








A guideline for the clinical management of basal cell naevus syndrome (Gorlin–Goltz syndrome)*

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1.0 Purpose and scope

The overall objective of this guideline is to provide up-to-date, evidence-based recommendations for the diagnosis and surveillance of all symptoms in children and adults with either basal cell naevus syndrome (BCNS), a clinical suspicion of BCNS, or a parent with BCNS. In the last two groups, the guidelines should be followed until the diagnosis of BCNS can be rejected with certainty. The guideline aims to:

- Update and expand on the previous guidelines by an appraisal of all relevant literature from January 2011 up to January 2021
- Address important, practical, clinical questions relating to the primary guideline objective
- Provide guideline recommendations
- Discuss potential developments and future directions

The guideline is presented as a detailed review with highlighted recommendations for practical use in the clinic by dermatologists and other healthcare professionals, including general practitioners, clinical geneticists, paediatricians, ophthalmologists, craniomaxillofacial surgeons, neurologists, cardiologists and psychologists.

1.1. Exclusions

The guideline does not cover therapeutic recommendations for (nondermatological) symptoms, as the guideline mainly focuses on screening and follow-up of symptoms. Therapeutic recommendations for basal cell carcinomas (BCCs) in general have been published in international BCC guidelines.^{1,2}

1.2. Stakeholder involvement and peer review

The guideline was developed at the Maastricht University Medical Centre (MUMC+), the Dutch BCNS expert centre accredited

by the Dutch Ministry of Health, Welfare and Sport.³ The guideline development group (GDG) consisted of two dermatologists, a clinical geneticist, a molecular geneticist, an ophthalmologist, a paediatrician, a gynaecologist, a craniomaxillofacial surgeon and a paediatric neurologist, all of whom worked at the MUMC+. Two residents in dermatology were also part of the GDG and acted as project managers. Furthermore, three patient/carer representatives commented on drafts of the guideline. The GDG developed clinical questions relevant for the management of patients with BCNS, all of which related to the diagnosis and surveillance of symptoms. During the development of the guideline, the GDG met twice face-to-face, and if input from the complete GDG was requested to resolve disagreements, it was solicited via email.

2.0 Methodology

This guideline was developed using the Appraisal of Guidelines Research and Evaluation II and Grading of Recommendations Assessment, Development and Evaluation (GRADE) instruments.⁴ A systematic literature search of the PubMed and Embase databases was conducted to identify key articles in English using the search terms 'basal cell nevus syndrome' and 'Gorlin syndrome' from January 2011 to January 2021. A total of 2747 articles were found. All titles were screened and case reports on general features, image quizzes, and unrelated articles were excluded ($n = 1112$). The reference lists of all relevant articles were scanned for additional suitable articles ($n = 13$). The titles and abstracts of the remaining 1648 articles were screened and 1576 articles were excluded as they did not provide the highest level of evidence available or information pertinent to the scope of the guideline. In the final analysis, 72 articles were included (Table S1; see Supporting Information). The level of evidence was graded according to the GRADE system (high, moderate, low, very low) by two authors (B.J.A.V. and B.C.). Recommendations were based on evidence drawn from the systematic review of the literature and discussed with the GDG during the consensus meetings. For each recommendation, benefits, risks and side-effects were systematically considered. Expert opinion of the GDG was used to generate recommendations if documented evidence-based data were not available.

3.0 Limitations of the guideline

This guideline was set up by a multidisciplinary team of physicians, which was restricted to a Dutch care centre. Diagnostic strategies and involved medical (sub)specialists may vary according to the healthcare system and local conditions. BCNS is a very rare disorder and the literature on specific symptoms is scarce. Randomized controlled trials are lacking and for most recommendations only indirect evidence was available. GRADE strength of recommendations (GSoR) are therefore often based on low or very low GRADE evidence certainty (GEC) levels.

4.0 Updating the guideline

Results of future studies may require changes to some of the recommendations. These guidelines will be re-evaluated after 5 years to determine whether a (modular) update will be necessary.

