Voice of the Patient Report

Gorlin Syndrome Externally Led Patient Focused Drug Development Meeting

"The Bad, the Ugly, the Pain, the Anxiety"

Meeting Date: October 8, 2021

Meeting hosted by: The Gorlin Syndrome Alliance

Submitted to U.S. Food and Drug Administration (FDA).

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Voice of the Patient Report: *Living with Gorlin Syndrome*

The mission of the Gorlin Syndrome Alliance (GSA) is to thoughtfully support, comprehensively educate, and aggressively seek the best treatments and a cure for those affected by Gorlin syndrome. The term 'alliance' emphasizes the union that formed between patients, the medical community, the pharmacological industry and the hope for a cure.

This Voice of the Patient report was prepared by the GSA as a summary of the input shared by people and families living with Gorlin syndrome during an Externally Led Patient Focused Drug Development Meeting (EL-PFDD). This meeting was hosted virtually on October 8, 2021.

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Acknowledgements:

This meeting is dedicated to those living with Gorlin syndrome and their loved ones. Many people living with Gorlin syndrome minimize or deny their problems, but at the meeting they shared what goes on behind closed doors: the bad, the ugly, the pain, the anxiety. The GSA thanks everyone in the Gorlin syndrome community, particularly the presenters who willingly shared their struggles and stories at the meeting. Thank you again for going to those dark places and telling your stories.

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Report Overview and Key Meeting Messages

> "*We are not cancer survivors. We are cancer livers, and I'm not talking about the organ, the liver. We live with cancer every day.*" – Julie, an individual with Gorlin Syndrome

This report provides a high-level summary of the perspectives generously shared by individuals and their families living with Gorlin syndrome who participated in the October 8, 2021, EL-PFDD meeting, and includes selected comments submitted through the online portal. The GSA has provided this report to the FDA, and it is publicly available for the many stakeholders in the Gorlin syndrome community, including government agencies, regulatory authorities, pharmaceutical and biotechnology companies, scientists, and health care professionals.

The input received from the October 8, 2021, EL PFDD meeting reflects a wide range of Gorlin syndrome experiences. As Gorlin syndrome has over 50 possible manifestations, some symptoms and impacts may not be captured here. This report intends to identify themes that emerged directly from people and families living with Gorlin syndrome to create a better understanding of (a) the health concerns and burdens of Gorlin syndrome in daily life, both common and more rare experiences that exist, and (b) the challenges and trade-offs in selecting an appropriate treatment, which highlights a massive unmet medical need for more effective and "less brutal" treatments for people living with Gorlin syndrome. Key meeting messages are as follows:

1. **Individuals with Gorlin syndrome experience a lifelong cancer burden**. The unremitting and recurrent nature of this rare genetic disorder means that more BCCs, jaw cysts and manifestations will always appear and/or recur. People living with Gorlin syndrome experience no relief, break or remission, and they know that undergoing painful, invasive, and disfiguring treatments will always be necessary. They also live with an underlying fear that the BCCs could metastasize and kill them or that some other manifestation could lead to a premature death.

2. **There is no cure and there are no FDA-approved treatments for the multitude of Gorlin syndrome manifestations**. Existing treatment approaches and lifestyle modifications do not stop the appearance of new BCCs, nor do they prevent jaw cysts and other from growing or recurring. Surgeries are often brutal, painful, and disfiguring, and treatment outcomes may be uncertain.

3. **Most individuals with Gorlin syndrome have a tremendous number of basal cell carcinomas during their lifetime, many over 1000**. Removal of these cancers is always painful, negatively impacts quality of life, and require time for recovery. These procedures cause increasing disfiguration over one's lifetime, as more skin is cut away.

4. **Gorlin syndrome can manifest in any organ system in the human body.** Most people living with Gorlin syndrome have multiple manifestations of the disease, which vary from one person to the next even within the same family. Manifestations can include basal cell carcinomas, jawbone tumors, hydrocephalus, ventricular asymmetry, brain tumors

(malignant and benign), ovarian cysts, large skulls, improperly formed bones, palmar pitting, as well as many other symptoms.

5. **Gorlin syndrome imposes a heavy psychological burden. This point was emphasized throughout the meeting.** People living with Gorlin syndrome spend their entire lives on high alert, waiting for "what's next", especially cancer and tumor occurrence and recurrence. They have endless worries and uncertainty about the future. Despite displaying unbelievable resilience, many people living with Gorlin syndrome described being worn down by the unrelenting nature of the disease and the long-term treatment impacts; these may include but are not limited to disfigurement, pain, and the erosion and loss of self-esteem. For this reason, some stop or burn out on being treated. This has led to pre-mature death.
6. **All activities of daily life are impacted.** Extreme lifestyle modifications are necessary to prevent sun and UV light exposure in this sensitive population. Monitoring and treatment by a variety of medical specialists is a way of life. It significantly impacts quality of life and the ability to live as the typical population does. Symptoms and treatments create barriers to regularly attending school, working, participating in sports and social activities, and developing relationships. To avoid passing the gene to the next generation, many described the excruciatingly difficult decision of not having children. Significant time and resources (financial and personal) are required to navigate the healthcare system to maintain high level of vigilance and appropriately manage the multitude of appointments and treatments (surgical and others) needed to care for oneself or a loved one. A global survey concluding in 2020 by the Gorlin Syndrome Alliance revealed that affected individuals and loved ones missed, on average, 25 days of work/school/activities in the prior year for treatments, appointments, and recovery.
7. **Diagnosis is often delayed by years or decades.** While the first signs and symptoms of Gorlin syndrome can occur in utero or infancy, a formal Gorlin syndrome diagnosis is often delayed for many years. The time before a diagnosis is characterized by uncertainty, bewilderment and fear, as new symptoms keep appearing. This time is also potentially catastrophic for those who receive x-rays and other ionizing radiation that will cause more BCCs later in life.
8. **Safe and effective treatments are needed**. People with Gorlin syndrome need a better way to prevent and manage the endless flood of basal cell carcinomas; a clinically meaningful outcome for the Gorlin syndrome community is a 30% reduction in BCCs. Preventing transmission to the next generation and treating the root cause of the disease were also priorities. People living with Gorlin syndrome need a better way to treat and reduce the recurrence of jaw cysts that can result in the loss of permanent teeth, disfigurement, and facial numbness.

   More humane treatments will <u>not only</u> lessen the physical damage and scarring but tremendously improve the psychological impact and quality of the lives of all those affected with and by Gorlin syndrome.

Introduction and Meeting Overview

The Gorlin Syndrome Externally Led Patient Focused Drug Development (EL PFDD) meeting was hosted by the Gorlin Syndrome Alliance (GSA). This meeting was held to provide listeners a deep understanding of the symptoms and burdens associated with Gorlin syndrome in daily life, as well as the massive unmet treatment needs of this community. It took place virtually for participant's health and safety due to the COVID-19 pandemic and to permit increased participation across the United States and around the world.

This EL-PFDD meeting was modeled after the work of the FDA's Patient-Focused Drug Development (PFDD) initiative. EL-PFDD is a systematic way of gathering patient perspectives on their condition and on available treatments. The information gathered at the meeting is presented in this *Voice of the Patient* report. The information in this report will be used to guide therapeutic development and should inform the FDA's benefit-risk evaluations when assessing therapies to address Gorlin syndrome. The hope is that this information will ultimately catalyze better treatments and ultimately a cure for those affected by Gorlin syndrome.

Overview of Gorlin Syndrome

(*This overview was adapted from the slides and clinical overview presentation provided by Dr. Joyce Teng, a Professor of Dermatology and Pediatrics at Stanford University at the October 8, 2021, EL-PFDD meeting*.)

Gorlin syndrome is a rare genetic disorder with a tremendous lifetime disease burden. Gorlin syndrome is also known as basal cell nevus syndrome, nevoid basal cell carcinoma syndrome, basal cell carcinoma nevus syndrome (BCCNS) or Gorlin-Goltz syndrome after Drs. Robert Gorlin and Robert Goltz who first described the syndrome in 1964. More than thirty years later, a mutation in the *PTCH1* genes was identified as an underlying cause of the syndrome. Over 90% of patients carry a mutation in *PTCH1* gene and a small percentage of patients have mutations within the *PTCH2* and *SUFU* genes. The *PTCH1* gene is a tumor suppressor gene, which functions to inhibit the Hedgehog signaling pathway. When the gene is mutated, it is unable to perform this inhibitory function, allowing the Hedgehog signaling pathway to drive cancer and tumor development.

Gorlin syndrome is primarily a hereditary disorder inherited in an autosomal dominant fashion, which means that for some families, multiple generations are affected. Forty percent of people living with Gorlin syndrome have a *de novo* mutation, which means that no other family members are affected. The disease affects an estimated one in 30,000 - 50,000 people.

Prior to the availability of genetic analysis, Gorlin syndrome was diagnosed by a combination of clinical characteristics and findings. Gorlin syndrome is a multi-system disorder and can affect all parts of the body. Basal cell carcinomas (BCCs), the most common manifestation, are a type of skin cancer that appear on the entire body, even in some children. Benign but aggressive and frequently recurrent jaw cysts called odontogenic keratocysts (OKCs) or keratocystic odontogenic tumors (KCOTS) are another major manifestation. Gorlin syndrome has myriad of other manifestations including palmer/plantar pits (small depressions or pits in the palm of the hand and soles of the feet), calcification of the falx cerebri (in the brain), improperly formed bones of the spine, ribs, and a large skull (macrocephaly), as well as ocular anomalies. Gorlin

syndrome includes many other types of cancers such as medulloblastoma (in the brain), as well as ovarian or cardiac fibromas. The disease manifests early: often a large skull is apparent before or at birth, with hydrocephalus, as well as some developmental abnormalities such as cleft lip/palate and scoliosis. Not all people living with Gorlin syndrome will experience every manifestation, but lifelong surveillance and diagnostic imaging is required as new growths and symptoms keep emerging and recurring.

Gorlin syndrome has a significant physical burden related to the unrelenting skin cancer development as well as the resulting surgeries, pain, and disfigurement. The psychological burden of Gorlin syndrome cannot be understated, as it profoundly impacts people living with the syndrome, their families, and caregivers. Employment, marriages, family relationships, and social lives are significantly impacted. People living with Gorlin syndrome, and their loved ones live in constant fear and anxiety for the future, because of the uncertainty about when and where cancer will appear next.

Results of a survey conducted by Stanford revealed that on average, people living with Gorlin syndrome experience over 200 surgeries in their lifetimes. Each basal cell carcinoma requires certain surgical interventions such as cryosurgery (freezing), photodynamic therapy, laser surgeries, electrodessication, excision, or Mohs micrographic surgery. Some of the medical treatments include retinoids (topical and systemic), imiquimod (5-FU/itraconazole/ingenol mebutate [IMB]) are frequently prescribed. Jawbone cysts require invasive and painful surgeries. Hedgehog inhibitors (vismodegib, sonidegib) are a relatively new therapy for Gorlin syndrome. While these are efficacious as measured by reductions in tumor size, therapy has significant adverse events that patients require therapeutic holidays and tumors return soon after the therapy is discontinued. Overtime resistance to therapy may develop and some of these skin cancers could metastasize that lead to increased risk of mortality.

As 25% of all human cancers were believed to have some portion of their oncology driven by excess hedgehog signaling, a therapy to help people living with Gorlin syndrome is likely to have enormous impacts for people living with other cancers as well.

Meeting summary

The October 8, 2021, Gorlin Syndrome Externally Led Patient Focused Drug Development (EL PFDD) meeting was co-moderated by Julie Breneiser, Executive Director of the Gorlin Syndrome Alliance and Larry Bauer, a Senior Regulatory Drug Expert with Hyman, Phelps and McNamara. They opened the meeting by welcoming and thanking meeting participants for their attendance. An overview of the meeting structure was provided and individuals with Gorlin syndrome and their caregivers were encouraged to contribute to the dialogue via online polling, calling in by phone, and contributing written comments using the online portal.

Dr. Felisa (Sally) Lewis, a medical dermatologist and Clinical Reviewer in the Division of Dermatology and Dental Products within the Center for Drug Evaluation and Research at the FDA provided a welcome from the FDA. She explained the role of the FDA in protecting and promoting public health by regulating drug development and research and in monitoring the status of drugs when they are on the market. She described the patient-focused drug

development process and how the FDA wants to hear from patients about how Gorlin syndrome impacts their daily lives and how patients view the benefits and risks of possible new treatments. Dr. Lewis defined a clinically meaningful outcome as one that improves a patient's experience in terms of survival, feeling, and function. Dr. Joyce Teng, a Professor of Dermatology and Pediatrics at Stanford University provided a medical and clinical overview of Gorlin syndrome.

Online polling was used to determine the demographics of the meeting attendees living with Gorlin syndrome and are summarized below and presented in **Appendix 1**. Almost half, or 49% of poll respondents were individuals with Gorlin syndrome and 51% were relatives or care partners of someone living with Gorlin syndrome. Just over half of poll respondents (52%) were located in the US Eastern time zone, followed by the US central time zone (19%), US mountain time zone and Canada (8% each), with additional representation from US Pacific time zone, Hawaii, Europe, as well as other countries. Just over half, or 54% of people living with Gorlin syndrome represented at the meeting were female, 41% were male and 4% identified as other. While 32% of poll respondents represented people over the age of 51 years, an equal number, 32%, represented children aged six to 15 years. Both the 21-35 and 36-50-year age groups included 17% of respondents. All poll respondents first experienced Gorlin syndrome symptoms before the age of 35, with over half of poll respondents, or 52%, first experiencing a Gorlin syndrome symptom before the age of five years. Julie Breneiser pointed out that the emergence of symptoms is not always equated with a diagnosis, and for many, a formal diagnosis is delayed.

The total meeting attendance was 270, with 48 people living with Gorlin syndrome, 39 caregivers, 16 family members and 64 friends, 39 FDA representatives, 29 industry and biotech representatives, 19 health care providers and medical students, 9 scientists, and 5 attendees from non-profit organizations.

The Gorlin Syndrome EL-PFDD meeting was structured around two key topics. The morning session was structured around Topic 1: *Symptoms and Daily Impacts of Living with Gorlin Syndrome*. The afternoon session addressed Topic 2: *Current and Future Treatments for Gorlin Syndrome*. The meeting agenda is in **Appendix 2**, and the questions provided for meeting discussion are in **Appendix 3**.

The morning session continued with five pre-recorded panelists who were selected to represent a range of experiences of people or loved ones living with Gorlin syndrome. They described the stories of challenging childhoods, the emergence of distressing symptoms and delayed diagnoses. Even with genetic testing now available, there can still be a lengthy journey to diagnosis. They described a myriad of symptoms and the impacts that these have had on their lives. Larry Bauer moderated a discussion between several people who served on a live Zoom panel as well as people who dialed in by phone. Additional relevant comments entered through an online submission form were read by Julie Breneiser. The names of panelists and callers are listed in **Appendix 4.**

The afternoon session opened with a pre-recorded panel of five people living with or related to individuals with Gorlin syndrome who described different medical therapies and other treatments they use to address their disease manifestations. Panelists described painful procedures, disfiguring surgeries and soul-deteriorating recurrences. Again, meeting attendees participated in online polling, called in and submitted written comments. Their voices were added to the moderated discussion by Julie Breneiser and Larry Bauer. At the end of panel 2, James Valentine provided a summary of the key meeting points and Julie Breneiser concluded the meeting by thanking all the participants and attendees.

The online polling results are included in the body of the report, both as graphs and as narrative**.** Photos of Gorlin syndrome manifestations are included in **Appendix 5**. To include as many voices as possible, an online comment submission portal was open for two weeks before and 30 days after the meeting. Selected comments are included in the body of this report, and all submitted comments are included in **Appendix 6**. Unless otherwise indicated, quotes in this report are from individuals living with Gorlin syndrome.

This *Voice of the Patient* report was provided to the Food and Drug Administration and is also available for sponsors, industry leaders developing new treatments for Gorlin syndrome, and any other interested individuals. The final report, the meeting transcript, and a recording of the meeting can be found at: (https://gorlinsyndrome.org/). According to YouTube statistics, the meeting has been streamed over 520 times as of March 7, 2022.

TOPIC 1: Symptoms and Daily Impacts of Gorlin Syndrome

During the Gorlin syndrome EL-PFDD meeting, attendees shared their stories about discovering the first symptoms in themselves or their children, stories of diagnosis and even more disturbingly, delayed diagnosis. They described what it was like to develop yet another bewildering manifestation, and then after enduring lengthy, painful, and invasive treatments, have the same symptoms recur, again and again.

Leslie, the mother of a five-year-old boy with Gorlin syndrome, described how Gorlin syndrome manifestations affected him in his first five years of life. Before birth, her son's head size and large ventricles were of concern. The cleft in his soft palate interfered with nursing and was surgically repaired at 10 months of age, a challenging and painful surgery. A medulloblastoma was removed with a craniotomy in a full day surgery, followed by six months of aggressive chemotherapy. "*Getting the Gorlin syndrome diagnosis was like the pieces of a puzzle finally fitting together. … In many ways, it was a relief to have a diagnosis. We now had a clear path. We now knew what to expect, but it was also overwhelming."* Leslie's son's diagnosis was made before the age of four, which is atypically early.

