

# Cancer Association of South Africa (CANSA)



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## Fact Sheet on Gorlin-Goltz Syndrome

### Introduction

Gorlin-Goltz syndrome (also known as Gorlin syndrome or Gorlin's syndrome, nevoid basal-cell carcinoma syndrome (NBCCS), basal-cell naevus syndrome, and multiple basal-cell carcinoma syndrome) is an autosomal dominant disorder with a high degree of penetrance and variable expressivity. It is characterised by basal cell carcinomas, odontogenic keratocysts, palmar and/or plantar pits, and ectopic calcifications of the falx cerebri. More than 100 minor criteria have been described.

The presence of two major and one minor criteria or one major and three minor criteria are necessary to establish a diagnosis. Early diagnosis and treatment of Gorlin-Goltz syndrome, as well as family screening and genetic counselling are essential as it may be associated in 10% of the patients with aggressive basal cell carcinomas and malignant neoplasias. (Jawa, *et al.*).

[Picture Credit: Gorlin-Goltz Syndrome]

The pictures on the right show the multiple typical Basal Cell Carcinoma (BCC) on the face of the patient as well as the palmar pits in the palm of the hand.

Gorlin-Goltz Syndrome, also known as nevoid basal cell carcinoma syndrome (NBCCS), basal cell nevus syndrome, multiple basal cell carcinoma syndrome, and Gorlin syndrome, is an inherited medical condition involving defects within multiple body systems such as the skin, nervous system, eyes, endocrine system, and bones. People with this syndrome are particularly prone to developing a common and usually non-life-threatening form of non-melanoma skin cancers.

About 10% of people with the condition do not develop basal cell carcinomas (BCCs).

First described in 1960, NBCCS is an autosomal dominant condition that can cause unusual facial appearances and a predisposition for basal cell carcinoma, a type of skin cancer which rarely spreads to other parts of the body. The prevalence is reported to be 1 case per 56,000-



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164,000 population. Recent work in molecular genetics has shown NBCCS to be caused by mutations in the *PTCH* (*Patched*) gene found on chromosome arm 9q. If a child inherits the defective gene from either parent, he or she will have the disorder.

[Picture Credit: Robert J Gorlin]

The name *Gorlin syndrome* refers to the researcher Dr Robert J Gorlin (1923–2006) pictured on the left.

### Incidence of Gorlin-Goltz Syndrome in South Africa

The National Cancer Registry (2012) does not provide any information regarding Gorlin-Goltz Syndrome in South Africa.

According to the National Cancer Registry (2012) the following number of Basal Cell Carcinoma cases was histologically diagnosed in South Africa during 2012:

Group - Males 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	9 112	1:17	24,70%
Asian males	49	1:125	5,85%
Black males	347	1:263	3,06%
Coloured males	891	1:15	20,55%
White males	7 815	1:5	38,97%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	6 694	1:32	17,78%
Asian females	34	1:224	3,13%
Black females	324	1:472	2,02%
Coloured females	717	1:27	17,17%
White females	5 609	1:8	35,34%

The frequency of histologically diagnosed cases of Basal Cell Carcinoma in South Africa for 2012 were as follows (National Cancer Registry, 2012):

Group - Males 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	8	38	275	892	1 764	2 477	2 223	1 297
Asian males	1	0	3	4	8	11	13	7
Black males	1	0	17	39	73	99	74	35
Coloured males	1	4	21	87	163	245	200	135
White males	5	34	226	740	1 491	2 062	1 866	1 081

Group - Females 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	5	51	294	291	1 687	813	1 536	1 178
Asian females	0	0	1	4	6	9	8	7
Black females	2	9	30	37	46	72	62	62
Coloured females	1	6	31	58	127	177	150	131
White females	2	36	227	564	955	1 346	1 272	950

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

### Signs, Symptoms and Diagnosis of Gorlin-Goltz Syndrom

The most common symptom of Gorlin-Goltz syndrome is the development of basal cell carcinoma early in adolescence or young adulthood. Gorlin-Goltz syndrome is also responsible for the development of other cancers early in a person's life, including:

- medulloblastoma
- breast cancer
- non-Hodgkin's lymphoma
- ovarian cancer

People who have basal cell nevus syndrome often have unique physical features as well. Examples include:

- pitting in the palms of the hands or on the feet
- large head size
- cleft palate
- eyes that are spaced far apart
- a protruding jaw
- spinal problems, including scoliosis or kyphosis

Some people with basal cell nevus syndrome will also develop tumours in their jaw. These tumours are known as keratocystic odontogenic tumours and can cause the person's face to swell. In some instances, the tumours will displace the teeth.

If the condition is severe, additional symptoms may result. For example, it can affect the nervous system. This can cause:

- blindness
- deafness
- seizures
- mental retardation



#### Clinical features.

(a and b) Facial appearance of patient showed dysmorphic facial features, including relative macrocephaly (a) and ocular hypertelorism (b).

(c and d) Lateral and frontal view showing pectum excavatum.

(e) Vertebral anomaly characterized by cyphoscoliosis.

Casaroto *et al.* *Head & Face Medicine* 2011 7:2 doi:10.1186/1746-160X-7-2

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The doctor can diagnose Gorlin-Goltz Syndrome. He or she will ask about the patient's health history, if ever diagnosed with cancer, and if there is a history of the disease in the family. The doctor will also perform a physical examination to see for any of the following:

- keratocystic odontogenic tumours
- fluid on the brain that leads to head swelling (hydrocephalus)
- abnormalities in the ribs or spine

To confirm the diagnosis, the doctor may also order additional tests including:

- an echocardiogram
- MRI of the head
- biopsy (if you have tumors)
- X-ray of the head and jaw
- genetic testing

(Healthline).