5.0 Background

BCNS (OMIM #109400), also known as Gorlin–Goltz syndrome, is a rare autosomal dominant disorder with an estimated prevalence varying from 1 : 31 000 to 1 : 256 000.^{5,6} The most common genetic cause of BCNS is a heterozygous germline mutation in the patched-1 (PTCH1) gene.⁷ This gene encodes the transmembrane glycoprotein PTCH1, a tumour suppressor of the Hedgehog (Hh) signalling pathway.⁸ In addition to its important role in embryonic development, the Hh signalling pathway is involved in cell proliferation and differentiation. During the inactive state, PTCH1 has an inhibitory effect on smoothed (SMO), and downstream signalling is inhibited. Further downstream, the suppressor of fused (SUFU) also inhibits the pathway by directly binding to glioma-associated (GLI) transcription factors and preventing translocation to the nucleus. Mutations in PTCH1 could relieve its inhibitory effect on SMO and subsequently SUFU is activated. This results in translocation of GLI transcription factors to the cell nucleus and upregulation of the Hh signalling pathway. Mutations in other genes of the Hh signalling pathway, either as germline mutation or postzygotic mosaicism, have been described but are less common.^{9–12} The most common features of BCNS are BCCs and odontogenic keratocysts (OKCs) of the jaw, but a broad scale of other characteristic features has been described.¹³ Owing to the low prevalence and broad variety of symptoms, the management and follow-up of patients with BCNS is often challenging. In 2011, Bree *et al.* proposed a management protocol for the surveillance of patients with BCNS. However, at that time, genetic analysis played a less important role and the differences between patients with heterozygous mutations in PTCH1 and SUFU were not yet evident.¹⁴ Here, we provide an up-to-date, multidisciplinary, practical, guideline for the clinical management of patients with BCNS (or suspicion of BCNS).

6.0 Diagnosis

Diagnostic criteria for BCNS were first proposed by Evans *et al.* in 1993, modified by Kimonis *et al.* in 1997 and revised by Bree *et al.* in 2011.^{14–16} According to the most recent publication,¹⁴ the diagnosis of BCNS can be established based on: (i) one major criterion and genetic confirmation; (ii) two major criteria or (iii) one major criterion and two minor criteria (Table 1). In patients with suspected BCNS, it is important to obtain a complete medical (family) history during the first consultation and perform a physical examination to search for dysmorphic features, skeletal

Table 1 Diagnostic criteria and clinical manifestations of basal cell naevus syndrome (BCNS)

Diagnosis: the diagnosis of BCNS can be established based on:	
(1) One major criterion and genetic confirmation	
(2) Two major criteria	
(3) Or one major criterion and two minor criteria	
Major criteria	
(1) BCCs prior to age 20 years or multiple BCCs	(4) Lamellar calcification of the falx cerebri
(2) OKCs prior to age 20 years	(5) Medulloblastoma (desmoplastic variant)
(3) Palmar or plantar pitting	(6) First-degree relative with BCNS
Minor criteria	
(1) Rib anomalies	(5) Lymphomesenteric cysts
(2) Macrocephaly	(6) Ocular abnormalities (i.e. strabismus, hypertelorism congenital cataracts, glaucoma, coloboma)
(3) Cleft/lip palate	(7) Other specific skeletal malformations and radiological changes (i.e. vertebral anomalies, kyphoscoliosis, short fourth metacarpals, postaxial polydactyly)
(4) Ovarian/cardiac fibroma	
Prevalence: 1 in 31 000–256 000	
Incidence: 1 in 18 976 births ⁵	
Genetic test: In 50–70% of patients with a clinical diagnosis of BCNS, an underlying <i>PTCH1</i> mutation is found and ±4% of patients have an underlying <i>SUFU</i> mutation. In case of high clinical suspicion, postzygotic mosaicism can be ascertained by finding an identical mutation in at least two BCCs	
Genetics: An autosomal dominant inheritance with 50% chance of passing on the mutated gene to offspring	
In 20–40% of patients, the disorder is due to a <i>de novo</i> mutation	
BCCs, basal cell carcinomas; OKCs, odontogenic keratocysts.	

abnormalities and skin abnormalities. Possible features are listed in Table 2.

7.0 Summary of recommendations

All recommendations are listed in Table 3. Table 4 provides a clear surveillance checklist for each age category.