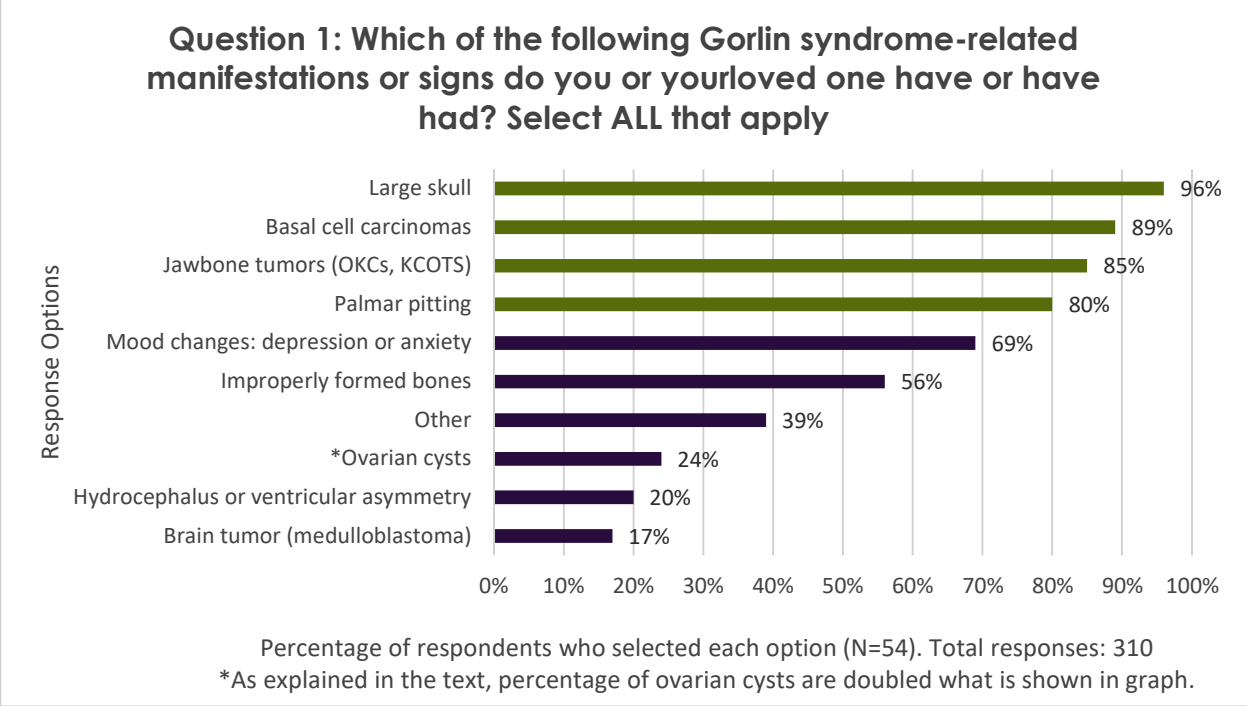
Duane, the grandfather of a 13-year-old boy with Gorlin syndrome described the appearance of mysterious symptoms in his grandson. *"Unfortunately, from birth, there were a lot of questions. We did not know what was going on. In spite of being in Chicago with great facilities at the Children's Memorial Hospital, where he had his initial six-hour cranial reconstructive surgery at 10 months of age, he was not formally diagnosed with Gorlin syndrome thru genetic testing until he was eight years old. He is now 13."*

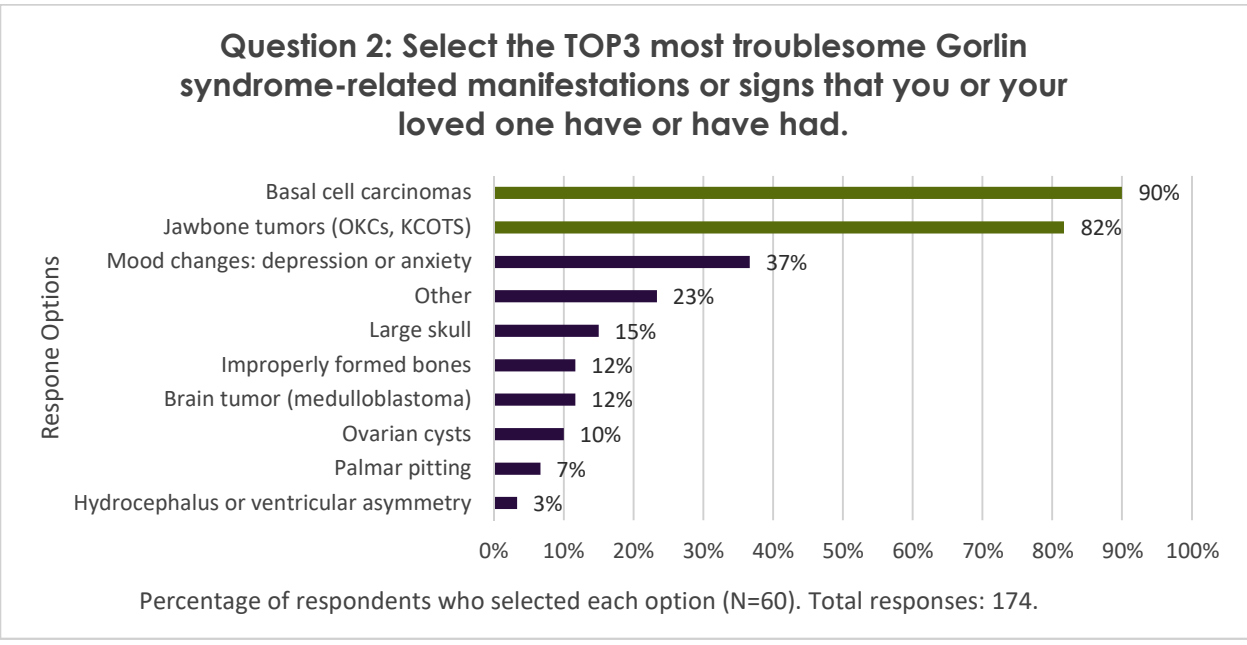
Meeting attendees used many poignant metaphors to describe what it was like to live with Gorlin syndrome.

Erika, the mother of a child with Gorlin syndrome described the disease as a "*medical time bomb*", "*a riptide*" and "*a train wreck*". She expressed how her coping strategy was to hover at a place between reality and denial. Roni, the mother of an adult son with Gorlin syndrome described the disease as "*living on a volcano, where you absolutely have no idea what's coming next. … You know though, it's coming."* John J. described how Gorlin syndrome, "*Is a juggernaut that quietly churns away in your body. It's unstoppable. And you never know when it's going to make an appearance."*

Gorlin syndrome-related manifestations or signs

Meeting attendees used online polling to first select all the Gorlin syndrome-related manifestations that they or their loved ones had experienced. They were then asked to select their top three most troublesome. The first graph shows more than 80% of poll respondents experienced a large skull, BCCs, jawbone tumors (OKCs), and palmar pitting. These top responses are shaded in green. Each poll respondent selected an average of 5.7 manifestations or signs.





The second graph above clearly shows the most troublesome manifestations of Gorlin syndrome. BCCs were selected by 90% of poll respondents and jawbone tumors were selected by 82% of poll respondents.

Each of the Gorlin syndrome-related manifestations are described in descending order of the most troublesome, along with selected quotes. Additional symptoms identified during the meeting and in the online comments are also described.

Gorlin syndrome manifestations are illustrated by powerful photographs in **Appendix 5**. Readers are also encouraged to read the impactful and full-length comments submitted online, in **Appendix 6**.

Basal cell carcinomas

Basal cell carcinomas were selected by 90% of poll respondents as the most troublesome manifestation and are the second most prevalent manifestation, experienced by 89% of poll respondents. This is consistent with a recent Global Gorlin Syndrome Community Survey, which included 261 responders.[1] People living with Gorlin syndrome experience hundreds - if not thousands - of BCCs over their lifetimes. BCCs are malignant and need to be removed by painful procedures such as Mohs surgery, curettage, cryotherapy, laser therapy and other approaches, including topical creams.

Since his diagnosis with Gorlin syndrome 40 years ago as a teenager, John W. said, *"The manifestations of my syndrome then and since have been BCC skin cancer lesions and OKC jaw tumors. I stopped counting my BCC skin cancer lesions years ago once I surpassed 1000 BCC biopsies and procedures."*

Bob described how his BCCs escalated in childhood and as he got older, their treatment became invasive and required "*repeated removal of 10 – 15 at a time, five to six times a year. …The scarring from the continued removal of some cancers became a challenge both physically and mentally*."

Brian experiences constant bleeding from his untreated BCCs. **"***I have at least 40 BCCs on my face with about 100 on my shoulders and back. They bleed a lot! If I rub my nose a few will start bleeding, or if someone rubs or grabs my back, I start bleeding. I wear black shirts so people don't see my blood stained shirt. My bed sheets and bed are always bloody from me rolling in my sleep*."

Please refer to the photos of BCC shown in **Appendix 5**.

Jawbone tumors (OKCs or KCOTS)

Jawbone tumors, including odontogenic keratocysts (OKC's, or previously named keratocystic odontogenic tumors - KCOT or KOT) are the second most troublesome Gorlin syndrome-related

[1] Neale H, Breneiser JA, Hawryluk EB. Pediatric basal cell carcinoma burden and management preferences in Gorlin syndrome: A survey study. *JAAD International* 2021; **5**: 49-51.

manifestation reported by 82% of respondents and are experienced by 85% of all poll respondents. The terms OKCs and KCOTs both refer to the same cystic/lytic tumor, however OKC is used in this report.

Despite having numerous jawbone tumors excised throughout their teens and into early adulthood, often involving both tooth loss and reconstructive surgeries, these tumors keep recurring. Kristi said, "*One thing I'd like the FDA to know is keratocystic odontogenic tumors are not your run of the mill dental cyst. … These are specific to this condition and are much more invasive and much more difficult to control. Sometimes they're not recurrences, but new occurrences because there are sister cysts that are lying there dormant, waiting to ignite*."

For Bob, *"My first jaw cyst had grown undetected for years. What was scheduled to be a routine tooth extraction, evolved into an all-day surgery and the loss of several [permanent] teeth. I was 15 years old at the time. Having [already] had many years of syndrome related issues, this procedure was the beginning of a Gorlin's diagnosis and a life of reconstructive surgery."*

Please refer to the photos of jaw cysts shown in **Appendix 5**.

Mood changes: depression or anxiety

The third most troublesome Gorlin syndrome-related manifestation was mood changes: depression or anxiety. This was selected by 37% as one of the top three impacts and experienced by 69% of poll respondents. Mandy said, *"Having Gorlin syndrome, I have always felt different.… I have suffered from anxiety and depression my whole life trying to deal with this syndrome."*

People living with Gorlin syndrome and their families described anxiety about pain and procedures. Kevin described how his son with Gorlin syndrome "*Has a disturbingly deep anxiety about pain, which is a terrible thing for a kid who has to continually go to the doctor with Gorlin syndrome.*"

Gorlin syndrome negatively impacts the quality of lives of those affected with and by the disorder in a variety of ways. The description, of "mood changes", does not even begin to describe the heavy psychological burden that this disease has on the individuals living with Gorlin syndrome, as well as their parents, spouses, children, and caregivers. The psychological burden of Gorlin syndrome is described at the end of this section, on page 18.

Other

A total of 23% of poll respondents selected "other" manifestations as one of their top three most troublesome, and 39% of poll respondents reported experiencing "other" manifestations. People living with Gorlin syndrome described these manifestations during the meeting and in online comments, and they included: other growths and tumors, congenital abnormalities- such as cleft lip/palate, webbed toes and a missing kidney, delayed development and speech issues, pain - including nerve pain, leg cramps, arthritis and headaches, ocular challenges, numbness from nerve damage, gastrointestinal issues such as irritated bowel syndrome (IBS) and polyps,

meningeal calcifications, and tragically, death from metastatic disease in spite of vigilant self-care.

Other growths and tumors. Participants described pelvic osteosarcoma, malignant and benign brain tumors, cardiac and ovarian fibromas, mediastinal masses and keratosis, and non-cancerous growths on the skin.

Brandon was diagnosed with a medulloblastoma at 4, a pelvic osteosarcoma at 19, and a meningioma at the age of 26. He described his pelvic osteosarcoma. "*This malignant peripheral nerve sheath tumor was a long-term side effect caused by the spinal radiation treatments I received for the brain tumor 15 years prior. ... This massive tumor was embedded in my pelvic bone and was cutting off the nerves to my leg. I lost the ability to walk. … Last year, I was diagnosed with another brain tumor called meningioma. Doctors say it is either a radiation induced meningioma from the radiation for the first brain tumor when I was four, or it could be from having Gorlin syndrome, because it also happens to Gorlin Syndrome patients that have not had brain irradiation. Either way, it's there."*

Sherry described how her adult son with Gorlin syndrome was recently diagnosed with numerous growths. "*In the last year his surgeon thinks he saw something in his nasal passage so had scans done. And another doctor who was seeing him about pain in his neck due to scoliosis saw nodules on his lung*."

Congenital abnormalities including cleft lip/palate, webbed toes and missing kidney.

Delayed development and speech issues. Bob described how, "*My birth and toddler years were complicated by a very large head, as well as being slow to talk, a speech impediment requiring speech therapy as a child, and challenges to this day*."

Leslie, the mother of a boy with Gorlin syndrome described how her son experienced, "*Frequent ear infections, torticollis, which affected his movement on his right side and required physical therapy for that as well as challenges with head control, rolling over and later crawling and walking*."

Pain - including nerve pain, arthritis, and headaches. For Clara, "*The most painful thing for me is an ongoing nerve damage done from one of these jaw cysts*." She described how the nerve damage leaves her entire mouth burning all the time.

John H. said, *"I have painful arthritis in my neck, hands, knees and shoulders."* He vividly described extreme headaches due to arthritis in his neck, which sometimes cause him to pass out.

Ocular challenges. Meeting attendees described cataracts, pre-glaucoma, strabismus, and other ocular issues.

For Meredith's daughter with Gorlin syndrome, "*She had an eye patch because her eyes had difficulty collaborating. By the time she was four, she had had two eye muscle surgeries*."

John stated he is blind in one eye due to a congenital cataract.

Julie described how her son with Gorlin syndrome was diagnosed with pre-glaucoma at the age of 13.

Charlotte experienced a catastrophic outcome of cataract surgery at the age of 26, which resulted in internal bleeding, the shrinking of her eye, and ultimately the loss of vision in that eye.

Numbness from nerve damage. John H. described how his jaw cysts, and surgery to remove them have damaged the nerves to the lower half of his face. "*Without feeling, I can't feel it when I've cut myself shaving."*

Gastrointestinal issues. Bud described having, "*Ongoing abdominal issues like IBS and polyps in my colon*."

Death. Even with the best and most proactive care, the cancer sometimes metastasizes to other organs.

Roxanne "Rocki" described her late husband with Gorlin syndrome. "*Even though he was proactive in his own care, the skin cancer went from his lymph nodes to his lungs, and he had an agonizing and breathless death."*

Ovarian cysts

Ovarian cysts are a top concern for 24% of all poll respondents. This gender specific manifestation is experienced by approximately half of female poll respondents.

When Elizabeth presented with a rapidly growing ovarian fibroma at the age of 12, she suddenly looked six months pregnant. "*I had an ovarian fibroma that grew to be the size of a football in a week. Essentially, it took out one of my ovaries*." The fibroma was a solid mass which was removed in one piece, leaving Elizabeth with an enormous scar.

After giving birth to twins, Kevin described how his wife with Gorlin syndrome, "*underwent surgical intervention to remove both ovaries as a result of fibromas that were discovered during delivery, as well as a benign mass in her lower left abdomen. Both of these are related to Gorlin syndrome."*

Large skull & Cranial bone issues

A total of 15% reported a large skull (macrocephaly) as one of their most troublesome Gorlin syndrome-related manifestations, yet 96% of all poll respondents experienced this manifestation. For many, a large skull was the first indication of Gorlin syndrome.

Kevin described how his infant was, "*diagnosed with sagittal craniosynostosis, which means the bones at the top of the skull fused together prematurely, causing his forehead to become quite bulbous*."

For some, invasive surgery is required. Duane's grandson with Gorlin syndrome had an enlarged skull and metopic synostosis. "*Before he was one year old, he had a six-hour cranial*

reconstruction surgery. At the age of six he had another skull surgery to insert three plates over the skull where it never grew together. Up until that time he wore a helmet for any outdoor activities. Due to the surgeries, he has permanent scarring and hair loss from ear to ear."

Please refer to the photos of skull malformations shown in **Appendix 5**.

Improperly formed bones

Improperly formed bones were in the top three most troublesome Gorlin syndrome-related manifestations for 12% of poll respondents and were reported by 56% of poll respondents. People living with Gorlin syndrome described this manifestation.

John H. said, "*I have dextroscoliosis in my back. Other bony issues include bifid ribs and a missing rib. My legs are turned outward at the hips, which puts me in new shoes every three to four months*."

Kevin described how his son's many skeletal issues affect him. *"His S shaped scoliosis was relatively minor [at diagnosis] and didn't require treatment. But three years later, it's become more pronounced*." He also described how his son "*can't roll his shoulders due to elevated scapula from Gorlin syndrome, which makes throwing a challenge*."

Brain tumor (medulloblastoma)

A total of 12% reported brain tumors (medulloblastoma) as one of their top three most troublesome manifestations, and 17% of poll respondents reported experiencing this.

Connie's daughter with Gorlin syndrome had a malignant medulloblastoma and benign meningiomas. These are brain tumors that are Gorlin syndrome manifestations. "*My daughter was diagnosed with a medulloblastoma when she was 15 months old. She had two years of chemo followed by radiation to the brain and spine at the age of three. She's had multiple meningiomas in her brain, ovarian fibromas, as well as multiple basal cell carcinomas.*" It should also be noted that despite a lifetime of manifestations, Connie's daughter was not diagnosed with Gorlin syndrome until the age of 32.

Brandon was diagnosed with medulloblastoma at the age of four years. "*The tumor made me very sick. The surgery to remove the tumor left a big scar. And the radiation treatments left me with many challenging and permanent side effects*."

Palmar pitting

Although palmar pitting was the fourth most reported manifestation, experienced by 80% of respondents, only 7% of poll respondents reported this as a top three most troublesome manifestation, and very few comments were made about palmar pitting during the meeting.

Hydrocephalus or ventricular asymmetry

Hydrocephalus is an abnormal buildup of fluid in the ventricles (cavities) deep within the brain. It can cause pressure on delicate brain tissues and lead to developmental delay, as well as other lifelong impairments. Ventricular symmetry is an unequal accumulation of fluid in one brain

ventricle compared with the other and may cause similar problems to hydrocephalus. One fifth, or 20% of the poll respondents reported experiencing these symptoms. While only 3% reported this as one of their top three most troubling manifestations, the impacts can be extreme.

Kevin described the trauma experienced by his infant son with Gorlin syndrome, who was in the pediatric intensive care unit for 15 weeks. *"He was experiencing significant intracranial pressure caused by hydrocephalus, which resulted in incessant crying and continual projectile vomiting after virtually every meal. We watched in horror as this frontal bossing [from extra fluid inside the brain expanding the infant skulls' size] became significantly more pronounced over the weeks and months*. **…** *At six months when he was old enough to withstand anesthesia, he underwent a cranial stripectomy in which doctors removed a 17-centimeter strip of bone, which is roughly the size of a dollar bill, from the top of his skull. They also implanted a ventricular peritoneal shunt to help alleviate the buildup of fluid [hydrocephalus] on his brain*."

Psychological burden of Gorlin syndrome

Although not presented as a response option on any of the online polls, many meeting attendees described the psychological burden of Gorlin syndrome.

Bob said, *"Not to diminish the medical burdens of having Gorlin syndrome, but the mental and emotional burden is never easing and never ending."*

Dan said, *"I am not a survivor. How can I be a survivor, when I know every six to eight months, I have to go endure five more skin cancers removed that were not there six months ago? I have done this for more than 40 years. And until there is a cure, will continue to every year I am still alive. I'm not sure many people understand the psychological pain to a disease like BCCNS. It's a toll. A 50-year-old man, lying on a table, tearing, not from pain, but just knowing I'm in a fight I can never win. So many facets of this syndrome are brutal."*

John H. spoke to the never-ending nature of the disease. "*Manifestations last a lifetime - there is no point at which one grows out of this or emerges from a phase of this."*

***Gorlin syndrome is traumatic for children*.** For Kevin's son with Gorlin syndrome, "*the discovery of his first jaw tumor at age nine was psychologically impactful. His oral surgeon performed a marsupialization to remove the cyst, but the hardware from his procedure impacted him in a way that we had not imagined possible. It made him hesitant to smile for pictures. No nine-year-old should ever be made to feel self-conscious about smiling."*

Kaylene was diagnosed with a cardiac fibroma in early childhood. "*It was a shock to my family. …We were eventually able to find a surgeon who would do this type of surgery, but it was very emotionally draining for my parents, very emotionally draining for me… I can remember being just being so scared about that surgery. … that was just such a traumatic experience, just having to go through an invasive surgery like that*."

Some described being bullied for the way that they looked. DB said, "*When I was younger, I was bullied for my symptoms like my 'Jimmy Neutron' head.*"

For Bob, "*Bullying began at elementary school and was relentless due to my head size. [The fact that I was] required to go to the speech bus in the parking lot each morning only added to the ridicule. Through middle and high school, the harassment from my very large head would continue*."

Some expressed anger about their situation. Beth described how her teenage son living with Gorlin syndrome has started to react to his complicated treatment routines involving topical creams and chemotherapy for BCCs, as well as sunscreen. "*He understands that not doing that is going to cause more surgeries, but at the same time, he's angry. He's angry that he has to get up and go through this process every morning, every night. And for all of his friends, this is not part of their lives.*"

The psychological burden is particularly heavy for caregivers and parents. Beth confided that she wished that her child living with Gorlin syndrome had a different, more treatable cancer. *"Sometimes I wish that he had leukemia or a brain tumor or something that was treatable. And we could say, 'Now you're in remission, and we can move on from this.' There will never be a day that I will wake up when I will know my son is cancer-free, and there will never be a day for him that he will wake up and say, "I am cancer free.*" That is a heavy burden for a child.

