shown), leading to the nuclear action of the Gli proteins, which regulate target genes. Thick blue arrows pointing up or down indicate activating or inactivating mutations, respectively, that might induce the pathway. Inhibitors of the pathway with potential therapeutic value (red lines) include: agents that block the action of Smo in the receptor complex, such as the plant alkaloid cyclopamine; agents that inhibit specific aspects of the transduction of the signal, including the nuclear import or activation of Gli proteins; and agents that specifically inhibit Gli function.

Reproduced with permission from: Ruiz i Altaba A, Sanchez P, Dahmane N. Gli and hedgehog in cancer: tumours, embryos and stem cells. *Nat Rev Cancer* 2002; 2:361. Copyright © 2002 Nature Publishing Group.

<http://www.nature.com>

UpToDate®

Picture 1.

## Palmar pits associated with nevoid basal cell carcinoma syndrome

---



---

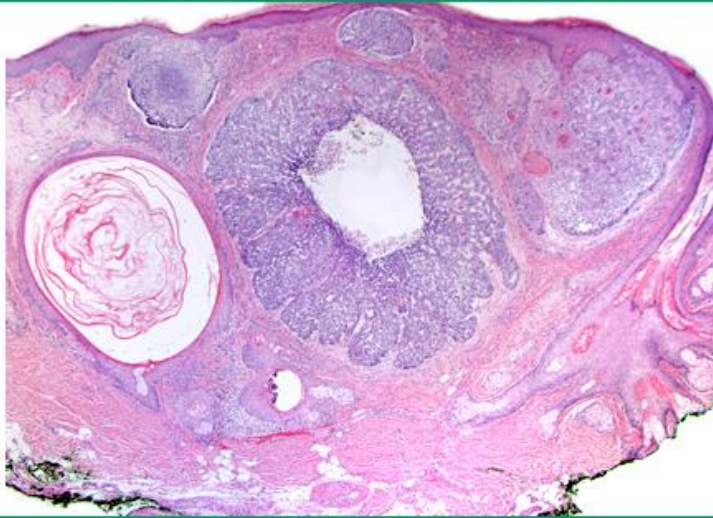
Palmar surface of hand showing 1-to-2 mm, sharply marginated, depressed red lesions, ie, palmar pits.

*Reproduced with permission from: Fitzpatrick, TB, Johnson, RA, Wolff, K, Suurmond, D. Color Atlas & Synopsis of Clinical Dermatology. Common & Serious Diseases. (4th Ed). McGraw-Hill, New York 2001. pgs. 268 & 289. Copyright © 2001 McGraw-Hill.*

UpToDate®

Picture 2.

**Nodular basal cell carcinoma (10x)**

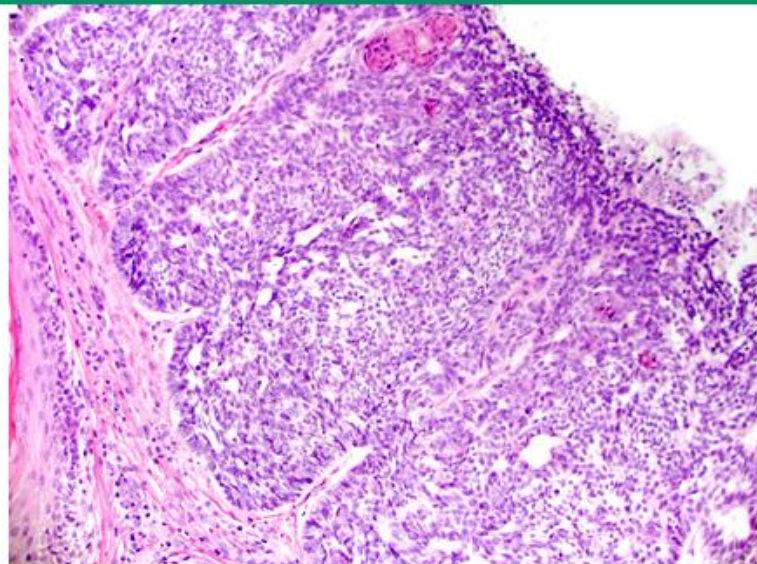


*Courtesy of Gary Goldenberg, MD.*

UpToDate®

Picture 3.

**Nodular basal cell carcinoma (20x)**



*Courtesy of Gary Goldenberg, MD.*

UpToDate®