7.1. Establishing the diagnosis

7.1.1. Should radiological examination be avoided as a diagnostic tool?

Patients with BCNS harbour a germline mutation in a tumour suppressor gene and only one additional mutation (second hit) is necessary for tumorigenesis.¹⁷ It is known that children have a higher susceptibility to secondary malignancy after high-dose radiation, owing to the known age dependence of radiosensitivity.^{18,19} However, the extent to which low-dose radiation (such as X-rays, < 0.05 Gy) contributes to DNA damage is still unclear.²⁰

Table 2 Clinical manifestations of basal cell naevus syndrome

Clinical manifestations	
Dysmorphic features	Macrocephaly (> 95th percentile, 50%), coarse face, biparietal/frontal bossing, broad nasal bridge, mandibular prognathism, facial asymmetry, congenital cleft lip/palate, malocclusion, hypertelorism, synophrys, coloboma, epicanthus
Development	Intellectual disability (5%)
Ocular system	Hypertelorism (70%), strabismus (10–20%), cysts on the eyelids (5–10%), congenital cataract (3–8%), nystagmus (1–5%), coloboma of the iris, choroid and/or nervus opticus (1–5%), congenital glaucoma (1–5%), iris transillumination defects (1–5%), subconjunctival epidermoid cysts (1–5%), microphthalmia (1–2%) myelinated nerve fibres, epiretinal membranes, macular hole, retinal hamartomas
Stomatological system	Odontogenic keratocysts (44–92%), schisis (5%)
Skin	BCCs (> 20 years of age, 51.4%; > 40 years of age, 71.7%), palmar (70%) and plantar (50%) pits (< 10 years of age, 30–65%; < 15 years of age 80%; > 20 years of age, 85%), facial milia (30%), epidermal cysts (50%), multiple naevi (< 20 years of age, 30–50%, > 20 years of age, 70%)
Skeletal system	Macrocephaly (> 95th percentile, 50%), abnormal skull formation (frontal, biparietal/temporal bossing and large calvaria, 70%), scoliosis (40%), spina bifida occulta 40–60%, rib anomalies (bifid/fused/splayed) (30–60%), Sprengel deformity (10–40%), bone cysts (35% in metacarpalia), kyphoscoliosis, increased mean height (women 174 cm, men 183 cm; 15% extremely tall), pectus deformity, vertebral abnormalities, short fourth metacarpal, polydactyly, syndactyly, brachymetacarpalism
Gastroenteric system	Lymphomesenteric cysts
Central nervous system	Ectopic calcification of the following: (i) falx cerebri (70–95%¹³; 65%),¹² (ii) tentory cerebelli (20–40%), (iii) ‘spotted’ meningeal calcification (rare)¹³ or (iv) complete or partial bridging of the sella turcica (25%). Medulloblastoma (1–4%), meningioma
Genitourinary system	Ovarian fibroma (6–60%), ovarian cysts; ovarian calcifications; hypogonadotropic hypogonadism (5–10%), horseshoe kidney, L-shaped kidney, unilateral renal agenesis, renal cysts, duplication of the renal pelvis and ureter (5%)
Cardiovascular system	Cardiac fibroma (3–5%)
BCC, basal cell carcinoma. Manifestations in bold occur in > 5% of patients.	

Table 3 Recommendations and grades of evidence

Recommendation concerning	Recommendation	GRADE evidence certainty ^a	GRADE strength of recommendation ^a
Diagnosis	Radiological examination for diagnostic criteria without therapeutic consequences should be avoided as much as possible	Very low	Strong
	If possible, we recommend performing genetic testing in all patients with suspected BCNS	Very low	Strong
	We recommend a stepwise approach that first includes genetic testing of the PTCH1 gene. If no mutation is found, but the clinical suspicion is high, we advise testing for mutations in SUFU. If again no variant is found in the presence of a high clinical suspicion, DNA from at least two different BCCs can be isolated and genetically tested for PTCH1 and SMO with sensitive next-generation sequencing technologies to examine the possibility of postzygotic mosaicism. If a variation is found, the relevance of the mutation and its consequences for the protein function should be verified	Very low	Weak
Dermatologists	There is insufficient evidence for genetic testing of PTCH2	Low	Strong
	Adequate sun-protective measures are very important and should be discussed during every visit	Very low	Strong
	Total body inspection, including nonsun-exposed sites, is recommended annually until the development of the first BCC. From that moment on, the follow-up frequency should be intensified to up to every 3–6 months, depending on the number and frequency of new BCCs	Very low	Strong
	Treatment of BCCs should be carried out according to international guidelines	Evidence varies per treatment and is summarized in these guidelines ^{1,2}	Strong
	Radiotherapy is relatively contraindicated	Very low	Strong
Nondermatological symptoms of BCNS	Treatment with oral HPLs can be considered for the treatment of multiple BCCs	Moderate	Strong
Development	Physicians should be aware of the possible increased risk of developmental delay and monitor the development of children with BCNS	Very low	Strong
Bone deformities	Physicians should identify bone deformities via physical examination at diagnosis to make early intervention possible when needed	Very low	Strong
Cardiac fibroma	At diagnosis, all patients with BCNS should be screened with a cardiac ultrasound. If cardiac symptoms occur in a patient with BCNS, a cardiac ultrasound should be repeated to exclude a late-onset cardiac tumour	Very low	Weak
Medulloblastoma	In children with a PTCH1 mutation, MRI should be considered when clinical symptoms or abnormal psychomotor development are present. However, routine MRI is not indicated	Low	Weak
	Where there is a clinical diagnosis without genetic testing or in children with a SUFU mutation, a baseline MRI is recommended and should be repeated every 4 months until the age of 3 years and twice per year until the age of 5 years	Low	Weak
	When BCNS is diagnosed in adulthood, a baseline brain MRI is not necessary	Low	Strong
Ophthalmological symptoms	In patients with BCNS, a baseline ophthalmological examination including an ocular pressure measurement (if possible) is recommended	Low	Strong
Odontogenic keratocysts	From the age of 8 years only patients with a heterozygous PTCH1 mutation should be screened for OKCs every 2 years with an orthopantomogram (OPG)	Very low	Weak
	After the first OKC, follow-up with an OPG is recommended annually	Very low	Weak
	After the age of 22 years, follow-up can be continued by a dentist and additional OPGs can be performed in case of pain/unexplained positional change of the teeth	Very low	Weak