Stacy, the mother of a daughter with Gorlin syndrome, says- "*We know more surgery, more needles, more permanent scarring are in her future. Some days it is incredibly overwhelming that I start crying just getting her ready for school or swim class. BCCs grow everywhere, even on her labia. They're relentless. I wish more than anything it was easier to manage, and I know there will be other manifestations we'll need to address and manage as she grows. So, this is just the tip of the iceberg*."

Patricia, the mother and caregiver of a son living with Gorlin syndrome described how, "*Seeing what our loved ones go through with this disease is extremely stressful, and it's really hard because the future is so unknown, and you don't know what they're going to be facing next and when these things might happen. … It's so important that we also recognize the burden on the caregivers on this journey, because that is the best support system that the patients have sometimes. And sometimes it gets to be a little much*."

Roni, a caregiver for her adult son with Gorlin syndrome, agreed. "*The grind of it, the daily grind of it, it never leaves you. You don't have that moment in life where you have that release where you could say, 'I just don't need to worry about this for now.' [Gorlin syndrome] doesn't affect only the person who has it, or even the caregiver. It's your entire family, and how you spend your time, and what you do with it*."

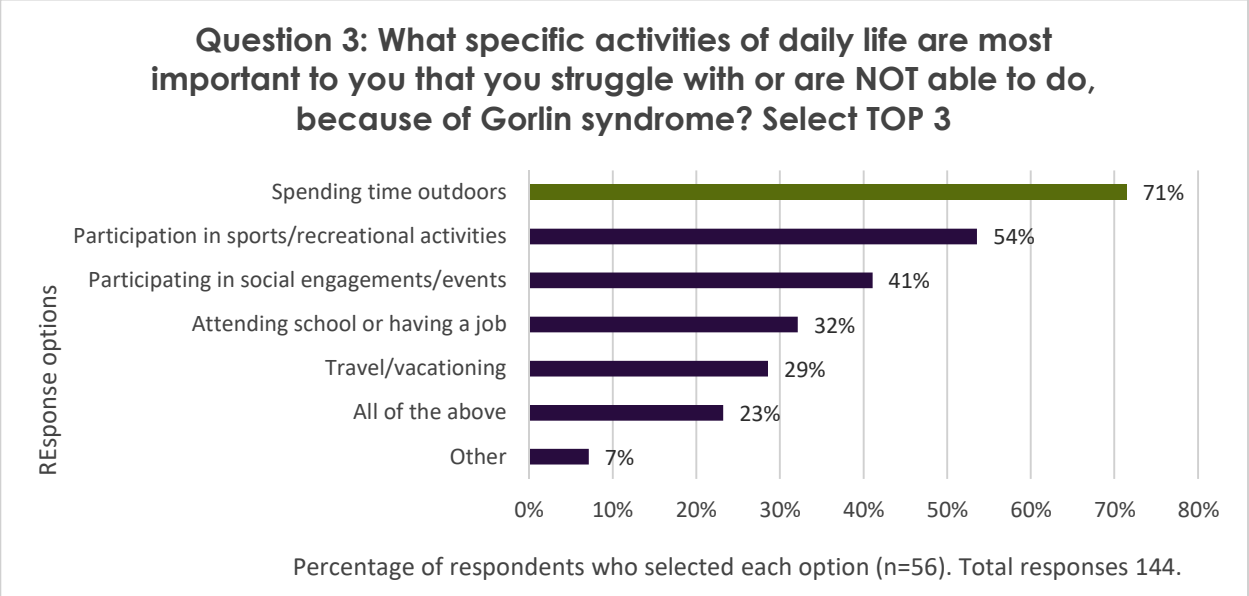
As an individual living with Gorlin syndrome, Alice described what it was like raising a child who does not have the disease. *"I feel blessed every day to know that he does not have Gorlin syndrome. It's been a challenge for me just trying to keep things as normal for him and have him not be affected by being sucked into the routines and the stress of [me] being treated all the time*."

Specific activities of daily life that are affected by Gorlin syndrome

> *"I can hear the disease invading me when I am idle. The only time I cannot hear it is when I'm creating enough noise to silence it. Therefore, I must work, I must run. You see, living with Gorlin is tough to explain, and even harder for others to understand. We are vulnerable, we are targeted*. – Bob, an individual with Gorlin syndrome

Meeting attendees used online polling to select the top three activities of daily living that were the most important to them that they were not able to do or that they struggled with due to Gorlin syndrome. Impacts and activities are described below.

Readers are encouraged to read the impactful and full-length comments submitted online, **Appendix 6**.



Spending time outdoors

Spending time outdoors is the activity of daily life that is most challenging to people living with Gorlin syndrome. Skin exposure to ultraviolet light creates more BCCs because people living with Gorlin syndrome are missing a functional tumor suppressor gene.

For Beth's son who is living Gorlin syndrome, "*The biggest challenge in his life currently is the sun. He's 13, he wants to go outside, he wants to play with his friends. He has to wear a bucket hat. He has to wear sun protective clothing. It's hard to tell your child, your son, when they want to go outside and play that they should probably stay inside because the UV rays are high that day. …Everything outside is a struggle. Water sports, any outdoor sport really. Every time we're outside, it's harmful for my son."*

Lornna said, "*We live in Hawaii where the sun almost always shines bright, and we are surrounded with beautiful beaches to enjoy. Since [our son was] diagnosed with Gorlin*

syndrome, our family has settled for going to the beach early in the morning and leaving by 10 am to avoid the damaging effects of the sun."

With Gorlin syndrome, Sasha says that "*Limiting the outdoor errands and activities I do per week are necessary because of the risks of this syndrome, even at the cost of seeing friends and family."*

Participation in sports/recreational activities

Over half, or 54% of meeting participants reported that Gorlin syndrome interferes with participating in sports and recreational activities. Meeting participants described challenges with finding appropriate sports equipment, challenges with poor vision and weak muscle tone.

For Brandon, "*Before the pelvic osteosarcoma, I was able to play soccer, basketball, and other sports with my brother and friends, go for long adventurous bike rides and was learning how to drive a car. Now, because of the damage to the nerves in my leg and the changes to my body from the osteosarcoma surgery, I can't safely play any sports, propel myself on a bike or drive a car."*

The mediastinal mass in John H.'s chest damaged his diaphragm to the point where he finds it difficult to catch his breath. He is also impacted by having vision in only one eye from a congenital cataract, a Gorlin syndrome manifestation. *"With no depth perception, ball sports have been out of bounds for me, for most of my life. Sports are such an integral part of so many people's lives. I would give anything to simply catch a ball."*

For Kevin's son, *"The pain of always being picked last - or worse, being left out entirely has turned him off of sports altogether, which is especially difficult because he has a twin brother who is more typical in that regard."*

Participating in social engagements and events

A total of 41% of respondents reported that Gorlin syndrome interfered with their participation in social engagements and events. Many described how Gorlin syndrome was socially isolating, has created awkward situations, and prompted them to withdraw from social life.

Brandon described the social impacts of Gorlin syndrome, particularly the BCCs. *"People react differently to you when you have a piece of your scalp healing from a skin graft after Mohs surgery. It's not a pretty sight and most people don't know how to handle it, what to say, or even make eye contact with you. Makes it very hard to be in social situations, attend events or relationships."*

Toby described how, "*My uncle and mother had so many surgeries, grafts, radiation burns, etc., that they seldom went out in their later years. People stare at oddities*."

Jenni described how Gorlin syndrome, "*Affects anybody in my circle, in my family, with my friends, when we're planning events. They have to plan, … Are we going somewhere where there's shade? Can Jenni find shade? Do we have to plan our events during cooler times, in the*

evenings or early mornings? … If you're planning a vacation with multiple people, it affects everybody in that group."

Attending school or having a job

Almost a third, or 32% of poll respondents reported that Gorlin syndrome interfered with attending school or having a job.

Several described how disfigurements and bleeding interfered with finding and maintaining employment.

Tom described the fine line between balancing work and treatments. *"Gorlin syndrome affects people's ability to go to work. For some, the disease is so disabling, whether it's the brain, the speech, the sight, … they can't work. Even if people are not disabled to the point where they can't work, it still can be very difficult to get a job or hold a job because they need so many surgeries or treatments which often involve travel because a lot of times they don't have these medical resources near them. There's the frequency of those treatments and there aren't enough sick days and vacation days to cover that."*

The learning challenges resulting from Brandon's medulloblastoma made school difficult. *"The noise and confusion at school was often overwhelming. I still have trouble with time management and organization, remembering things, and often need to be reminded to look after myself. It takes me longer to learn something new, which also affects my employability.*" He added, *"The unpredictability of this rare disease and the resulting side effects of treatments and surgeries have a serious impact on my employability, social life and my ability to be self-sufficient.*

Travel/vacationing

Almost a third, or 29% of poll respondents reported that Gorlin syndrome interferes with travel and vacations. Many described using all their vacation time for treatments or recovery and having to reschedule or cancel family vacations for procedures. A *"surgical summer"* is how AB described her vacation when she was 11 years old, which included the removal of a calcified ovarian fibroma the size of a grapefruit and two jaw cysts, followed by surgery to remove multiple basal cell carcinomas.

Trudy has between 11 to 14 BCCs removed every second month, "*because if I don't, this disease will become unmanageable really quick. … I use my vacation days solely for Gorlin syndrome appointments, so I can maintain employment to finance this relentless disease.*"

Judith, an elementary school teacher, described how, "*Every school holiday is spent having surgery - but I'm thankful I have a job that gives me such extensive time to have multiple surgeries*."

John W. said, "*I usually go to work right after Mohs surgery the same day, not wanting to let my Gorlin syndrome steal any more vacation time than it already does. Because Mohs is time*

sensitive, some years, my Gorlin syndrome has consumed more than half of my paid time off for sickness or vacation."

All of the above

Nearly a quarter, or 23% of poll respondents reported that Gorlin syndrome interfered with all of the activities of life described in the polls. For Ronnie, "*Gorlin's syndrome impacts my life and the life of my family every day all day. Scheduling surgeries, recovering from surgeries, the anxiety of more surgeries, time off from work, deformities, pain and the pain of our loved ones who suffer as well. Staying out of the sun...without suffering and losing life's precious gifts. Keeping up with all of the appointments and tests."*

Other

Only 7% of poll respondents selected "other" as an option and described challenges of spending time as a family.

Beth said, "*When you have one son who's healthy and the other son who has these limitations, it's difficult to give them both what they need*"

Gorlin syndrome can create friction and resentment.

Erika described how her children feel about their sibling who has Gorlin syndrome. *"It's been very apparent the feelings of resentment that one of them has towards the attention that the other is getting for these procedures. And it's ongoing … it's a lot of resentment, and that's the whole psychological 360 degrees of this disorder."*

Kevin described how only one of his twins has Gorlin's syndrome. "*Comparing yourself to others is common. Although he doesn't necessarily verbalize it, not being able to do the same things as his twin is hard for him*."

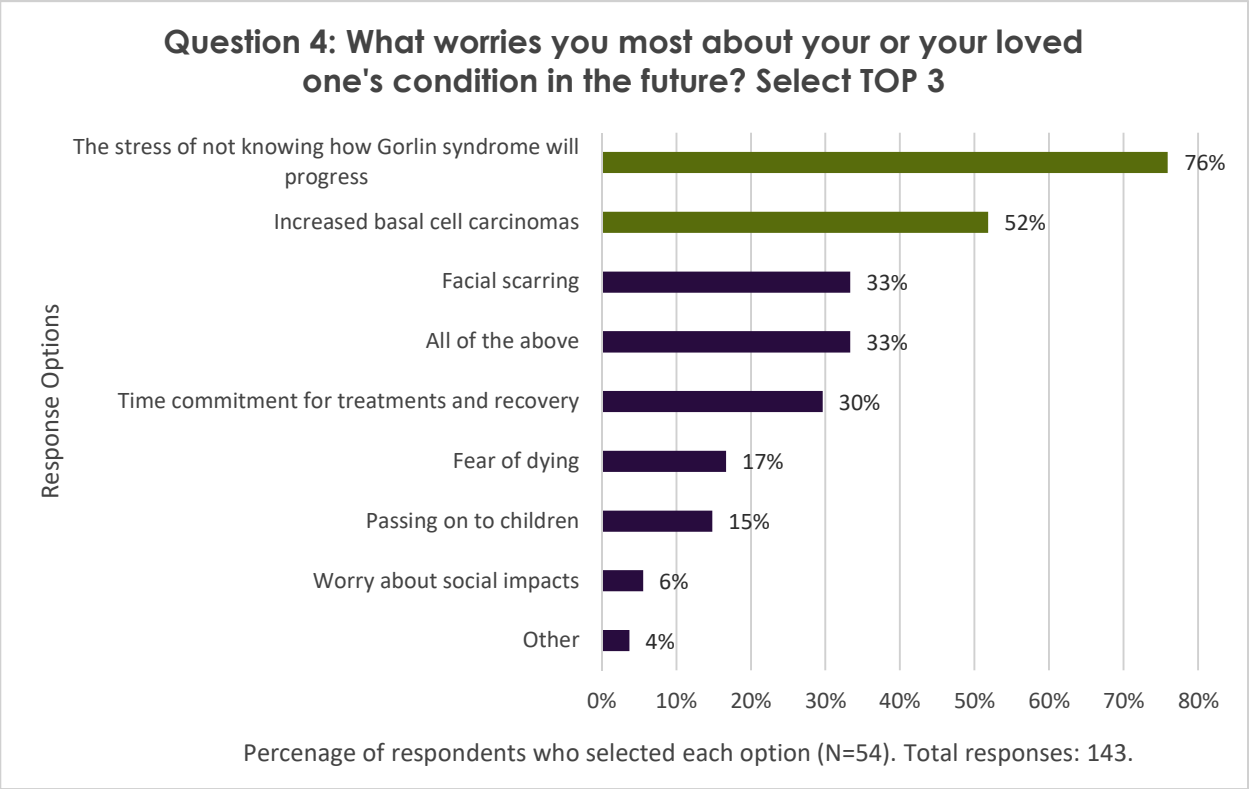
Several participants described how Gorlin syndrome interfered with romantic relationships, sometimes causing one to remain single. Miriam said, "*This affects me emotionally, physically, financially and professionally. I worry, is how I look now - as a woman in her mid-20s going to be the best I ever look, with the clearest, kinda scarred body? …Will I be able to find a spouse and not be as worried, [that] they will stop loving me due to all the scars, or lack of hair?"*

For John H., jaw cysts have damaged the nerves to the lower half of his face. "*It affects my lips and mouth as well. I would give anything to simply feel the pleasure of a kiss."*

Worries about Gorlin syndrome in the future

> *"In my mind's eye, I see my daughter's joyful face transformed into one with shining scars spread like leopard spots that torque and pull her features and eat away at her nose and her eyelids and her ears. The ache of knowing a future I cannot protect her from is deep and penetrating. There is a morbid assurance of constancy that comes with this disease. There will never be a time when she can pause the march of cuts across her body. How do I prepare a child for that?"* - Meredith, mother of a teen-aged daughter with Gorlin syndrome.

People living with Gorlin syndrome used online polling to select their top three worries about their or their loved one's condition in the future, and the stress of not knowing how Gorlin syndrome will progress. An increase in basal cell carcinomas was selected by the most poll respondents. These top concerns are shaded in the graph in green.



The stress of not knowing how Gorlin syndrome will progress

The stress of not knowing how Gorlin syndrome will progress was the top worry, selected by 76% of the poll respondents. People living with Gorlin syndrome emphasized that living with unrelenting cancers is a life of constant fear, with constantly emerging symptoms and recurrences.

Meredith, mother of a teenage daughter with Gorlin syndrome said, "*Having Gorlin Syndrome means a lifetime of watching and waiting for a cancer that may never come or may come with an attack so brutal and vicious that there's never an end in sight*."

John J. summed up, *"The worst part of Gorlin syndrome is that it never goes away. Regardless of the number, length and extent of the diverse types of procedures and treatments one undergoes, it always returns. Cancers and tumors recur. The syndrome comes back, attacks and forces one to surrender more tissue, teeth, bone or hair. There is no détente, no victory, no final resolution, just a continuing battle to minimize the losses. But the losses keep accumulating."*

Sasha said, *"There is a constant fear in the back of my mind of what the future will hold with this syndrome…. I've already lost out on being able to live my life without constant fear*."

Leslie, the mother of a son with Gorlin syndrome said, "*Our mind is always on preparing for what's next."*

Trudy said, "*I'll deal with worrying about what's next - will my brain be impacted by the calcification of the falx? Am I overlooking a tumor in my brain, spine, or heart? - and what else am I overlooking because doctors depend on me to point things out to them with this disease due to their lack of experience/exposure*."

Worries about increased basal cell carcinomas

Worrying about increased basal cell carcinomas was the second most selected concern, chosen by 52% of participants.

Erika said, "*When you're missing the gene that inhibits tumor growth, there always seems to be something growing. The weeks or months between symptoms being diagnosed should be a relief. Instead, the reprieve is just the waiting room for more cutting, draining, or burning. It's a constant cycle, a riptide of anxiety, fear and resentment*."

As Cindy described, "*Fear of continuing to have cancer, 200 plus on me now, fear of getting other cancers due to us missing the tumor suppressor gene, emotional stress, not only worrying about myself, but my daughter and grandson. He already has a jaw tumor."*

Worry about facial scarring

A third, or 33% of poll respondents mentioned worrying about facial scarring. This is not surprising, considering that the biggest treatment drawback of Gorlin syndrome is disfigurement (described on page 39).

Sarah, the parent of a daughter with Gorlin syndrome said, "*I'm dreading what may/will come in dealing with BCCs - pain, scarring, fear, disfigurement, time off work (job loss), time where she may not want to leave the house and worries about health insurance*."

Worries about all of the above (all worries)

A third, or 33% of poll respondents selected "all worries" offered as a poll response option.

Roni, the mother of an adult son with Gorlin syndrome. "*I actually put 'all of the above'. I thought it was a laundry list of all the things that kind of keep me up at night, when I go there. And I try really hard not to go there*."

Worry about time commitment for treatments and recovery

Constant worry about the time commitment for treatments and recovery was a top concern selected by 30% of poll respondents.

Cindy, who has Gorlin syndrome as well as her daughter and grandchild, said that she is getting tired of "*doctor appointments and having to use vacation hours for appointments and recovery time. Planning surgery during school breaks...there is no "real" break for Gorlin patients. It is a snowball effect...impacting everyone else in the family*."

Fear of dying

Fear of dying was a top worry selected by 17% of poll respondents.

Bud said, "*This type of cancer looks you in the mirror every day. One can't help but feel as if it is taking you a piece at a time with only so many pieces in the whole. When will it spread to my lungs, my brain, or my bones? When will I develop other types of cancers associated with the disorder? When will it be the end?"*

Beth described her pre-teen son's fear of death. "*He'd wake up at night and say 'I don't want to die'. And these are words from a 10, 11, 12-year-old. …And it's horrifying as a mother, to watch your child have these unnatural thoughts because of this disease."*

Barbara O. is the mother of a daughter living with Gorlin syndrome. "*A lot of people don't understand what it is like to be afraid to go in and wake your child up for school, afraid she might be dead due to another colloid cyst in her brain. The doctors at Mayo Clinic told me that we were lucky to find it when we did, or she could have died in her sleep*." Now her daughter is an adult and she still worries. "*My worry is, am I going to get that phone call one day?"*

Worry about passing Gorlin syndrome on to children

Passing Gorlin syndrome on to children was a top worry selected by 15% of poll respondents and was often reflected in decisions to not have children.