A diagnosis of Gorlin-Goltz syndrome can be made if there are 2 major or 1 major and 2 minor criteria.

#### Major criteria

- Multiple (>2) basal cell carcinomas at any age or one basal cell carcinoma less than 20 years or >10 basal cell naevi
- Histologically proven odontogenic keratocyst or a polyostotic bone cyst
- Palmar or plantar pits (3 or more)
- Ectopic calcification: lamellar or early (<20 years) calcification of the falx cerebri
- Family history of Gorlin-Goltz syndrome

#### Minor criteria

- Congenital skeletal defects: bifid, fused, splayed, or missing rib, or bifid, wedged, or fused vertebra
- Large head with occipitofrontal circumference >97th percentile, with frontal bossing
- Cardiac or ovarian fibroma (benign tumour in heart or ovary)
- Medulloblastoma (a malignant brain tumour that usually arises in young children)
- Lymphomesenteric cysts (abdominal cysts full of lymph fluid)
- Congenital malformation: cleft lip and/or palate, polydactyly (extra fingers or toes), congenital eye defect such as cataract, microphthalmos (small eye) or coloboma (iris tumour)

(DermNet NZ).

### **Manifestations of Gorlin-Goltz Syndrome**

Gorlin-Goltz syndrome is a condition that affects many areas of the body and increases the risk of developing various cancerous and non-cancerous tumours.

In people with Gorlin-Goltz syndrome, the type of cancer diagnosed most often is basal cell carcinoma, which is the most common form of skin cancer. Individuals with Gorlin-Goltz syndrome typically begin to develop basal cell carcinomas during adolescence or early adulthood. These cancers occur most often on the face, chest, and back. The number of basal cell carcinomas that develop during a person's lifetime varies among affected individuals. Some people with Gorlin-Goltz syndrome never develop any basal cell

carcinomas, while others may develop thousands of these cancers. Individuals with lighter skin are more likely to develop basal cell carcinomas than are people with darker skin.

Most people with Gorlin-Goltz syndrome also develop non-cancerous (benign) tumours of the jaw, called keratocystic odontogenic tumours. These tumours usually first appear during adolescence, and new tumours form until about age 30. Keratocystic odontogenic tumours rarely develop later in adulthood. If untreated, these tumours may cause painful facial swelling and tooth displacement.

Individuals with Gorlin-Goltz syndrome have a higher risk than the general population of developing other tumours. A small proportion of affected individuals develop a brain tumour called medulloblastoma during childhood. A type of benign tumour called a fibroma can occur in the heart or in a woman's ovaries. Heart (cardiac) fibromas often do not cause any symptoms, but they may obstruct blood flow or cause irregular heartbeats (arrhythmia). Ovarian fibromas are not thought to affect a woman's ability to have children (fertility).

Other features of Gorlin-Goltz syndrome include small depressions (pits) in the skin of the palms of the hands and soles of the feet; an unusually large head size (macrocephaly) with a prominent forehead; and skeletal abnormalities involving the spine, ribs, or skull. These signs and symptoms are typically apparent from birth or become evident in early childhood. (Genetics Home Reference).

### **The Sun and Gorlin-Goltz Syndrome**

Individuals with Gorlin-Goltz Syndrome have an increased sensitivity to radiation, including radiation from the sun. This means that they need to take extra care in the sun. This is the same for anyone with Gorlin-Goltz syndrome, whether they have had a skin cancer or not. Sufferers should always use a high factor sunscreen (SPF 50) and cover up properly in the sun.

(Cancer Research UK).

### **Treatment of Gorlin-Goltz Syndrome**

Treatment of patients with Gorlin-Goltz syndrome involves surveillance for and treatment of the associated findings. Because most of the findings involve tumours (benign and malignant), treatment is often surgical (eMedicine.Medscape).

The first sign of Gorlin-Goltz syndrome may be the development of a medulloblastoma in a child aged 2 to 5 years, but luckily this is uncommon. Only a few children with medulloblastoma also have Gorlin-Goltz syndrome. If detected early enough, the tumour may be treated by surgery and chemotherapy.

Patients with Gorlin-Goltz syndrome often require surgery to remove jaw cysts in their 20s. Often, it is not until they are in their 30s or 40s that the basal cell carcinomas begin to appear so the diagnosis of the syndrome is often delayed.

All patients with Gorlin-Goltz syndrome should see a dermatologist for regular skin examinations so that basal cell carcinomas can be treated when they are small. This may require surgery or one of the many other treatments available for these tumours including cryotherapy, photodynamic therapy, fluorouracil cream and imiquimod cream. They should

not receive treatment with irradiation as this is liable to provoke the development of more tumours.

Some patients may require long term treatment with oral retinoids such as isotretinoin or acitretin. Advanced basal cell carcinomas may sometimes be treated with vismodegib.

Sun protection is vital to reduce the number of skin cancers developing but even complete protection will not prevent all basal cell carcinomas in patients with Gorlin-Goltz syndrome. (DermNet NZ; Jawa, *et al.*).

## **About Clinical Trials**

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

### Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

**Treatment** - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

**Prevention** - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer

**Screening** - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

**Diagnostic** - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

**Quality of life or supportive care** - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

### Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

### Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

### Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

### National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

### Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People

who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different “phase” in the clinical research process. The following phases are used for cancer treatment trials:

### Phases of a Clinical Trial

**Phase 0.** These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

**Phase I (also called phase 1).** These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

**Phase II (also called phase 2).** These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

**Phase III (also called phase 3).** These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for



a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

### Use of Placebos

The use of placebos as comparison or “control” interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

### Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

#### Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

#### Correlative research studies and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

#### When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by

patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care. (National Cancer Institute).

### **Medical Disclaimer**

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

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### Gorlin-Goltz Syndrome

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