(continued)

Table 3 (continued)

Recommendation concerning	Recommendation	GRADE evidence certainty ^a	GRADE strength of recommendation ^a
Ovarian fibroma	Gynaecological ultrasound examination and surveillance in nonsymptomatic patients is not strictly advised. In cases of abdominal complaints such as pain or menstrual irregularities, female patients should undergo gynaecological ultrasound examination to investigate the presence of an ovarian fibroma	Very low	Weak
(Lympho) mesenteric cysts	Physicians should screen for (lympho)mesenteric cysts with ultrasound examination in patients with BCNS and unexplained abdominal pain	Very low	Strong
Psychological distress	Psychological evaluation for support and counselling after the diagnosis is recommended for all patients (and their families). During follow-up, physicians should pay attention to psychological distress and address the possibility of a psychological consultation	Very low	Strong
Patient care	To provide optimal care for patients with BCNS we advocate a multidisciplinary approach	Very low	Strong

BCC, basal cell carcinoma; BCNS, basal cell nevus syndrome; HPI, Hedgehog pathway inhibitor; MRI, magnetic resonance imaging; OKC, odontogenic keratocyst; OPG, orthopantomogram. ^aAccording to Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Radiological examination for diagnostic criteria without therapeutic consequences should be avoided as much as possible. (GEC, very low; GSoR, strong)

7.1.2. Should genetic confirmation be preferred?

Genetic testing can be expensive, is not currently available in some centres/countries, and presymptomatic testing can have social consequences (for example, when patients are taking out a life insurance policy). However, techniques have improved, which has made genetic testing more affordable in most countries. Knowing the causal familial mutation is helpful in providing (pre)symptomatic testing for family members. Furthermore, the specific gene involved (PTCH1 or SUFU) warrants a different follow-up regime.²¹ Sites and countries that perform genetic testing are listed at Orphanet (<https://www.orpha.net/consor/cgi-bin/index.php>).

If possible, we recommend performing genetic testing in all patients with suspected BCNS. (GEC, very low; GSoR, strong)

7.1.3. Which steps should be followed in genetic confirmation of the diagnosis?

A mutation in the PTCH1 gene can be detected in 50–70% of patients, depending on the clinical symptoms specified.^{21–24} Standard genetic tests are not capable of detecting genomic rearrangements or deep intronic variants causing cryptic splicing in

PTCH1.²⁵ Also, mutations could be located in other components of the Hh signalling pathway. The SUFU gene is responsible in approximately 4% of BCNS cases.²¹ Mutation loads < 5%, which could conceivably be present in cases with postzygotic mosaicism (in PTCH1 or SMO), are impossible to detect using Sanger sequencing.^{11,12,26} Mutations in the PTCH2 gene have also been reported,^{10,27,28} but probably have an insignificant contribution to the cause of BCNS.²⁹ If a variation is found, the relevance of the mutation and its consequences for the protein function should be verified according to the standards and guidelines set forward by (inter)national organizations.³⁰ Only pathogenic variants, or likely pathogenic variants, may explain the patient's clinical symptoms and confirm the diagnosis.³⁰