Roxanne "Rocki" reported that her adult children, "*They have decided not to have children, so our name will not continue on. The emotional, physical, and financial toll that this skin cancer takes is unmeasurable on patients, caregivers, and their families*."

Kristi said, "*My son who's 47 has chosen never to have children because he does not want to pass this gene along. Even though I passed it to him because I'm affected as well*."

Several used assisted reproductive therapy to select embryos not carrying the mutated gene.

Mandy said, *"I wanted to make sure my children never had this syndrome as well, so I went through IVF to conceive. To have my daughter, we paid $60,000*."

This approach didn't always work as expected. Kevin and his wife with Gorlin syndrome used IVF accompanied by pre-implantation genetic disorder testing. He reported that after birth, his wife, "*Almost immediately she recognized the telltale signs of Gorlin syndrome in [one twin]. Macrocephaly, frontal bossing, and wide set eyes."*

Worry about social impacts

The worry about social impacts of the disease was selected by 6% of poll respondents.

Bud described how Mohs surgery was leaving him, "*Increasingly mutilated at an alarming rate."*

Other worries

A total of 4% of meeting attendees selected "other" worries, including worries about how Gorlin syndrome impacts treatments for other diseases, worries about how their children will manage in the future, worries about the long-term treatment impacts.

Worries about how Gorlin syndrome impacts treatments for other diseases, including the diagnosis of acute injuries. Roni, the mother of an adult son living with Gorlin syndrome described how Gorlin syndrome, "*limits the diagnostic and treatment opportunities you have if you're diagnosed with something else*." She declined an X-ray for her son's broken limb and instead told the doctor, "*You're going to put him in a cast no matter what*." She said that the situation is more difficult when cancer is involved. "*Radiation therapy, that's not an option, really. So, you have to weigh all these things, and sometimes you consent to those diagnostic or treatment tools because you know that it's necessary. But other times, you don't, whereas the average patient would. And then the question is, how did it compromise your treatment and your outcome?"*

Note: Radiation therapy and all forms of ionizing radiation induces the growth of basal cell carcinomas. See first photo in **Appendix 5**.

Parents worry about how their children will manage their disease in the future. Kevin has a son with Gorlin syndrome and described how, "*His mother and I share the same prayer as every parent of a child with Gorlin's. We pray that he will take his health care seriously, and that he will always have medical providers who understand the multitude and manifestations of the syndrome."*

Julie, a mother with Gorlin syndrome and the mother of two young adults with Gorlin syndrome. *"As a parent of young adults, I have done my best now to hand off the care to my kids. I've provided them with names and phone numbers of practitioners that they need to see where they live, and, to a degree, it's very hard to hand over the responsibility of care without being a nagging, 'Have you been, when's your next appointment?' type of parent."*

Worries about the long-term treatment impacts. Miriam R. shared her worries about initiating therapy as a young woman. **"***Most people also don't take Erivedge for decades. If I start now, am I stuck with symptoms or running out of options down the road? What will happen after that then? … If what I take doesn't work, will that exclude me from other trials or being able to switch to other medicines?"*

Financial worries. Sasha said, "*There is a constant fear in the back of my mind of what the future will hold with this syndrome and how much money I have in my bank account for possible medical expenses."*

Bob described how *"With several surgeries per year, some very calculated and complicated, both BCCs and OKCs. … there has always been a financial burden brought on to my family by Gorlin Syndrome*."

TOPIC 2: Current and Future Treatments for Gorlin Syndrome

> *"Since 1982, my body has been burned, cut, scraped, frozen, x-rayed, lasered and electrodesiccated. There are scores of scars from my shins to my scalp. The normal adult mouth has 32 teeth. After decades of ENT and oral surgery [for OKCs], I have 18 teeth remaining."*- John J.

Medications or medical treatments used to treat Gorlin syndrome

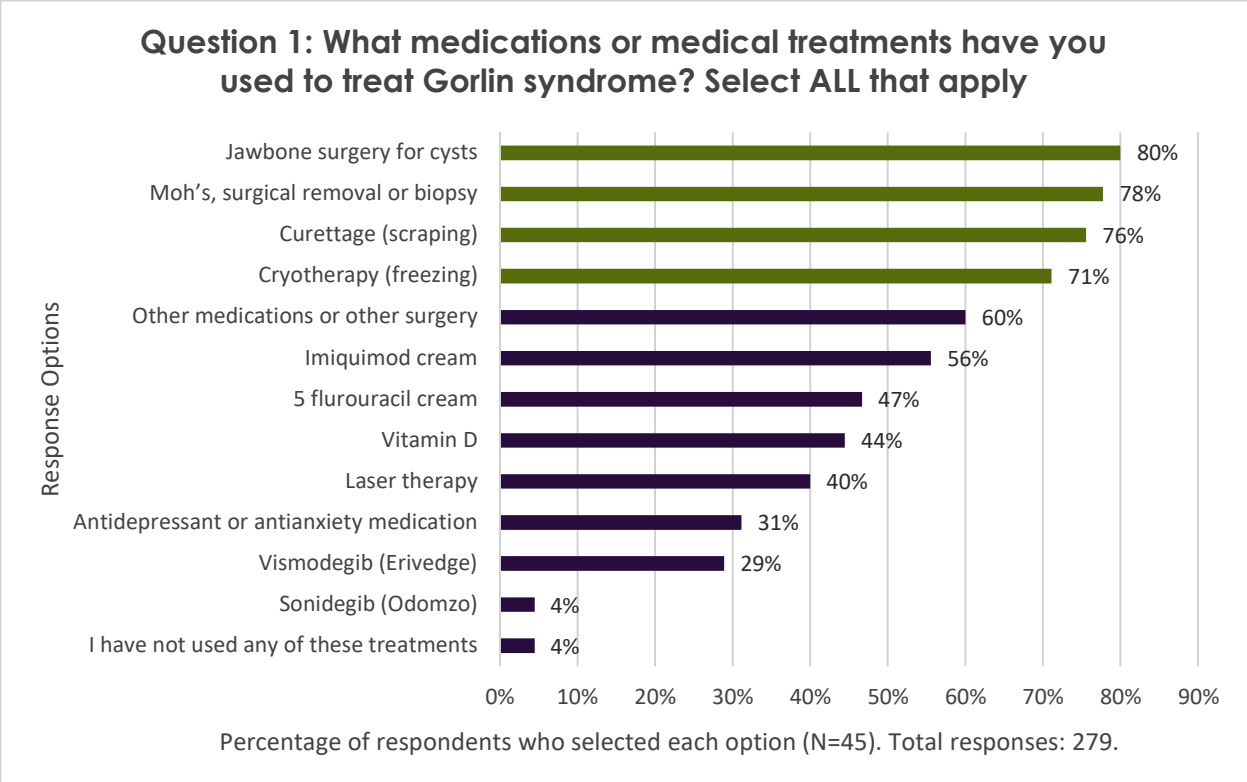
None of the Gorlin syndrome treatments are optional, as Julie reminded everyone, "*Without surgical procedures, [Gorlin syndrome] is life-threatening*."

We have included photos of two people who died of metastatic BCCs in the photo gallery in **Appendix 5**.

Bud described all his treatments. "*I've endured pretty much every modality of removal for BCCs: ED&C, burning and scraping, excisions, photodynamic therapy, interferon injections, Efudex cream (5FU), and eventually landing on the gold standard of Mohs surgery*."

Again, readers are also encouraged to read the impactful and full-length comments submitted online, in **Appendix 6**.

Using online polling, people living with Gorlin syndrome selected all medications and medical treatments that they had tried. The top four approaches are indicated in green in the graph, and include jawbone surgery to remove cysts, as well as treatments to remove BCCs: Mohs, surgical removal, biopsy curettage and cryotherapy.



Jawbone surgery for odontogenic keratocysts (OKCs)

The top medical treatment experienced by 80% of poll respondents was jaw surgery for the removal of OKCs. Aggressive surgical intervention is needed because of the destructive nature of the OKC's, the risk of losing permanent teeth, and the high recurrence rate. These are invasive procedures, and there are no alternatives.

Brandon said, "*Since the age of eight, I have had five jaw tumors removed. One of those tumors caused bone damage that prevented my teeth from meeting on one side of my mouth. I underwent a surgery for upper jaw expansion followed by three years of braces. Each oral surgery was painful and required a special diet for nutrition and healing."*

Nichole described how, "*A lot of times I've had jawbone taken away. Recently I've had some jawbone grafts done. I've lost six permanent teeth as a result, but no doctor wants to do implants on me. Either my teeth are completely missing in my mouth, or I have removable partials in my mouth. And that makes it hard for my smile*."

The many downsides of jaw surgery include tooth and bone loss, numbness of lips / face, speech impacts, essential reconstructive surgery, impaired self esteem, and the social impacts of losing one's smile. Another related issue is recurrence, and many people living with Gorlin syndrome described how the jaw cysts regrew in the same place and had to be removed again. Readers are directed to **Appendix 5** for photos of individuals who have experienced jaw cyst removal.

Mohs, surgical removal, biopsy, curettage, and cryotherapy

Most poll respondents underwent all these procedures: 78% selected Mohs surgical removal or biopsy, 76% selected curettage (scraping) and 71% selected cryotherapy (freezing).

All these procedures require anesthetic and as articulated by Duane, "*The surgeries, the cutting, the burning and all of the things that are necessary to remove these BCCs are nothing short of barbaric."* Duane described that his 13-year-old grandson, "*At the age of 9 he had 139 of them removed under anesthesia at one time."*

Meredith described her daughter's first experience with Mohs surgery at the age of 13 years. "*The average age for first time Mohs patient is 68. She had three lesions on her lash line. For four hours, they repeatedly anesthetized her lid and scooped out diseased tissue while she watched. The next day, she returned for plastic surgery to repair the lid. She repeated Mohs again this summer to remove a piece of flesh from her scalp.*"

Jenni described how her Moh's procedures are done*. "They take one layer at a time of the area, put it under a microscope to look for cancer cells. Hopefully they come back after that first time and say, 'The area is clean. There are no more cancer cells.'"* She described that typically, "*There's about a 45 minute to an hour wait for the results. Then you go back into the procedure room."*

Bud described one Mohs challenge. "*With Mohs, the cutting continues until a clear margin is achieved. In my case, often the surgeon would run into another lesion by the time a clear margin could be accomplished."* Other attendees reported having similar experiences.

Other medications or treatments

More than half, or 60% of poll respondents experienced other medications or other surgeries not listed in the poll. They described having to have other surgeries, photodynamic and laser therapies, clinical trials, surgical insertion of drain tubes and stent insertions as a first phase of OKC surgeries, off-label immunosuppressants, antibiotics, niacinamide and Accutane, as well as supportive braces.

Other surgeries*.* These may include, among many others, cranial surgery for large skulls, premature fusion of skull bones, or medulloblastoma as previously described. Removal of cardiac and ovarian fibromas, eye problems, reconstructive surgeries, and many others may need to be performed.

Judith described how her son with Gorlin syndrome," Was *born with a cleft lip and palate, so his dental/ mouth problems have been very extensive - over 20 operations in his 40 years, and that doesn't include the surgeries for BCCs.*"

For DB, "*The biggest surgeries for me were when I was in the 6th and 7th grade, I had two tarsal coalitions [in two separate surgical procedures] removed from each foot that allowed me to move and run properly*."

Julie said, "*My 29-year-old daughter has had dozens of BCCs surgically removed thus far as well as 15 surgeries related to her other Gorlin syndrome manifestations. Prior to the age of 30, she's had over 40 invasive surgeries because of this disease."* Julie herself has experienced more than 20 Gorlin syndrome-related surgeries and has had over 1,000 BCCs removed.

Surgery sometimes involves difficult decisions. When Meredith's daughter was nine months old, *"We had a hard conversation with her neurosurgeon about an intervention. The risk of doing nothing was that the fluid would put pressure on her brain and cause permanent brain damage. The risk of the intervention was that he could inadvertently cut the blood supply to her brain and cause permanent brain damage. We elected to move forward and felt very lucky that it was completely successful*."

Photo dynamic therapy (PDT) for treatment of BCCs. Maria received "game changing" photodynamic therapy as part of a clinical trial. "*You put the medicine on the spots that you want to treat and shine the light on that area and then the drug burns off those spots. It's not pleasant. It's not easy. You have to sit there for 20 minutes and the longer the light is on it, the more it hurts until eventually the medicine burns off. … you're able to treat multiple spots at one time*."

While PDT worked well for some, others found the side effects challenging. Stacy, mother of a young girl with Gorlin syndrome described PDT, "*It made her skin red and sore and her eyes swelled shut after each visit when we treated them. Eventually her skin would peel and some of*

the BCCs would be gone. It worked better in some areas than in others, but also caused areas of her skin to [permanently] change color."

Clinical trials. Many meeting participants described participating in clinical trials, even choosing to travel long distances to do so.

For John W., *"I participated in three drug trials in the shared hope of discovering the miracle drug."* He experienced a positive outcome while in the Patidegib trial and was devastated when it was discontinued. "*My doctor visits and my need for surgery were mostly eliminated while on the trial medication. I had my life back. … The positive impact was incredible. But apparently, the statistics were not good enough to keep the trial going. This is devastating to me. …To know that I'm headed back down the road of surgeries, scars, and disfigurement is disheartening. We are never cancer free, never in remission ever, but some of us could be."*

Lizzy discussed her reasons why. *"If I can help that next generation to not have to do what I've had to do, to not live with the scars that are visible. … I think it gives us hope."*

Bud described feelings of empowerment and gratitude from his clinical trial experiences. "*I've just entered my ninth clinical trial, and on this quest, I've reached out to researchers across the country and literally around the world. I've traveled to Germany, Holland, and England meeting with some of the top researchers for the disorder who have developed new treatments or led the way with therapies for the disorder. "*

Drain tubes/stents. Erika explained how stents may be surgically inserted into a jaw cyst to drain them, thus reducing the size. After a period of time, a more radical procedure is done to remove the boney jaw cyst. She said that it is *"An okay treatment if you're going to drain a jaw cyst once in your lifetime. But if you've got multiple jaw cysts and you're going to have that drainage and have your parent have to flush the drain daily, that's pretty brutal."*

Lornna described how challenging it was for her son with Gorlin syndrome to have a drain tube installed after the recurrence of his jaw tumor*. "At the age of seven, to have something like that put in... It fell out a few times. The doctor wanted it to be in for a couple of months, before he went back in. And we would have to go back in, have him get it stitched back up into his gums. And then to irrigate that thing every day as a parent... I mean, to a seven-year-old, that was just really crazy to do*."

Off-label immunosuppressants. Stacy described her daughter's treatment. "*We are using an off-label topical cream called sirolimus in a 1% solution, which seems to be preventing most new BCCs from growing and keeping her existing ones small in the areas that we use it. We can't use it on all of her body as too much could be absorbed and cause adverse side effects, and it's unclear what the long-term safety impact will be. But she hasn't had surgery in a year, which is a huge victory for us*."

Niacinamide and Accutane. Mimma said, "*I'm taking 20 mg of Accutane and 1000 IU of niacinamide daily. I've been told that this helps suppress some of the basal cells but I'm not sure it's helping since they're still coming out."*

Carnoy's solution. Maria described a treatment to prevent the regrowth of jaw cysts in her son. "*He had a lot of jaw cysts and one of the things that made a significant difference for him was a solution called Carnoy's solution. I shouldn't say stopped it, but made a huge difference in regrowth once his surgeon started using that*." (Note: Carnoy's solution is no longer FDA approved. During surgery to remove jaw cysts, it was placed in the cavity where the tumor had been to reduce recurrence.)

***Braces*.** For Meredith's daughter with Gorlin syndrome, anatomical differences related to the syndrome required bracing. "*She was late to roll over, crawl, and walk. She needed a neck brace to straighten her head. She wore foot braces to assist with walking."*

Imiquimod cream (Aldara)

Just over half, or 56% of poll respondents reported using imiquimod as a topical treatment of BCCs, an immune response modifier. Few described treatment successes.

Stacy's daughter experienced side effects. "*It made her tired and grouchy like the flu, but did nothing to her BCCs. Eventually, it caused a sore in an area not being treated as too much had absorbed into her system. And between that and the flu-like symptoms, which were significantly impacting her personality and joy in the world, we decided to stop using it*."

5-flurouracil cream (Efudex)

Almost half, or 47% of poll respondents reported using 5-flurouracil cream, a chemotherapy treatment used topically to treat BCCs and to prevent the regrowth of jaw cysts.

Stacy described the downsides of her daughter's 5-FU treatment. "*It was inconsistent and irregular in its effectiveness. Around her eyes, it burned off the skin which she was self-conscious about during school, but the BCCs grew back. On the back of her neck, the 5FU burned so far down that she now has scarring. The sores and peeling were incredibly uncomfortable for her and it was hard for me to continue putting it on her skin, knowing it was causing her so much pain.*"

After Martha's sinus cyst was removed, her surgeon "*stuffed [the area] with a packing of Efudex. And I think this is becoming more popular in preventing the recurrence of keratocysts."*

Laser therapy

A total of 40% of poll respondents reported using laser therapy to treat their BCCs.

Meredith described how her daughter began laser therapy when she was only 11 years old. "*It was quite painful, so we offered her a gummy bear for each time she would let [the physician] laser her skin. And by the time we completed that treatment, she would walk out with well over a hundred tiny red, what appeared to be cigarette burns, all over her clavicle, her neck, down her sides, and fistfuls of gummy bears and it wasn't enough*."

Antidepressant or antianxiety medications

Almost a third of poll respondents, 31%, reported using anti-depressant or antianxiety medications to address Gorlin syndrome symptoms.

Vismodegib (Erivedge)

A total of 29% of poll respondents reported using Vismodegib (Erivedge), a Hedgehog signalling pathway inhibitor, to manage BCCs.

For Craig, Erivedge represents a dream fulfilled. "*I'm 54 and when I was in my early twenties I would dream of better treatments beyond procedures/surgeries/reconstructive surgeries (these were my best treatment options) for myself and generations to come. Fast forward to my late forties and Erivedge came along and was a miracle for me and others at that time*."

Roxanne "Rocki" described her children's Erivedge treatment protocol. "*They take Erivedge for three months, and then they take a break for three months. Almost all of the skin cancers have disappeared. Some do reappear while they are not taking Erivedge, but not as bad. There are some side effects, such as leg cramps, loss of taste, and the most notable is hair loss. … But the good thing is they're not being cut. Erivedge also helps shrink some very small jaw cysts.*"[Note: The GSA is not aware of any published research evidence supporting this personal comment about Erivedge inducing shrinkage of OKCs.].

Kathy experienced anxiety and leg cramping as side effects of Erivedge. "*Regardless of the time of day or evening I take Erivedge I get really, really bad leg cramps at 3:00 AM. It keeps me awake for at least an hour*."

John J. started to take vismodegib, "*To avoid having pieces of my ear cartilage permanently removed".* He described how he lost all his hair. In addition, "*I experienced side effects from Erivedge which were painful and exhausting. After I stopped taking the capsules, some of my hair came back but it is very thin and sparse and I can no longer grow a beard. …I miss my hair, eyebrows and beard which helped to cover many scars…. The most disappointing thing is that the lesions on my ears came back and my cartilage is again vulnerable to permanent removal. There is no end to this battle."*

Sonidegib (Odomzo)

Sonidegib (Odomzo), another Hedgehog signalling pathway inhibitor, was reported to be used by 4% of poll respondents.

Charlotte described she has tried both Hedgehog inhibitors and is switching between the two. "*Muscle spasms from taking Erivedge and Odomzo are the worst. I can't see how any person,...can endure them. …I'm on Odomzo for four months after a three-year break from Erivedge just to stop muscle spasms*."

Vitamin D

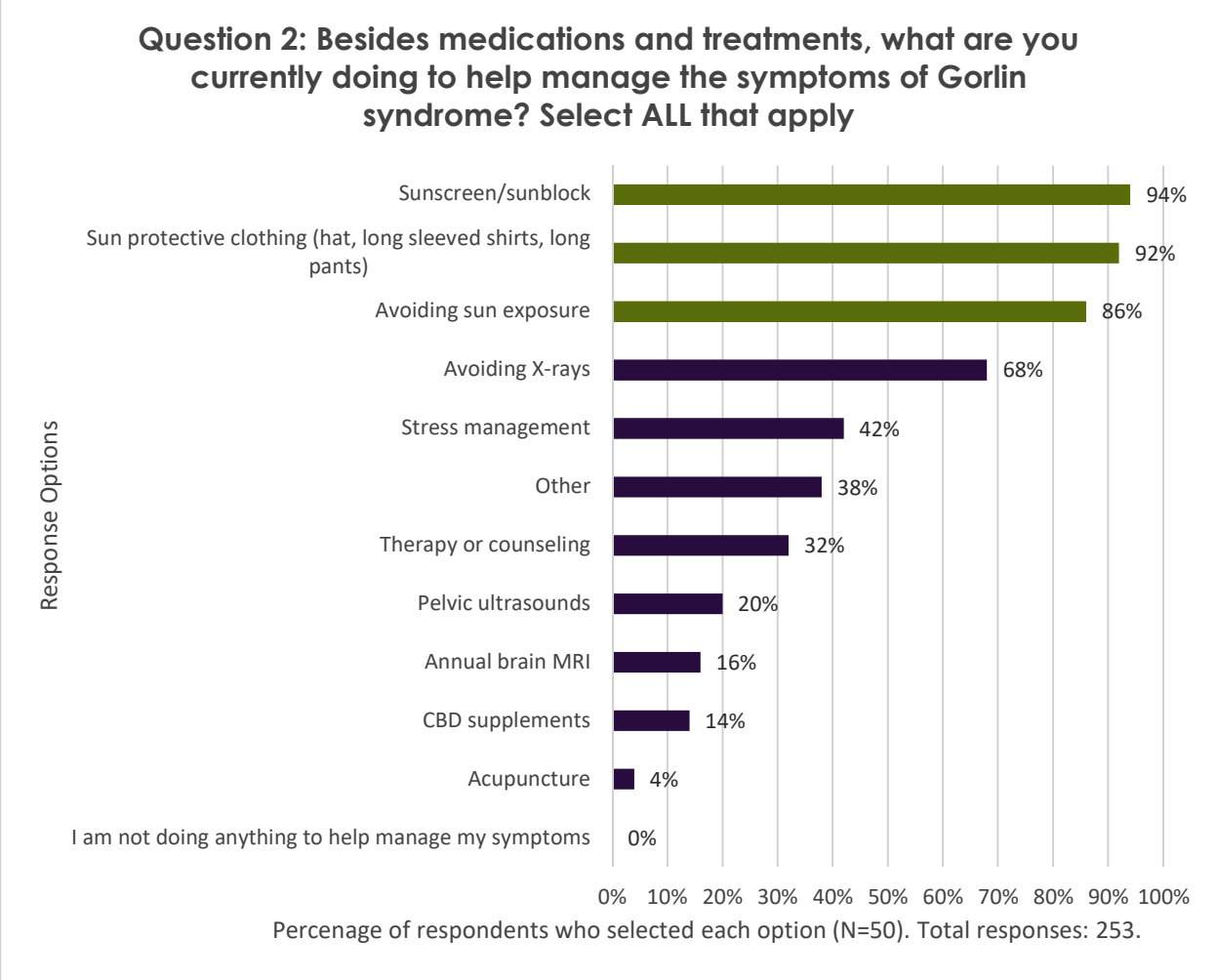
Vitamin D is a treatment option used by 44% of poll respondents, but few comments were made about this therapy during the meeting.

I have not used any of these treatments

Only 4% of poll respondents reported not using any of these treatments.

Current approaches to manage the symptoms of Gorlin syndrome besides medications and treatments

Online polling was used to capture some of the other strategies, approaches and products used to manage Gorlin syndrome symptoms. Poll respondents selected an average of five different approaches and mainly included prevention and surveillance approaches which Stacy explained are necessary "*for the huge multitude of anticipated manifestations of the syndrome."* Other approaches included stress management and both positive and negative coping strategies.



Reducing exposure to the sun

The top three strategies to avoid Gorlin syndrome manifestations all involve reducing sun exposure: using sunscreen and sunblock was selected by 94% of poll respondents, the use of sun protective clothing (including hats, long-sleeved shirts and long pants) was selected by 92% and avoiding sun exposure was selected by 86%.

Stacy explained how her daughter is living with Gorlin syndrome, "*Even with strict sun protection, [she] wears a hat, high SPF sunscreen, UV clothing, and sunglasses every day, with sunscreen reapplied at school, she still has BCCs everywhere*."

Leslie described a similar routine for her son with Gorlin syndrome. "*Every time he goes outdoors, he must always wear a hat, long sleeves, and long pants, and he must wear sunscreen every day. And we reapply frequently*."

Avoiding X-rays

This option was selected by 68% of poll respondents.

Julie said, "*Obviously if it's a life-threatening situation, you have to go with what is advised. But you also live with the fear that you are fertilizing the garden of basal cells by having any form of ionizing radiation, whether it's an X-ray for a broken bone or a CAT scan. Radiation therapy is something that really should be avoided unless it's the last option available*."

Meredith explained the conundrum. *"Managing these basal cells can occur simultaneously with managing jaw cysts, and the cruel twist is that you can't see the jaw cysts without imaging. The imaging requires radiation, the radiation fertilizes the basal cells."*

Stress management

Stress management was an approach selected by 42% of poll respondents, but very few described how they achieved this.

Other approaches to manage Gorlin syndrome symptoms

A total of 38% of poll respondents selected "other" approaches to manage Gorlin syndrome, and these included a range of negative and positive coping strategies.

Bob described using alcohol. "*I found myself growing into a pattern of binge drinking, being quick to embrace a fistfight with the biggest and toughest I could find. Looking back on it, for means of establishing my worthiness, something that Gorlin constantly strives to strip us of."*

Sandy also described how her family, many of whom have Gorlin syndrome, coped. "*Our family is very private, don't talk about issues, only drink*."

Constructive approaches included connecting with others in support groups and at conferences and becoming Gorlin syndrome advocates.

Duane described how connecting with a patient group provided the support his family needed to cope with his grandson's diagnosis. "*Our daughter immediately hooked up with the Gorlin Syndrome Alliance and received an insurmountable amount of help in … figuring out what was going on. …And she also formed friendships through that same network. So, the psychological help that started with the Gorlin's Alliance, and then...having that group of people that they know they can rely on is so important*."

Lizzy described how one of the biggest game changers for her, *"Was actually attending a few of the conferences … and getting to meet other women my age. A few of them have been instrumental. We talk, we Facebook message, just finding that support network, a group of people."*

Bob described mentoring others when the impact of his disease started to affect him in early adulthood. "*I started coaching Pop Warner youth football, realizing that I, likely more than anyone else, would be able to demonstrate to young men that life leaves no room for quitting. I showed up at games and practices both bandaged and bloody.*"

Therapy or counseling

Therapy or counseling was selected by 32% of poll respondents. They described speech therapy to adapt to missing teeth and the effects of jaw surgery and physical therapy. They also described psychological counselling to address anxiety and depression.

Beth's son experiences a great deal of anxiety about his life with Gorlin syndrome and treatments, as well as the fear of dying from the disease. "*We spent several years with a psychologist*."

Leslie described how her five-year-old son living with Gorlin syndrome, "*Receives weekly physiotherapy for lingering, gross motor issues and speech therapy for help with his articulation problems due to his palate function*."

Erika's daughter with Gorlin syndrome, "*Has had some speech issues because of [missing] teeth and she's in speech therapy constantly.*" She described that every time there is a jaw cyst recurrence, her daughter must undergo more surgery and start over with the speech therapy.

Other forms of therapies are necessary and used as well.

Pelvic ultrasounds and annual brain MRIs

Pelvic ultrasounds and annual brain MRIs are part of the ongoing monitoring activities required by people living with Gorlin syndrome. Pelvic ultrasounds [used to monitor for the manifestation, calcified ovarian fibromas] were selected by 40% of female poll respondents, and a total of 16% of poll respondents reported that they had an annual brain MRI.

CBD supplements, Acupuncture and Not doing anything

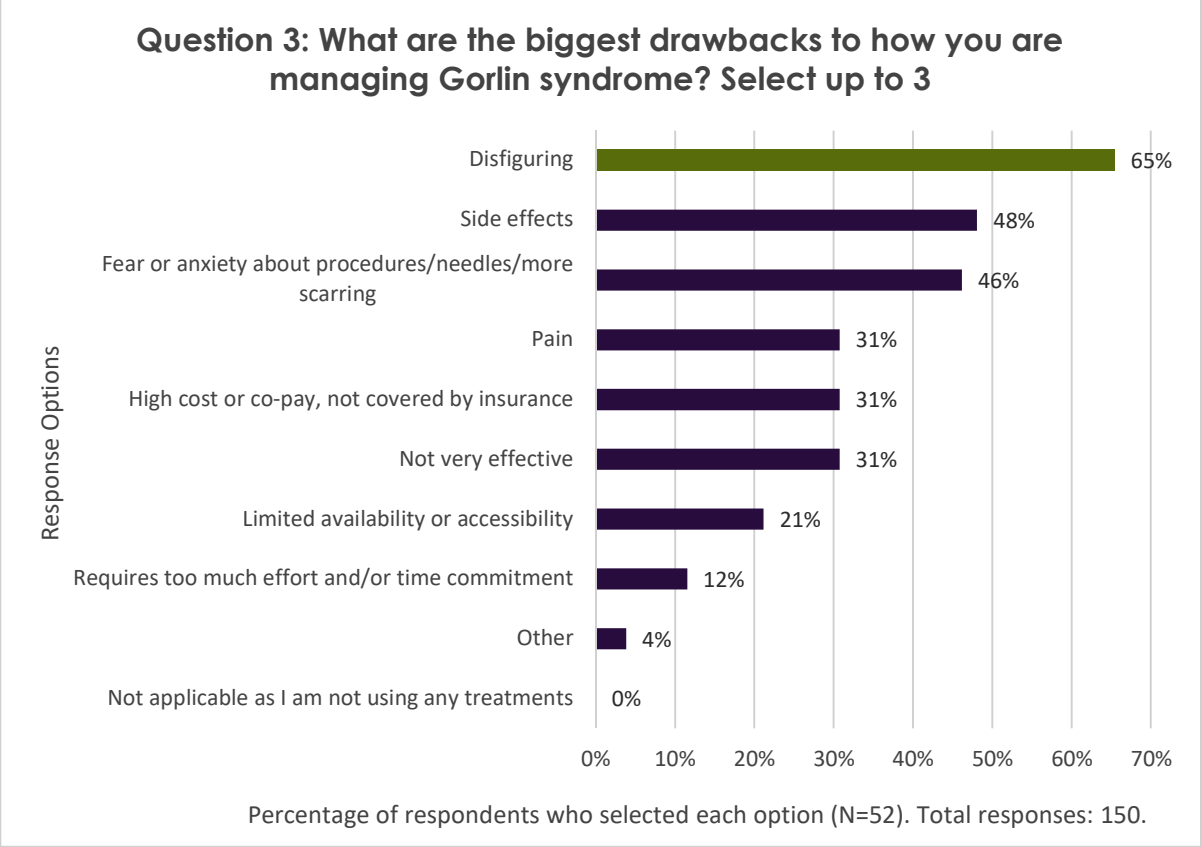
CBD supplements are used by 14% of poll respondents and acupuncture is used by 4% of poll respondents, but no comments were made about these approaches during the meeting.

None of the poll respondents reported that they chose not to manage their symptoms at all.

Biggest drawbacks to managing Gorlin syndrome

"Treatment shouldn't be torture." - Charlotte

When asked to select the three biggest drawbacks of how they were managing Gorlin syndrome, disfigurement was the top choice (highlighted in green in the graph), followed by side effects, fear, and anxiety.



Disfiguring

The biggest downside of Gorlin syndrome management, selected by 65% respondents, was that it is disfiguring.

Meredith, mother of a teenage daughter with Gorlin syndrome, described both the treatment and the gradual erosion of her daughter's appearance: "*How do you eat an elephant? One bite at a time. I have used this metaphor as a useful way to break down managing my child's disease into bite size chunks, and it also serves as an incredibly apt visual reminder for what can happen to her appearance over time.*"

Disfigurement resulted in Judith's father taking his own life. "*His whole body was made up of skin grafts - and I mean his whole body. No ears, and very minimal nose left. In his last surgery on his skull, they had a lot of trouble maintaining a blood flow. He had skin grafts over skin*

grafts - in some spots at least five regrafts. He lived 67 years in pain and eventually took his own life. I can only imagine what drug development could have done to make his life liveable."

Erika asked, "*When is that point when they realize their smile is actually scary to people instead of invoking that they're happy? To me, the scariest and the hardest part about the whole procedures is that they lose their smile and when you see the light go out of their eyes, and they don't even want to smile anymore*."

Maria described why BCC treatment is so disfiguring. "*Surgical repairs can stretch and pull skin, which affects facial/body structures. You can end up with hair growing somewhere it shouldn't be, or no hair where you need some. Ears are at high risk. The nose and lips are usually the center focus of a person's face, unless surgery has moved or disrupted them, making them an eye sore (pun intended). Eyelids are high value real estate. That's correct -- we have to evaluate our skin like property when determining how to use or repair it*."

Michael spoke of heartache. "*When my beautiful bride had her first Mohs surgery to remove a BCC, I was completely caught off guard and horrified at the result. A small spot that looked like a bug bite ended up in a four-inch suture line snaking across her face. Despite trying to keep her head raised at night and applying ice packs, the swelling grew large and painful. I tried to stay positive for her, but it was heartbreaking to watch, and I felt so angry and helpless. There has to be another way*."

Joan described how her face and scalp reflect her 117 surgeries. *"I have virtually no hair on my scalp due to many skin grafts. … My one eyelid that has suffered the worst of the surgeries - despite the best efforts of a plastic surgeon- doesn't close all the way so I must treat for dry eye issues. My tear duct was sacrificed as a result of extensive basal cell carcinoma involvement, so tears are continually running down my cheek. I have no control over that. My nose is an asymmetric mess due to multiple surgeries on the skin and cartilage. There's no tissue nearby to rebuild it because all the skin tissue has the potential to develop basal cell carcinomas."*

During the meeting, Alice pulled off her wig to show that, *"One of the treatments that I've done has eliminated my hair growth*." Alice described one of the biggest impacts of her appearance: she fears that her son is embarrassed by her.

Because of the removal of a cardiac fibroma at the age of four, Kaylene has a scar on her chest. "*It's not cosmetically the best scar to have. … When you're 22 years old, a lot of people like to wear things that are a little revealing, like V-necks and things like that. I don't have that opportunity to be able to do that… and feel comfortable in my own skin."*

Several parents described how hard it was watching their children lose their smiles because of missing teeth and jaw surgeries.

Side effects

Side effects was a treatment downside selected by 48% of poll respondents. Many of the side effects were described in earlier sections of the report and include those due to medications (skin burning, leg cramps, loss of taste, and hair loss) and side effects of surgeries and other treatments.

For Bud, "*While taking the hedgehog inhibitors, which have been much better than the surgical options, the side effects have been very difficult to live with on a daily basis and perform the tasks necessary to run my business. Extreme fatigue, abdominal issues like nausea, cramping, and bowel problems, extreme cramping throughout the body but especially in the legs, hair loss, are the bigger problems associated with the therapy. I'm basically tolerant of these side effects, and I do feel extremely fortunate as compared to my predecessors to even have the option, yet it is still a horrible way to live day to day. Definitely makes it difficult to keep up with a job or run a business."*

Trudy emphasized, "*Those side effects would be fine if they came along with a cure, but they come along with just a delay in surgery. I know there have to be better options. I'm not interested in settling for such harsh side effects.*

Fear or anxiety about procedures/needles/more scarring

This treatment downside was selected by 46% of poll respondents and was described throughout the meeting.

Kyle said, "*Each procedure is painful and makes me nervous. Yet, the symptoms keep coming back and I have to go through it all over again. Each time there is a surgery, there is also swelling and pain, and the risk of infection or other complications."*

Beth described the anxiety her 13-year-old son with Gorlin syndrome felt. *"After he was diagnosed, he started having anxiety about all of these procedures. He proceeded to pull out most of the hair on top of his head from the anxiety of just knowing what was coming next*."

Elizabeth said, "*I have a lot of anxiety going in for surgeries that my dermatologist, even the [medical assistant] staff that I worked with didn't even understand. It's the building up the courage to go in for that surgery after you've had the biopsies. Building up that courage takes a lot."*

A major source of the fear and anxiety is that treatment outcomes are always uncertain. As Nichole described, "*When I have a jaw cyst removal, am I going to have my teeth remaining? Am I going to have any jawbone remaining? …It's very frustrating because you never know what's going to happen, what's going to be the outcome. For surgeries,…am I going to come out with stitches, staples, or a skin graft?"* She described her anxiety about a recently discovered BCC deep underneath her skin. "*How are they going to treat it? Are they going to cut me open and stitch me up? Are they going to suck it out somehow? I have no, absolutely no clue what's going to happen at this point. And under the skin is very scary too, because you don't know what's going to happen. You don't know what else is in there*."

Pain

Pain was selected as a treatment downside by 31% of poll respondents and was also described throughout the meeting. Readers are advised to refer to some of the post-treatment photos included in **Appendix 5**.

Not very effective

A total of 31% of respondents reported that treatments were not very effective as is clearly illustrated by the recurrent nature of both jaw cysts and BCCs.

Meredith described the treatments that have not worked for her daughter. "*We have a cabinet full of topicals that we have tried. Some work for a little while, some work a little bit, some work not at all, but none of them have been adequate to keep the tide of basal cells from overcoming her*."

For John J., the BCCs keep recurring despite many treatments. "*I've been lasered on the shins. I've been frozen with nitrogen. I've been cut. I've had curettage, electrodesiccation, and all types of other approaches. Mohs in my scalp. I've lost hair, skin tissue. It's now in my ears. And I did [anything] to avoid surgery because the problem with surgery is once, even after you fix one spot, like everybody else has said here before, it comes back*."

For several people living with Gorlin syndrome, treatments became even less effective with time.

For Charlotte, "*As I've gotten older, I guess my age and the length of having Gorlin* syndrome*, the treatments have become less effective*."

High cost or co-pay, not covered by insurance

This response option was selected by 31% of the poll respondents who described the high financial cost of Gorlin syndrome as yet another burden of this disease.

Tom summarized the situation for many*. "So it becomes a real catch-22 in that the expense of the treatment and the travel when you don't have a job and no salary, and you don't have insurance coverage is really a huge, huge burden on top of all the other burdens that people have talked about today. So as far as any possible treatments, the cost is just such a huge factor in all of that too."*

Kaylene said, "*I have encountered medication inaccessibility firsthand through my experience of a co-pay being changed when I was on a hedgehog inhibitor. The cost of my medication went from free to thousands of dollars a month. Although this treatment was effective, it eventually became inaccessible to me since I am a young college student with a rare disease that is already so costly".*

Some reported that their medical insurance does not cover all their procedures, especially reconstructive surgery after the loss of jawbone and teeth.

Nichole described how, "*It's always been a fight with insurance [companies] because they consider it cosmetic in getting that covered"*.

People living with Gorlin syndrome described how insurance companies sometimes require patients and their physicians to choose which BCCs are removed.