We recommend a stepwise approach that first includes genetic testing of the PTCH1 gene. If no mutation is found, but the clinical suspicion is high, we advise testing for mutations in SUFU. If again no variant is found in the presence of a high clinical suspicion, DNA from at least two different BCCs can be isolated and genetically tested for PTCH1 and SMO using sensitive next-generation sequencing technologies to examine the possibility of postzygotic mosaicism. If a variation is found, the relevance of the mutation and its consequences for the protein function should be verified. (GEC, very low; GSoR, weak)

There is insufficient evidence for genetic testing of PTCH2. (GEC, low; GSoR, strong)

7.2. What should dermatologists be aware of?

The most common cutaneous manifestation in patients with BCNS is multiple BCCs, both nonpigmented and pigmented,

Table 4 Surveillance checklist by age category

Basal cell naevus syndrome checklist					
Specialism	Screen for	Physical and additional examination	Surveillance recommendations, 0–8 years	Surveillance recommendations, 8–16 years	Surveillance recommendations, > 16 years
Clinical geneticist	Dysmorphic features	Physical examination	At time of diagnosis	At time of diagnosis	Only at time of diagnosis, and in case of family planning decisions or in transition phase from paediatric to adult care
	Genetic counselling	Mutation analysis including prenatal testing	Repeat at time of family planning decisions	Repeat at time of family planning decisions	
Genetics and developmental paediatrician	General growth and development	General physical examination	At time of diagnosis Referral to paediatric orthopaedic surgeon or psychologist if indicated	At time of diagnosis Referral to paediatric orthopaedic surgeon or psychologist if indicated	Not applicable
Neurologist	Medulloblastoma	Neurological examination	SUFU: MRI cerebrum 4-monthly until the age of 3 years and twice per year until the age of 5 years ^a	If indicated	If indicated
Dermatologist	Neurological development	MRI cerebrum	PTCH1: no standard MRI ^a		
	BCCs, palmoplantar pits, basaloid follicular hamartomas, milia, epidermoid cysts	Total body inspection, including nonsun-exposed sites	Yearly, and after first BCC every 3–6 months depending on frequency of new BCCs	Yearly, and after first BCC every 3–6 months depending on frequency of new BCCs	Yearly, and after first BCC every 3–6 months depending on frequency of new BCCs
Oral and maxillofacial surgeon	Odontogenic keratocysts of the jaw	Orthopantomogram	Not applicable	PTCH1: at time of diagnosis and once per 2 years in cases where there are no abnormalities ^a SUFU: no standard screening ^a	PTCH1: at time of diagnosis and once per 2 years in cases where there are no abnormalities until the age of 22 years ^a SUFU: no standard screening ^a
Gynaecologist	Ovarian fibromas Prenatal screening	Pelvic ultrasound Depends on facilities per country	Not applicable	If indicated	If indicated
Cardiologist	Cardiac fibroma	Cardiac ultrasound	At time of diagnosis Repeat if indicated	At time of diagnosis Repeat if indicated	If indicated
Ophthalmologist	Cataract, glaucoma, coloboma	Ophthalmological examination including ocular pressure measurement	At time of diagnosis Repeat if indicated	At time of diagnosis Repeat if indicated	At time of diagnosis Repeat if indicated
Psychologist	Psychological distress	Psychological examination	At diagnosis, continue if indicated	At diagnosis, continue if indicated	At diagnosis, continue if indicated

BCC, basal cell carcinoma; MRI, magnetic resonance imaging. ^aThe difference between PTCH1 and SUFU is based on currently, sparse, available information in literature which is more elaborately discussed in the manuscript and Table S1 (see Supporting Information).

involving all histological subtypes and occurring on both sun-exposed and nonsun-exposed parts of the body.³¹ Some patients with BCNS will develop > 100 BCCs during their lifetime. The first BCC can develop during early childhood.³¹ Sunscreen use must be discussed frequently, as it can prevent the development of BCCs in patients with BCNS.^{32,33}

Other frequently found skin abnormalities (palmoplantar pits, basaloid follicular hamartomas, facial milia and epidermoid cysts) are benign and do not need treatment, but may be helpful in establishing the diagnosis.^{34–36}