Kathlyn said, "*Some insurance companies will limit you to the number of basal cell carcinomas to be removed by Mohs surgery in one day. … Then you have to choose, because of your insurance restrictions, which ones will be done, and when*".

Limited availability or accessibility

Limited availability or accessibility was selected by 21% of respondents, many who reported that some treatments are only available in a specialist or medical research setting.

Kathlyn explained that every time her family moved to a new state, "*I had to go searching typically for a university setting, a teaching setting. Because forgive the pun, they're typically on the cutting edge of research, so my son and I usually go together as patients."*

Sherry commented on the shortage of experienced physicians for her son. "*We have trouble finding and keeping doctors, especially any doctors that know or understand Gorlin syndrome".*

Maria said, "*I was one of the ones that chose limited availability because one of my preferred methods of treatment .. is photodynamic therapy".* While the blue light therapy is most common, Maria prefers the red-light therapy which is most effective but hard to find.

Another accessibility issue identified by Miriam was that "*Those drugs are only for adults not for pediatrics*". This makes the therapies inaccessible for the many children living with Gorlin syndrome represented at the meeting.

Requires too much effort and/or time commitment

Although only 12% of respondents selected this as one of their top three downsides, this issue received many comments.

Alice described how her BCCs have disrupted her life and she even provided an impact estimate. *"In my case, I've had 400 to 500 in the 35 years since my diagnosis. … So, we estimated two weeks time for treatment or surgery or topical solution. I figure that's roughly 40% of my life since my diagnosis I've spent in some kind of recovery or treatment or with bandages on my face or something."*

John H. said, "*As a patient with Gorlin syndrome, I have NEVER had a month of my nearly 60-year-long life without having to go to a doctor or hospital for something due to Gorlin syndrome - until the pandemic! "*

In addition to all the time required for treatment and downtime, individuals living with Gorlin syndrome described all the surveillance and diagnostic imaging required as well. In addition, follow up appointments with a variety of different subspecialties is necessary.

For Leslie's five-year-old son with Gorlin syndrome, "*We juggle a number of specialist appointments for him each year, including MRI, neuro-oncology, dermatology, cancer, genetics clinic, cranial facial clinic, ENT and audiology, ophthalmology, neuropsychology, and neurology. This is all in addition to his routine, pediatric and dental care*."

Roni, the mother of an adult son with Gorlin syndrome described how in the 20 years since his diagnosis, "*He has had tons of jaw cysts. We monitor him every six months. He goes for*

panorex's. He goes for MRIs to avoid the radiation. … And it's the stress of constant, repeated surgery. And we were under the misimpression that this would lessen and go away, really, as he became older, which has not been the case."

Other treatment downsides

Only 4% of respondents selected "other" downsides of treatment. They described how treatments are not yet approved for children, can be invasive and high risk, can make Gorlin syndrome symptoms worse later, and destroys hope and quality of life.

The oral medications, Erivedge and Odomzo are medications for advanced basal cell carcinomas. They are not FDA approved for Gorlin syndrome or for those under 18 as they may impact bone growth.

Invasive and high risk. Maria described a surgery that was recommended for her son. *"The doctor explained that the procedure that he wanted to do included breaking my son's jaw beneath his nose, and basically cracking his head open, like an egg, in order to get the best access to clear the cysts."*

Gorlin syndrome treatments may cause more serious problems later. Katerina's son with Gorlin syndrome received radiation when he was very young. *"Due to craniospinal radiation he received at age of three he faced early BCCs, jaw cysts and at 12 he got grade 2 meningioma on the brain. He was operated on and received medication for one year, and unfortunately the tumor recurred*."

Bud described how, "*Early on with all good intention, I was treated with ultraviolet light treatments weekly to eradicate acne so the doctors could be certain what they were removing were actually basal cells. This led to a rapid excessive growth of the BCCs later in life for me*."

Many spoke about having to endure repeated anesthesia to treat Gorlin syndrome manifestations and the potential impact this may have. The cumulative effects of repeated anesthesia are only beginning to be understood.

Leslie's son with Gorlin syndrome is only five years old and, "*he has been under anesthesia 20 times for MRIs and eight surgeries, all related to various manifestations of Gorlin Syndrome*."

Bob described that, "*In early adulthood … I began to realize the effects of repeated anesthesia …and this condition would dictate what I would do and become for the rest of my life."*

Impacts quality of life. Trudy described her most significant downside of living with Gorlin syndrome, "as *a general lack of hope for management of this syndrome changing anytime in my lifetime".*

John W. said, "*These experiences have challenged my morale and my quality of life".*

Erika, mother of a child with Gorlin syndrome, described the emotional toll of recurrence and repeated treatments. *"There is only so much skin, so much cutting, draining and burning that is viable. The thing is, it is never a once in a lifetime thing with Gorlin syndrome, its your lifestyle. Waiting, finding, draining, cutting, repeat."*

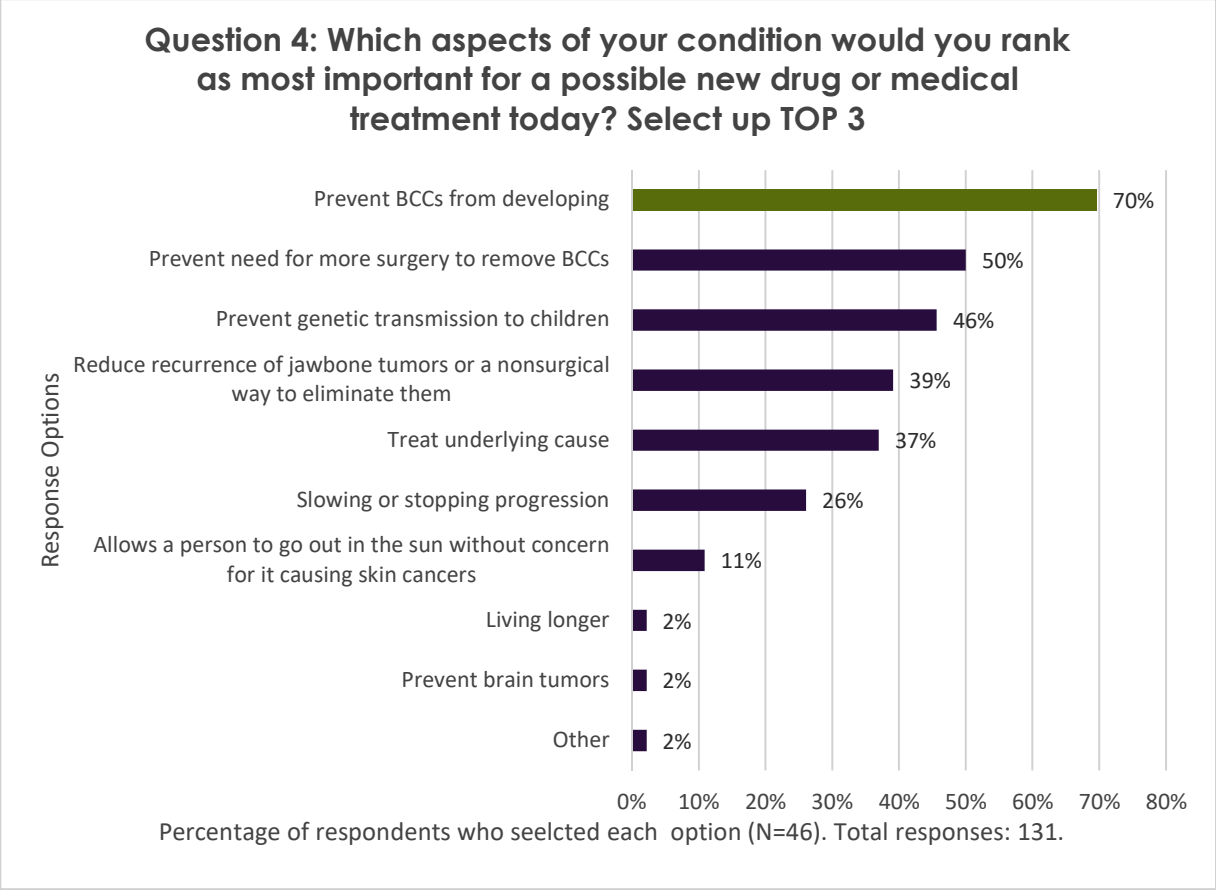
Three most important aspects of Gorlin syndrome for a possible new drug or medical treatment

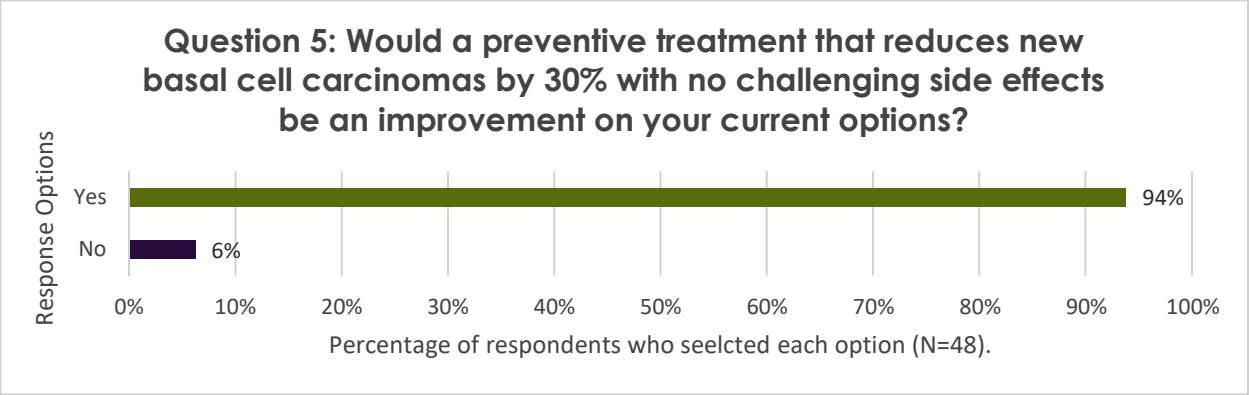
> "*Please help. In its random, relentless, sometimes slow but never-ending way, the syndrome slowly disfigures and wears us down over time. Any treatments or medications that could reduce or prevent the lesions and/or tumors with fewer side effects would be helpful. Targeted topical treatments could be a major improvement. Any medications with fewer side effects would be beneficial since it would relieve one from the stress of using them repeatedly. It is extremely hard to undergo the prolonged pain and difficulty of current treatments while knowing the benefits are only temporary and the symptoms of the syndrome will come back again, and again, and again*." – John J.

During the meeting, many people living with Gorlin syndrome begged for new treatments.

Maria acknowledged the need for multiple therapies and solutions. "*From all that we've heard today, there's such a variety of expressions of symptoms, that at least having options is such a valuable thing. It's hard to [select] just one [preferred treatment approach] because you want to help yourself and you want to help somebody else too.*"

People used online polling to select the three most important aspects of their condition to be targeted for a possible new drug or medical treatment today. The results are shown in the graphs below.





Prevent BCCs from developing

A total of 70% of poll respondents chose to prevent BCCs from developing as one of their top three options.

All were then asked in a second poll question, "*Would a preventative treatment that reduces new basal cell carcinomas by 30% with no challenging side effects be an improvement on your current options?"* During the meeting, 100% of the poll respondents selected an affirmative response. This number dropped to 94% in the final analysis, as three people voted "no" at the last moment before the polls closed.

Lizzy said, "*I think we all wish that [the reduction in BCCs] was a 100%, but 30% gives us hope*."

Duane, the grandparent of a 13-year-old boy with Gorlin syndrome expressed his hope that researchers, "*will figure out a way to develop some topicals that will enable us to prevent additional [BCCs]. And if not that then obviously in mercifully removing these BCCs."*

People living with Gorlin syndrome mentioned a desire for reduced side effects.

Sarah said, **"***My hope is future medicines will be 100% effective without debilitating side-effects."*

Prevent need for more surgery to remove BCCs

Exactly half of respondents would like to prevent the need for more surgery to remove BCCs.

A topical treatment for BCCs without side effects is important for Stacy, mother of a child with Gorlin syndrome. "*For her BCCs, I wish there was a topical treatment that didn't make her skin irritated and painful or make her grouchy and tired, that didn't need needles and anesthesia OR (operating room) time, and didn't result in permanent scarring each time.*"

AB said, "*Until there is a cure, I wish there were topical treatments that would shrink and prevent my skin cancers without an ugly irritated reaction."*

Ronnie said, *"It would be beneficial to have a drug or a cream/gel to use that didn't have severe side effects. To have treatments that would enable all of us to live a life with less anxiety and to present our better selves to the world around us."*

Nichole agreed. *"Most of my skin cancers are on my face. ... I would love to rub something on my face to make skin cancers go away."*

Prevent genetic transmission to children and treat underlying cause

Considering the impact that this disease has had on entire families, it was not a surprise that 46% of poll respondents would choose to prevent genetic transmission to children and 37% would choose to treat the underlying cause of Gorlin syndrome.

Erika the mother of a child living with Gorlin syndrome, pointed out that finding a genetic solution for Gorlin syndrome would positively impact many other people. *"I think that Gorlin is a rare disorder, as we grow tumors everywhere. But everyone in the world at some point in their life is going to grow a tumor. So any cures that we come up with, any treatments, everyone will benefit from in their life, even if it's just once. We're the Rosetta Stone for tumor growth. ... If you can fix us, you can fix anyone else."*

Duane described what he wants for his grandson with Gorlin syndrome. "*This is a genetic problem. ... I would hope that this group would push scientists to see if there is a genetic correction or something to get to the heart of this problem. That's my biggest wish*."

Reduce recurrence of jawbone tumors or a non-surgical way to eliminate them

A total of 39% of respondents would choose to reduce recurrence of jawbone tumors or find a non-surgical way to eliminate them.

Slowing or stopping progression

This response option was selected by 26% of poll respondents.

Charlotte described her hopes for future therapies. *"I'm hoping that they will come up with a cure or a treatment for the younger generation, so they don't have to get to a point where … things are metastasizing."*

Allows a person to go out in the sun without causing skin cancers

A total of 11% of poll respondents selected a treatment that allows a person to go out in the sun without causing skin cancers.

Living longer and preventing brain tumors

The poll response options of living longer and preventing brain tumors were each selected by 2% of respondents.

John H. said, *"Yes, the BCC's are so hard, so often, so damaging, so disfiguring - BUT, whilst they damage skin and appearance, brain tumours damage so, so, so much more*."

Other

Only 2% of poll respondents indicated that they had other preferences for possible new drug or medical treatments, including treatment for cardiac fibromas. They suggested that relieving the

psychological burden for people living with Gorlin syndrome is a meaningful clinical endpoint, and reducing the burden of the manifestations will lead to this.

Better treatments for cardiac fibroma*.* Kaylene said. *"Until there's a way that we can find a better treatment option or a cure for these cardiac fibromas, I'll never stop advocating for better treatment especially for these young children who have to go through it."*

Relieving the psychological burden for people living with Gorlin syndrome*.* While this is not something that researchers are able to directly address, having more humane treatments will not only lessen the physical damage and scarring but tremendously improve the psychological impact and quality of life of those affected with and by Gorlin syndrome.

More psychological interventions to help children and teens manage the psychological burden of the disease*.*

Better diagnostic approaches. Patricia said, "*There needs to be a better way to diagnose the lesions, the status/stage of them, the depth of them, as a way to decide on appropriate and effective treatments."*

Nichole requested better diagnostic imaging. "*We don't know what's going on underneath [the skin]*."

More education about Gorlin syndrome for the medical community**.** Kathlyn described her frustration with some specialists who know very little about Gorlin syndrome. *"The main thing is that the medical community needs to know about this disease. … I am constantly telling physicians what they're dealing with because they admit that they have never seen [a patient with Gorlin syndrome]."*

Patricia stated, "It is another stress for us that in some cases we have to be the ones that educate our medical providers about this condition."

Erika described needing to be your own expert. *"I grew up [learning] that you trust your doctors and whatever they say is law. ... But I've been in doctor's meetings where they've wanted to do a procedure that was completely against a Gorlin's protocol, and [I told] them what the procedure should be. …It scares me that you have to fight to get something done. And these kids can't speak for themselves."*

Incorporating Patient Input into a Benefit-Risk Assessment Framework

The FDA uses a Benefit-Risk Assessment Framework which includes decision factors such as the analysis of condition, current treatment options, benefit, risk, and risk management. The Framework provides an important context for drug regulatory decision-making and includes valuable information for weighing the specific benefits and risks of a particular medical product under review.

Table 1 speaks to the challenge of having a lifelong cancer burden that people living with Gorlin syndrome endure. It serves as the proposed introductory framework for the Analysis of Condition and Current Treatment Option to be adapted and incorporated in the FDA's Benefit-Risk Assessment. This may enable a more comprehensive understanding of this unique condition for key reviewers in the FDA Centers and Divisions who would be evaluating new treatments for Gorlin syndrome. The data resulting from this meeting may help inform the development of Gorlin syndrome-specific clinically meaningful endpoints for current and future clinical trials, as well as encourage additional researchers and industry to investigate options for treatments.

The information presented captures the perspectives of people living with Gorlin syndrome presented at the October 8, 2021, meeting, as well as polling results and comments submitted before, during and after the meeting through the online portal.

Note that the information in this sample framework is likely to evolve over time.

TABLE 1 Gorlin Syndrome Benefit Risk Table

	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
ANALYSIS OF CONDITION	**Gorlin syndrome is a rare genetic disorder. It can manifest in any organ in the human body.** Most individuals with Gorlin syndrome develop a tremendous number of basal cell carcinomas (BCCs) during their lifetime, many over 1000. Patients report this as the most troublesome aspect of the condition. Other manifestations can include, but are not limited to jaw tumors, hydrocephalus or ventricular asymmetry, malignant and benign brain tumors, ovarian and cardiac fibromas, large skulls, improperly formed bones, palmar pitting. The condition can induce anxiety and depression. **Gorlin syndrome impacts all activities of daily living**. Extreme lifestyle modifications are necessary to prevent UV light exposure in this sensitive population. To avoid passing the gene to the next generation, many described the excruciatingly difficult decision to not have children.	**Individuals with Gorlin syndrome experience a lifelong cancer burden**. The persistent nature of this disease means that more BCCs, jaw cysts and other growths will always appear. **People living with Gorlin syndrome and loved ones spend their entire lives on high alert for the next malignancy, the next manifestation**. They described fears about cancer recurrence and their future. Many said they are worn down over time by the unceasing nature of the disease and the long-term impacts of treatments including permanent scars and disfiguration, along with other disabling side effects. Others were bullied and felt isolated due to their disease. **Gorlin syndrome symptoms and treatments interfere with regularly attending school, working, participating in sports and social activities, and developing relationships.** In particular, disfigurements create barriers for employment, social life and relationships.
CURRENT TREATMENTT OPTIONS	**There is no cure for Gorlin syndrome and there are NO FDA-approved treatments for any of the 50 + manifestations of the disease**. For those over 18 years, the systemic treatments for BCCs have very challenging side-affects that cause many to discontinue treatment. There are topical therapies available for all ages which also cause difficult side affects. For examples, please see page 4 & 5 of Appendix 5. Patients' top treatment goal is to prevent and manage an endless flood of BCCs; most people living with Gorlin syndrome would consider a preventative treatment that reduces BCCs by 30% with no challenging side effects to be an improvement on their current options. Many patients and caregivers hope for a topical treatment for the BCCs that has minimal, if any, side effects and does not produce more scars. People with Gorlin syndrome also request treatments to reduce the formation and recurrence of jaw cysts.	**Treatments for BCCs and jaw cysts are brutal, painful and increasingly disfiguring over a lifetime**. Existing treatment approaches and lifestyle modifications do not to stop the formation or recurrence of skin and jaw tumors. Significant time and resources (financial and personal) are required to navigate the healthcare system to maintain high level of vigilance and appropriately manage the multitude of appointments and treatments (surgical and others) needed to care for oneself or a loved one. **Safe and effective treatments are needed for all Gorlin syndrome manifestations.**
	Please see the Voice of the Patient report – particularly Appendix 5, with photos – for more detailed information on the burdens of life with Gorlin syndrome.	