Regarding BCCs, treatment with surgical excision is the gold standard.^{1,2} When localized in functionally/cosmetically

sensitive areas such as the face, Mohs micrographic surgery is preferred.^{1,2} As multiple excisions lead to many scars and can have a high psychological impact,³⁷ noninvasive topical treatments can be useful alternatives.^{1,2} Radiotherapy is relatively contraindicated in patients with BCNS, owing to the increased risk of BCCs in the irradiated area.^{1,38} Hh pathway inhibitors (HPIs), such as vismodegib and sonidegib, may be indicated in advanced BCC^{1,2} and are very effective in the treatment of multiple BCNS-associated BCCs (Tables S2 and S3; see Supporting Information).^{39–43} These treatments are not a lifelong option because of side-effects, and BCCs will recur after treatment discontinuation (Table S4; see Supporting Information).^{39–46} Recently, small phase II clinical trials on topical HPIs have been conducted.^{47–49} Results from larger trials need to confirm whether topical HPIs could be a valuable addition to the treatment modalities.

Adequate sun-protective measures are very important and should be discussed during every visit. (GEC, very low; GSoR, strong)

Total body inspection, including nonsun-exposed sites, is recommended annually until the development of the first BCC. From that moment on, the follow-up frequency should be intensified to up to every 3–6 months, depending on the number and frequency of new BCCs. (GEC, very low; GSoR, strong)

Treatment of BCCs should be carried out according to international guidelines. (GEC, evidence varies per treatment and is summarized in these guidelines^{1,2}; GSoR, strong)

Radiotherapy is relatively contraindicated. (GEC, very low; GSoR, strong)

Treatment with oral HPIs can be considered for the treatment of multiple BCCs. (GEC: moderate, GSoR: strong)

7.3. When should surveillance for nondermatological symptoms be performed?

It is preferable that surveillance for specific symptoms and diseases is performed by the most experienced specialist and depends on the expertise of available (sub)specialists.

7.3.1. Overall development

The previous guideline by Bree *et al.* suggested routine developmental screening in all children with BCNS.¹⁴ Children with BCNS may have an increased risk of developmental delay. Intellectual disability has been noted in 4–21% of the BCNS cohorts.^{35,50} In most countries, routine developmental screening has been incorporated into the public healthcare system. Early recognition of developmental delay can ensure

that adequate intervention and/or support is available when needed.

Physicians should be aware of the possible increased risk of developmental delay and monitor the development of children with BCNS. (GEC, very low; GSoR, strong)

7.3.2. Bone deformities

Bone deformities are often described as a feature of BCNS and qualify as a minor criterion (Table 2).^{14,35} Macrocephaly, frontal bossing, (kypho)scoliosis, Sprengel deformity, pectus deformity, short fourth metacarpal, polydactyly and syndactyly can be observed on direct physical examination.

Features such as rib anomalies and frontal bossing do not have clinical consequences but can contribute to the diagnosis. Other bone deformities such as (kypho)scoliosis and Sprengel deformity may require treatment.

Physicians should identify bone deformities via physical examination at diagnosis to make early intervention possible when needed. (GEC, very low; GSoR, strong)

7.3.3. Cardiac fibromas

Approximately 3–5% of all patients with BCNS develop a cardiac fibroma, a benign and usually asymptomatic cardiac tumour with a mean age of onset of 0–1 month.^{14,35} Although cardiac fibromas typically present in infancy, rare manifestations of a late-onset cardiac tumour have been described.⁵¹ If a cardiac fibroma results in ventricular outflow obstructions or chamber abolition, it may lead to conduction delays, arrhythmia or heart failure. In such cases, excision of the cardiac fibroma is necessary.⁵²

All children with BCNS, suspicion of BCNS or children at risk should be screened with a cardiac ultrasound. If cardiac symptoms occur in a patient with BCNS, a cardiac ultrasound should be repeated to exclude a late-onset cardiac tumour. (GEC, very low; GSoR, weak)

7.3.4. Medulloblastomas

A medulloblastoma is a malignant tumour developing from the cerebellum. In patients with BCNS, medulloblastomas are mainly of the desmoplastic subtype and usually develop in the

first 3 years of life.⁵³ The risk for medulloblastoma differs between patients with heterozygous mutations in *PTCH1* and *SUFU*. In the recent literature, the estimated risk for developing medulloblastoma in patients with a *PTCH1* mutation was 1.2–2.4%, whereas in patients with heterozygous *SUFU* mutations the risk was estimated to be 20 times higher.^{21,54,55} Screening for medulloblastoma using magnetic resonance imaging (MRI) often requires general anaesthesia in young children. The risks related to general anaesthesia in global development in young children are still under debate.⁵⁶ Moreover, the MRI screening procedure using general anaesthesia can be stressful for parents and children.