Conclusion

The October 8, 2021, Gorlin Syndrome EL-PFDD meeting will help to advance the GSA's mission to thoughtfully support, comprehensively educate, and aggressively seek the best treatments and a cure for those affected by Gorlin syndrome. This meeting provided an opportunity for the FDA to hear directly from people living with Gorlin syndrome, their family members, and caregivers about their disease manifestations and experiences, the impacts on their activities and daily lives, and their worries related to living with Gorlin syndrome. Meeting participants described invasive surgeries and the other painful treatments that are necessary to remove BCCs, recurring jaw cysts and other tumors associated with the syndrome. However, BCCs and jaw cysts are only two of the multitude of manifestations of the disease, none of which have safe and effective FDA-approved treatments.

The participants at this EL-PFDD clearly demonstrated that short of a cure, reducing the rate of BCCs by 30% would be a meaningful clinical endpoint. Other top choices included preventing the need for more surgery to remove BCCs, preventing jaw tumors and reducing their recurrence or finding a non-surgical way to eliminate them, preventing genetic transmission to children, and treating the underlying cause of the disease. Other hopes include slowing or stopping disease progression and being able to go out in the sun without concern for UV exposure. Finding effective treatments for all the manifestations of Gorlin syndrome would alleviate the heavy physical and psychosocial burden of this disease.

The Gorlin Syndrome Alliance is grateful for this opportunity to share our voices through this *Voice of the Patient* report and, in turn, educate and inspire others to find better therapies to improve the quality and quantity of the lives of those affected with and by Gorlin syndrome. Thank you to the U.S. Food and Drug Administration for giving the GSA the opportunity to hold this meeting, and we wish to thank the FDA staff who took time out of their day to attend. We were incredibly grateful for this opportunity to share our experiences with you.

The GSA thanks Dr. Sally Lewis, a Medical Dermatologist and Clinical Reviewer in the Division of Dermatology and Dental Products within the Center for Drug Evaluation and Research at the FDA, for her perspectives on the Externally Led Patient-Focused Drug Development process. A very special thanks to William Lewallen FAC-P/PM, from the FDA Patient-Focused Drug Development Staff who guided us through the process. We also thank Dr. Joyce Teng, a Professor of Dermatology and Pediatrics at Stanford University, for her very educational and insightful clinical overview of Gorlin syndrome. We are grateful to you both for supporting us with your time and expertise.

The GSA would like to thank the team that made this meeting possible, including Larry Bauer and James Valentine.

Thank you also to the generous supporters who financially sponsored this meeting, including Palvella Therapeutics, Inc., Sun Pharma USA, Mayne Pharma, Feldan Therapeutics, PellePharm, and LEO Pharma. We appreciate your ongoing support for this meeting and for your work towards finding treatments and potentially a cure.

We hope that this meeting will encourage future research and successful new product development for people living with Gorlin syndrome, who urgently need more options.

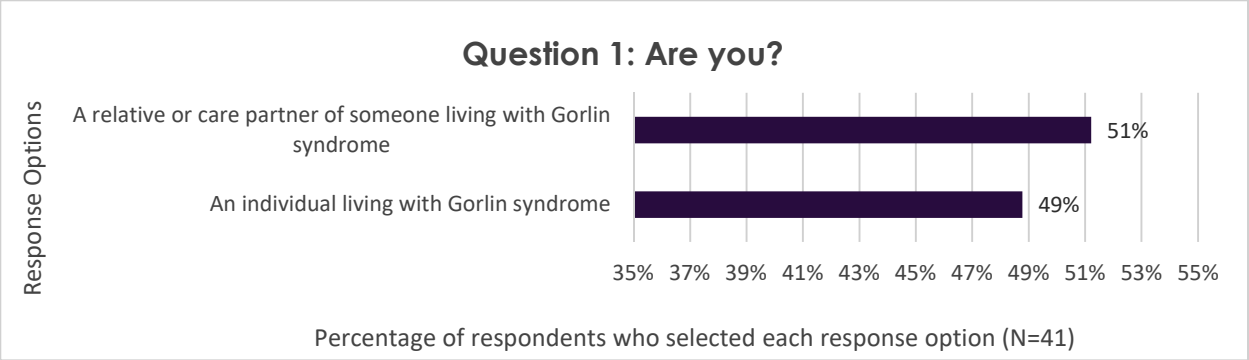
Bud summarized his hopes. *"I'm hopeful that in the future, there will be a combination of therapies to complement the hedgehog inhibitors, allowing individuals to take a lower dose or longer breaks from the drug. Topical medications, preventing new growths, new generations of drugs that are as effective without as many side effects would all be helpful. I'm hopeful for the future, and I look forward to the advancements to come."*

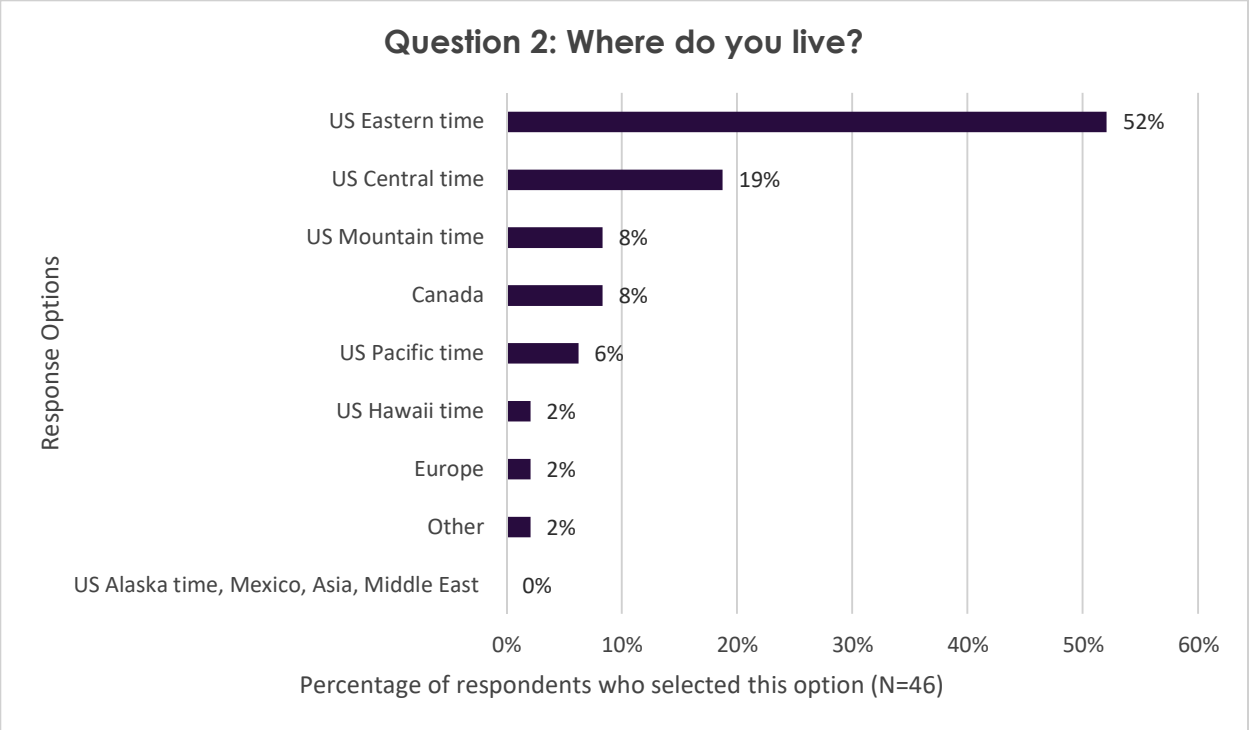
Duane, the grandfather of a boy with Gorlin syndrome articulated the hopes of many when he said, "*I hope the FDA really takes this to heart and realizes that even though this is a relatively rare problem in our society, it is substantial in the lives of the people that are affected by it*."

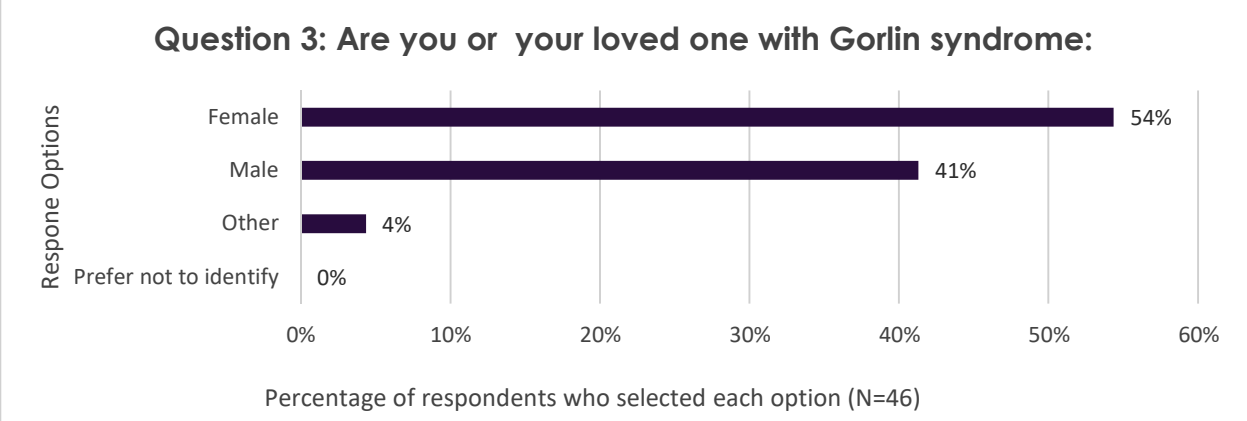
Appendix 1: Meeting Demographics

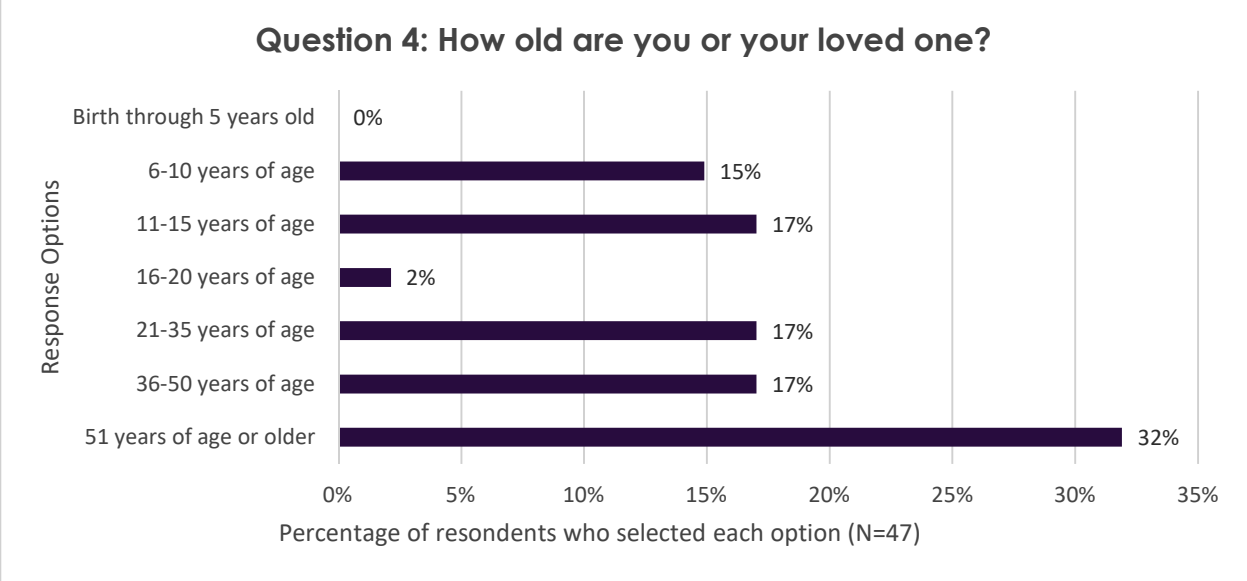
These graphs include those attendees who chose to participate in online voting. The number of affected individuals and caregivers who responded to each polling question is shown below the X axis (N=x).

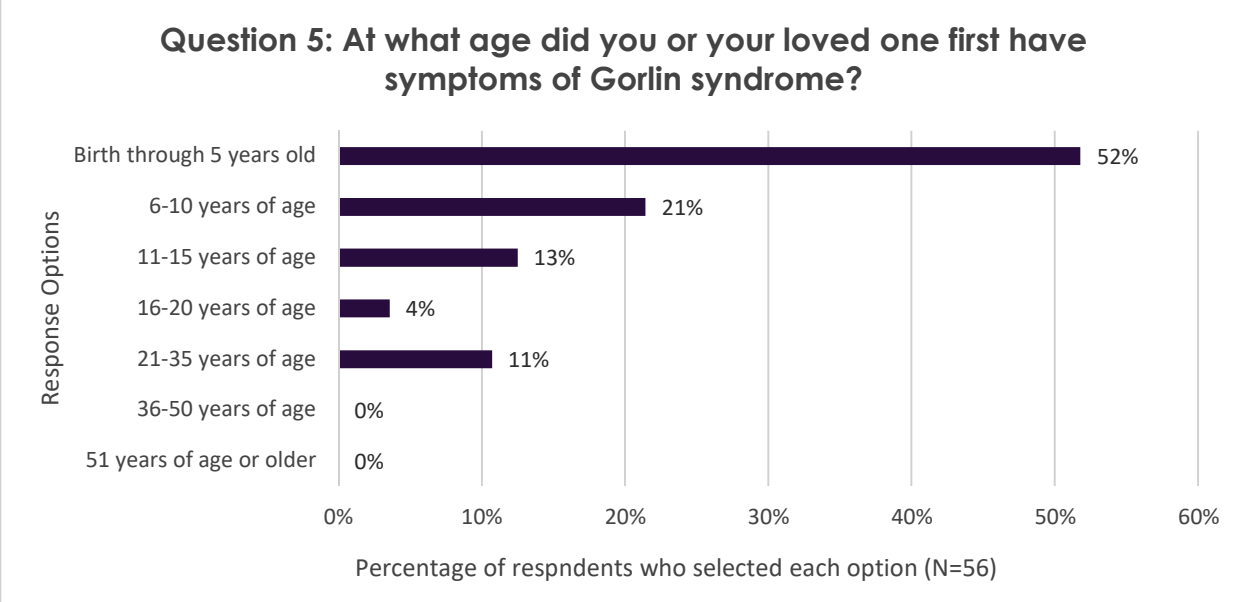
While the response rates for these polling questions is not considered scientific data, it provides a snapshot of those who participated in the EL-PFDD meeting and is intended to complement the live and pre-recorded comments throughout the meeting.






Question 3: Are you or your loved one with Gorlin syndrome:
Respone Options
Female
Male
Other
Prefer not to identify
54%
41%
4%
0%
0%
10%
20%
30%
40%
50%
60%
Percentage of respondents who selected each option (N=46)


Question 4: How old are you or your loved one?
Response Options
Birth through 5 years old
6-10 years of age
11-15 years of age
16-20 years of age
21-35 years of age
36-50 years of age
51 years of age or older
0%
15%
17%
2%
17%
17%
32%
0%
5%
10%
15%
20%
25%
30%
35%
Percentage of resondents who selected each option (N=47)


Question 5: At what age did you or your loved one first have symptoms of Gorlin syndrome?
Response Options
Birth through 5 years old
6-10 years of age
11-15 years of age
16-20 years of age
21-35 years of age
36-50 years of age
51 years of age or older
52%
21%
13%
4%
11%
0%
0%
0%
10%
20%
30%
40%
50%
60%
Percentage of respndents who selected each option (N=56)

Appendix 2: Meeting Agenda

Gorlin Syndrome Externally Led - Patient Focused Drug Development Meeting

October 8, 2021

10 a.m. – 3:00 p.m. Eastern Time

10:00 AM	Opening remarks
	Julie Breneiser, PA-C Emeritus, Executive Director, GSA
10:05 AM	Welcome remarks:
	FDA Representative Dr. Felisa (Sally) Lewis Division of Dermatology and Dental Products, CDER
10:15 AM	Scientific overview:
	Joyce Teng, MD, PhD, Dermatologist, Professor of Dermatology, Stanford University
10:30 AM	Introduction and Meeting Overview:
	Larry Bauer, RN, MA, Meeting Moderator Hyman, Phelps, & McNamara, P.C.
10:35 AM	Demographic polling of Gorlin syndrome patients and caregivers

Session 1: Gorlin Syndrome - Symptoms and Impact

10:40 AM	Panelist Presentations: Symptoms and Daily Impact
11:05 AM	Audience discussion and polling of Gorlin syndrome patients and caregivers
12:15 PM	Lunch Break

Session 2: Gorlin Syndrome - Treatments and Hopes for Future

12:45 PM	Introduction to afternoon session
12:50 PM	Panelists Presentations: Current and Future Treatments
1:15 PM	Audience discussion and polling of Gorlin syndrome patients and caregivers
2:30 PM	Summary
	James Valentine, JD, MHS Hyman, Phelps, & McNamara, P.C.
2:45 PM	Next steps and closing remarks: Julie Breneiser
3:00 PM	Adjourn

Appendix 3: Meeting Discussion Questions

Session 1: Living with Gorlin syndrome: Symptoms and Daily Impacts

1. Of all the symptoms and health effects of Gorlin syndrome, which 1-3 symptoms have the most significant impact on your or your loved one's life?
2. How does Gorlin syndrome affect you or your loved one on best and on worst days?
3. How have you or your loved one's symptoms changed over time? How has the ability to cope with the symptoms changed over time?
4. Are there specific activities that are important to you or your loved one that you or they cannot do at all or as fully as you or they would like because of Gorlin syndrome?
5. What do you fear the most as you or your loved one gets older? What worries you most about your or your loved one's condition?

Session 2: Perspective on current and future approaches to treatment

1. What are you currently doing to manage your or your loved one's Gorlin syndrome symptoms?
2. How well do these treatments treat the most significant symptoms and health effects of Gorlin syndrome?
3. What are the most significant downsides to your or your loved one's current treatments and how do they affect daily life?
4. Short of a complete cure, what specific things would you look for in an ideal treatment for Gorlin syndrome? What factors would be important in deciding whether to use a new treatment?

Appendix 4: Panel Participants and Callers

Unless otherwise specified, all panelists and callers are individuals living with Gorlin syndrome.