In children with a *PTCH1* mutation, MRI should be considered when clinical symptoms or abnormal psychomotor development are present. However, routine MRI is not indicated. (GEC, low; GSoR, weak)

In cases where there is a clinical diagnosis without genetic testing or in children with an *SUFU* mutation, a baseline MRI is recommended and should be repeated every 4 months until the age of 3 years and twice per year until the age of 5 years. (GEC, low; GSoR, weak)

When BCNS is diagnosed in adulthood, a baseline brain MRI is not necessary. (GEC, low; GSoR, strong)

7.3.5. Ophthalmological symptoms

Several eye abnormalities have been described in patients with BCNS (Table 2).^{57–59} To prevent a disturbance in the development of the visual system and visual loss, early recognition and intervention are important for more common ocular symptoms such as strabismus, microphthalmia, congenital cataract, coloboma of the iris/choroid/optic nerve, nystagmus, anterior segment dysgenesis and glaucoma.⁵⁹

In patients with BCNS, suspicion of BCNS or patients at risk, a baseline ophthalmological examination, including an ocular pressure measurement if possible, is recommended. (GEC, low; GSoR, strong)

7.3.6. Odontogenic keratocysts of the jaw

OKCs are benign and initially asymptomatic, but the typically slow progression may result in major tooth dislocation and even fractures of the jaw. Early detection enables adequate treatment, which may be crucial for maintaining jaw function.⁶⁰ OKCs of the jaw are present in 44–92%³⁵ of patients with BCNS and start to develop around the age of 8 years, when the deciduous teeth begin to change.⁶¹ Around the age of 22 years, the

teeth are permanent and do not grow or change any further. From that moment onwards, change in the position of teeth will be noticed by a patient. It has been reported that the development of OKCs tends to decrease after the age of 30 years.^{61,62} Patients with a *PTCH1* mutation often develop multiple OKCs with a recurrence rate ranging from 15.4% to 50.0% and a mean time to recurrence of 32 months.^{63–66} To date, no OKCs have been described in patients with a heterozygous *SUFU* mutation.^{21,67,68,69,70,71} Screening with an orthopantomogram (OPG) is recommended, as it is easily accessible, has low radiation levels (0.010 mSv) and low costs. Screening using MRI can be considered in order to avoid radiation, but accessibility and costs may be limiting factors. For preoperative planning of the OKC, a cone-beam computed tomography (CT) scan (0.05 mSv) or CT scan (2.1 mSv) is preferred because of the higher spatial resolution.^{72,73}

From the age of 8 years, only patients with a heterozygous *PTCH1* mutation should be screened for OKCs every 2 years using an OPG/MRI. (GEC, very low; GSoR, weak)

After the first OKC, follow-up with an OPG/MRI is recommended annually. (GEC, very low; GSoR, weak)

After the age of 22 years, follow-up can be continued by the dentist and additional OPGs/MRIs can be performed in cases where there is pain or unexplained positional change of the teeth. (GEC, very low; GSoR, weak)

7.3.7. Ovarian fibromas

Ovarian fibromas are estimated to occur in 13–60% of women with BCNS usually between the ages of 16 years and 45 years.^{35,61} In patients with BCNS, the ovarian fibromas are often bilateral and calcified and have a multifocal/multinodular growth pattern.⁷⁴ The ovarian fibromas are usually asymptomatic, do not affect fertility and rarely cause ovarian torsion.⁷⁵ In the absence of gynaecological symptoms, surgical treatment is not advised as it may result in decreased fertility or early menopause by reducing the amount of viable ovarian tissue.^{76,77} When surgical treatment is indicated in patients with a fertility desire, they should be counselled about minimally invasive methods in order to maintain future reproductive options.^{76,77}

Gynaecological ultrasound examination and surveillance in nonsymptomatic patients is not strictly advised. In cases of abdominal complaints such as pain or menstrual irregularities, female patients should undergo gynaecological ultrasound examination to investigate the presence of an ovarian fibroma. (GEC, very low; GSoR, weak)

7.3.8. (Lympho)mesenteric cysts

The presence of (lympho)mesenteric cysts is a minor diagnostic criterion with an unknown specific frequency.¹⁴ Only a few case reports have been published, but these types of cysts are probably under-reported in patients with BCNS.^{78,79} (Lympho)mesenteric cysts are benign, intra-abdominal tumours which are usually asymptomatic and often an occasional finding, although cases with abdominal pain have been reported.⁸⁰ The cysts can be seen on ultrasound examination, MRI and CT, but for definitive diagnosis, histological examination is necessary.⁸⁰ Surgical excision of cysts has been performed, but it is unknown whether this leads to a decrease in abdominal complaints.^{78,80}

Physicians should screen for (lympho)mesenteric cysts using ultrasound examination in patients with BCNS who report unexplained abdominal pain. (GEC, very low; GSoR, strong)

7.3.9. Psychological distress

The phenotype of BCNS varies to a great extent but, in general, patients will require many hospital visits and will undergo multiple (mutilating) surgical procedures. This can have a substantial impact on quality of life.^{37,81} Patients and patient carer representatives from our GDG expressed a strong need for psychological support in patients and patient carers. The underlying reasons for this need for psychological support were mainly the chronic aspect of BCNS, the multiple (mutilating) surgeries and the fear of developing new symptoms requiring treatment. Furthermore, patients often feel misunderstood by society, their employer and friends or family. A patient-reported outcome questionnaire, specifically developed to monitor the impact of BCCs in patients with BCNS, can be used to monitor health-related quality of life and gain insight into the patient's perspective.^{82,83}

Psychological evaluation for support and counselling after the diagnosis is recommended for all patients (and their families). During follow-up, physicians should pay attention to psychological distress and address the possibility of a psychological consultation. (GEC, very low; GSoR, strong)

8.0 How should patient care be organized?

In a national survey in the UK, the care of only 15% of patients with BCNS was managed by a multidisciplinary

team.⁸⁴ In our expert centre, children and adult patients with (suspicion for) BCNS are seen together by the dermatologist and clinical geneticist at the first consultation. For children, it is preferable that consultations with the genetic and developmental paediatrician and neurologist are planned to take place on the same day. During follow-up, the composition of the multidisciplinary team varies; in childhood, a (paediatric) neurologist and dermatologist are involved. From the age of 8 years, the dermatologist and oral and maxillofacial surgeon play a key role in the management of patients, owing to a high prevalence of BCCs and OKCs. Multidisciplinary care in the same (academic) centre decreases the burden of multiple visits to the hospital. Moreover, a case manager can play an important role in counselling patients and can ensure that patients receive all the necessary surveillance appointments. Providing all care in expert centres will probably increase the quality of care, avoiding delayed or incorrect diagnosis, treatment and follow-up of symptoms.

To provide optimal care for patients with BCNS we advocate a multidisciplinary approach. (GEC, very low; GSoR, strong)

9.0 Recommended audit points

Data collection should be coordinated between centres and include details of the management used for each case of BCNS and patient outcomes. For specialist centres, the following questions should be answered for each patient with BCNS:

- 1 Is the family history known and documented?
- 2 Has diagnostic genetic testing been performed and is the outcome known?
- 3 Has the patient received sun-protection advice and an explanation of the importance of sunscreen application, and is he/she aware of the disadvantages of radiological examination?
- 4 Have surveillance appointments been planned for the patient involving all relevant specialties mentioned in this guideline?

10.0 Future directions

As these guidelines demonstrate, there is a need for high-quality evidence to refine screening indications for different symptoms. Genotype–phenotype studies revealed that the occurrence of medulloblastomas is higher in patients with a *SUFU* heterozygous mutation, whereas OKCs do not occur in patients with this genotype. As BCNS is a rare disease, international collaboration between expert centres is important in order to be able to merge data on genetically substantiated cohorts. Furthermore, there should be more awareness of patients without a genetic

mutation, as this lack of mutation can either be attributed to genetic mosaicism or an unknown genetic cause. In some patients, there will be a desire for treatment of multiple BCCs with oral HPIs. However, the associated adverse events make oral HPIs unsuitable for lifelong use. Topical HPIs have been developed, but results of an international placebo-controlled trial are required in order to be able to make claims about the efficacy and safety of this new medication.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Summary of findings.

Table S2 Overview of all papers discussing oral hedgehog pathway inhibitor monotherapy for multiple basal cell carcinomas in patients with basal cell naevus syndrome.

Table S3 Efficacy of oral hedgehog pathway inhibitors in the treatment of multiple basal cell carcinomas in patients with basal cell naevus syndrome.

Table S4 Side-effects of oral hedgehog pathway inhibitors in the treatment of multiple basal cell carcinomas in patients with basal cell naevus syndrome.

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