Topic 1 - pre-recorded panel
Kevin, husband and parent of affected son
Bob
John
Brandon
Leslie, parent of affected son

Topic 1 - Live zoom panelists
Alice
John J., individual living with, and parent of affected son
Roni, parent of affected son
Jenni
Beth, parent of affected son

Topic 1- callers
Sandy, grandparent of an affected grandchild
Patricia, parent of an affected child
Anne
Erika, parent of an affected daughter
Elizabeth, individual affected by Gorlin syndrome, and parent of an affected child

Topic 2 - pre-recorded panel
Roxanne "Rocki", widow of affected husband and parent of two individuals living with Gorlin syndrome
Bud
John W.
Stacy, parent of affected daughter
Meredith, parent of affected daughter

Topic 2 - Live zoom panelists
Maria
Lizzy, individual living with, and parent of an individual living with Gorlin syndrome
Erika, parent of affected daughter
Kathlyn, individual living with and parent of affected son
Duane, grandparent of an individual living with Gorlin syndrome

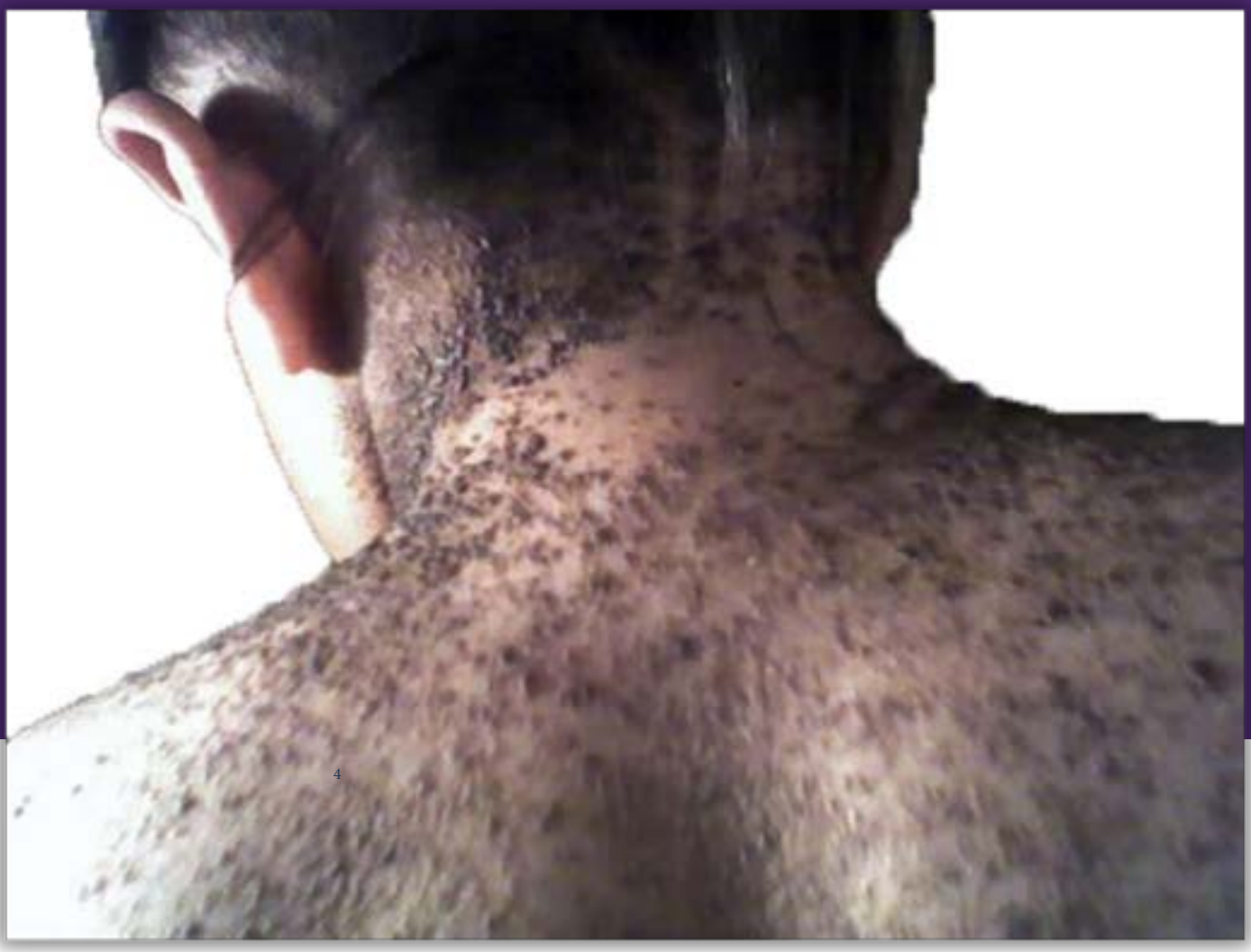
Topic 2- callers
Nichole
Kaylene
Lornna, parent of affected son
Tom
Charlotte
Kristi
Martha

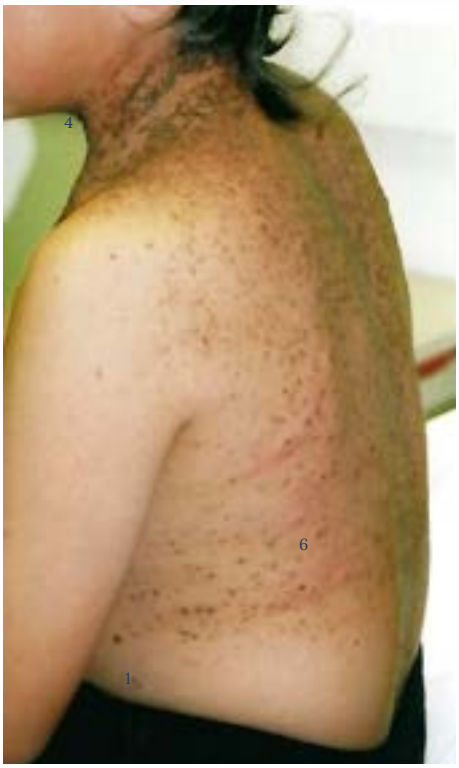
Appendix 5: Photo Gallery. The Bad, the Ugly, the Pain, the Anxiety.

Warning: many of these photos are of an extremely sensitive medical nature and may be disturbing to view.

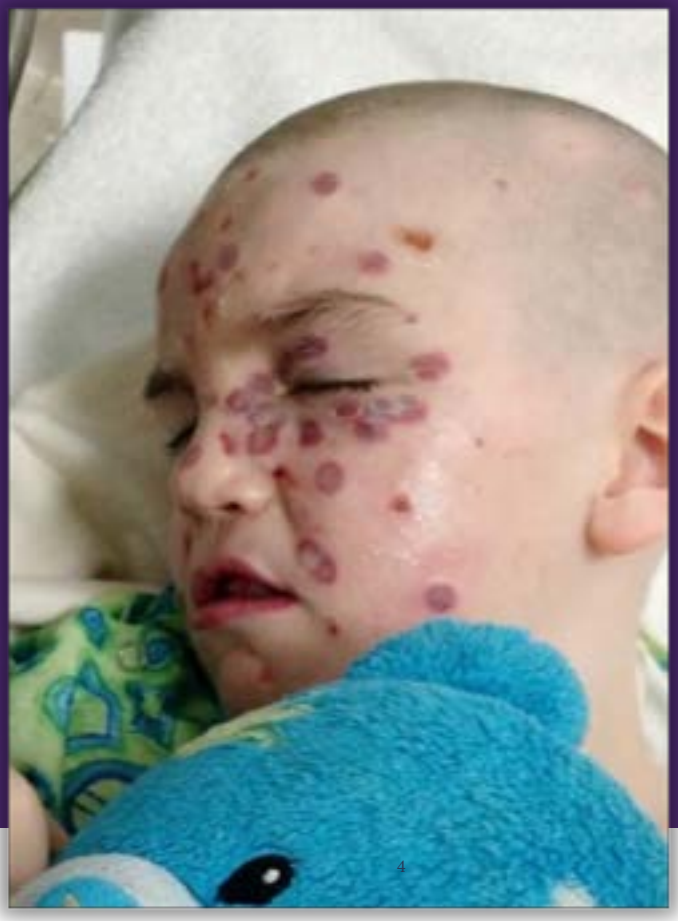
The rest of this page was intentionally left blank, and photos will start on the following page.

The photos in this appendix were included with the consent of the affected individuals and/or their families. Images of adults are shown on a page with a purple bar down the side of the page, and images of children are shown with a purple bar on the top of the page.





Pigmented BCCs blanket the back and neck of a 9-year-old after radiation therapy for a medulloblastoma as an infant, prior to being diagnosed with GS. Medulloblastoma is a malignant brain tumor, and is a manifestation of this syndrome.



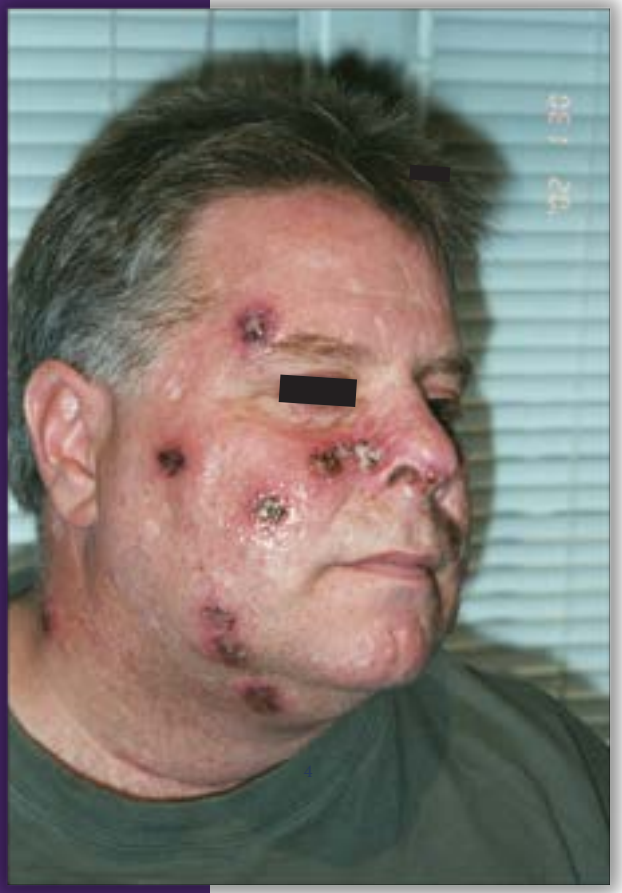
8-year-old after undergoing general anesthesia for laser ablation of multiple BCCS AND removal of odontogenic keratocyst.

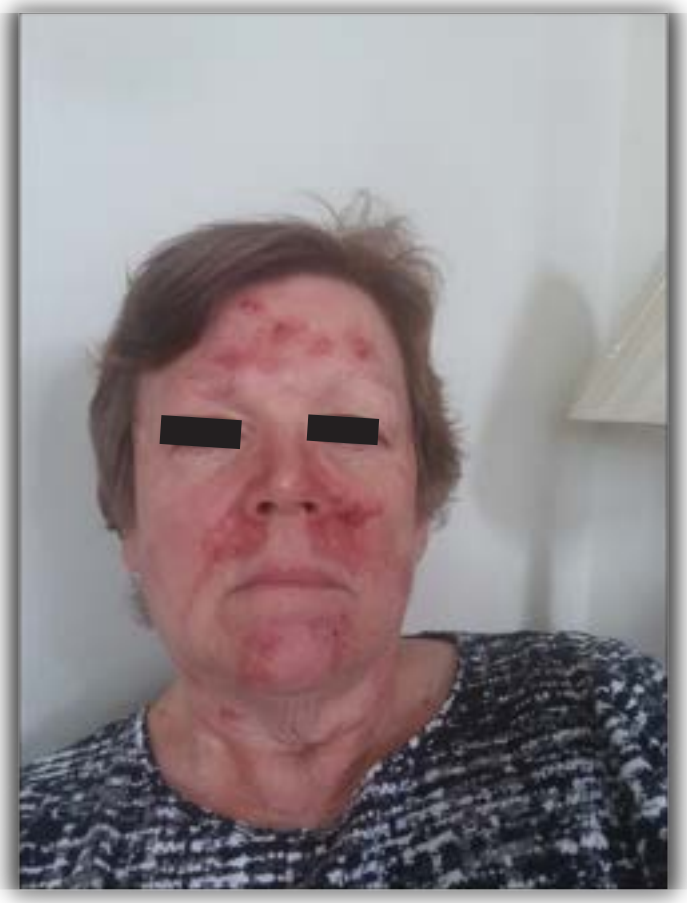
5-year-old three days after undergoing general anesthesia for laser ablation and PDT treatment of multiple BCCs.

These two men who had Gorlin syndrome died from metastatic BCCs to the lungs.

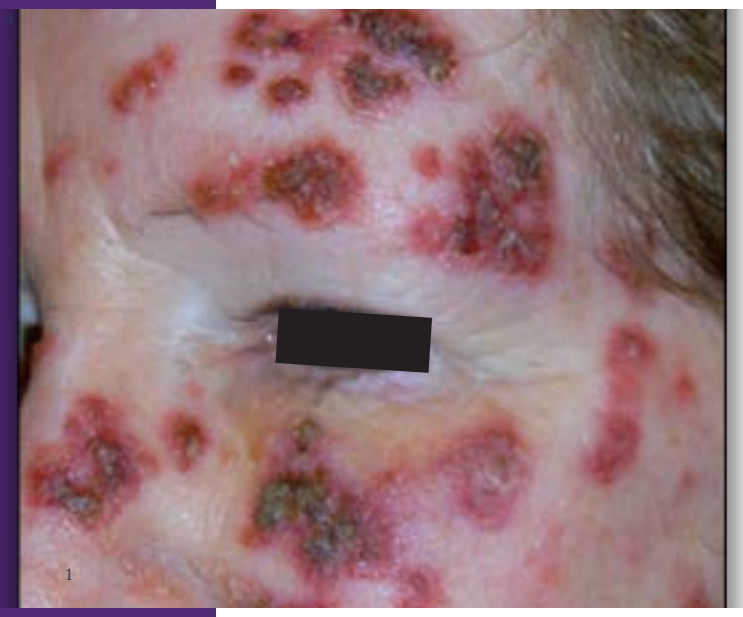
Having Gorlin syndrome is like “living with a ticking time bomb”.

Treatments can limit one's ability to function at home and in public.

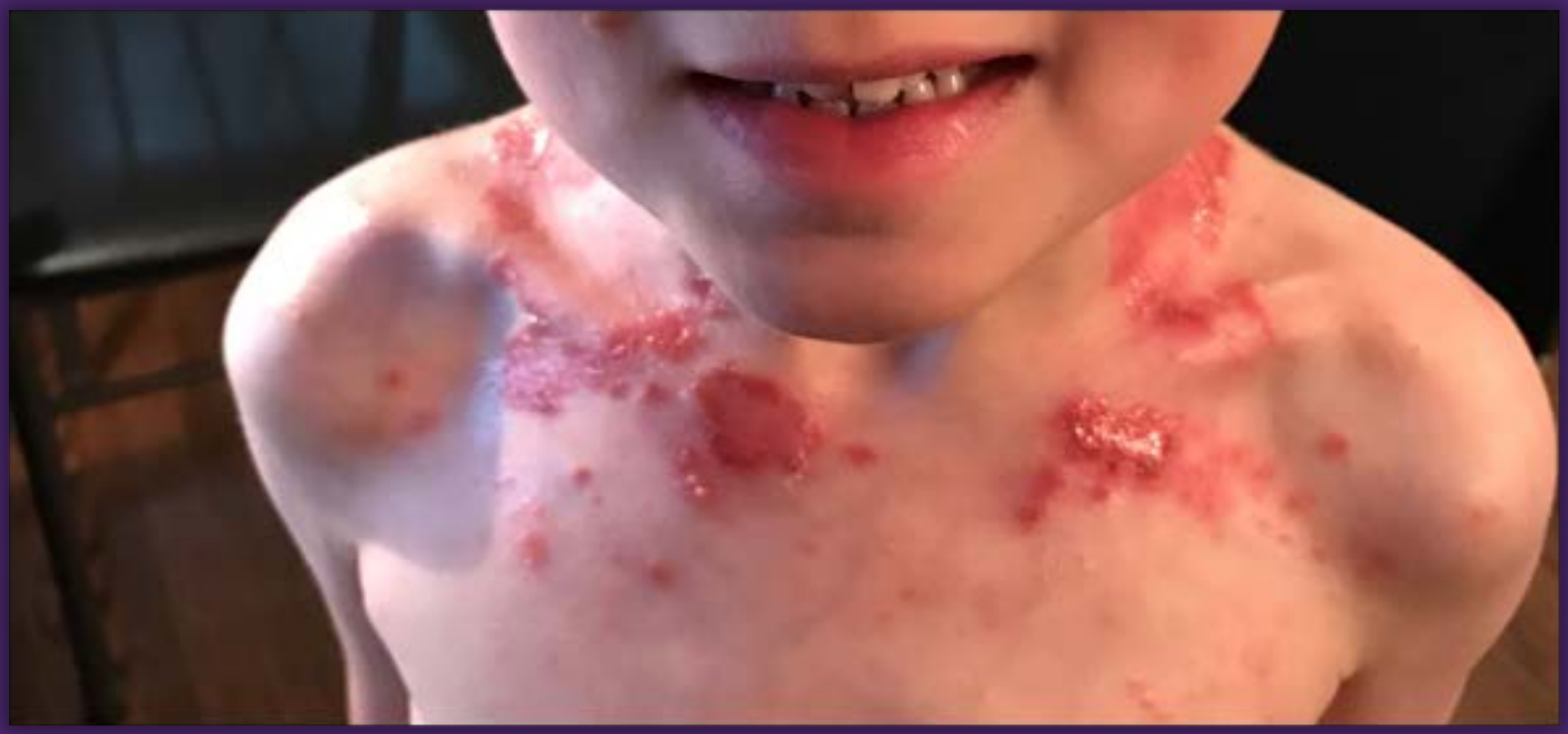


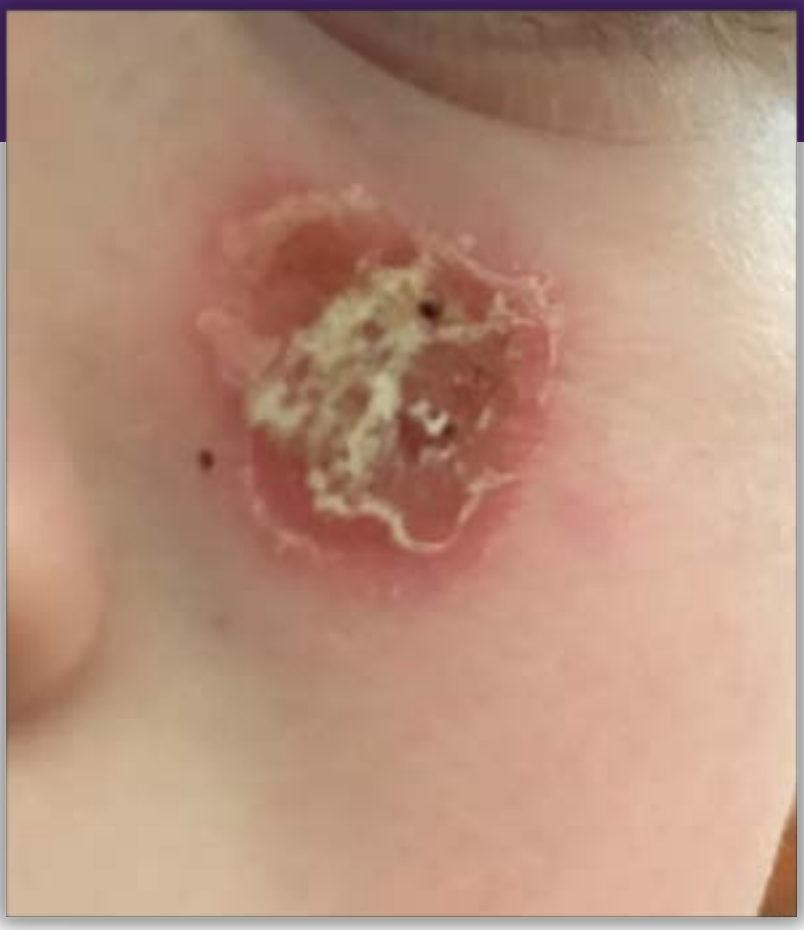


After photodynamic therapy (PDT) treatment of multiple facial BCCs.

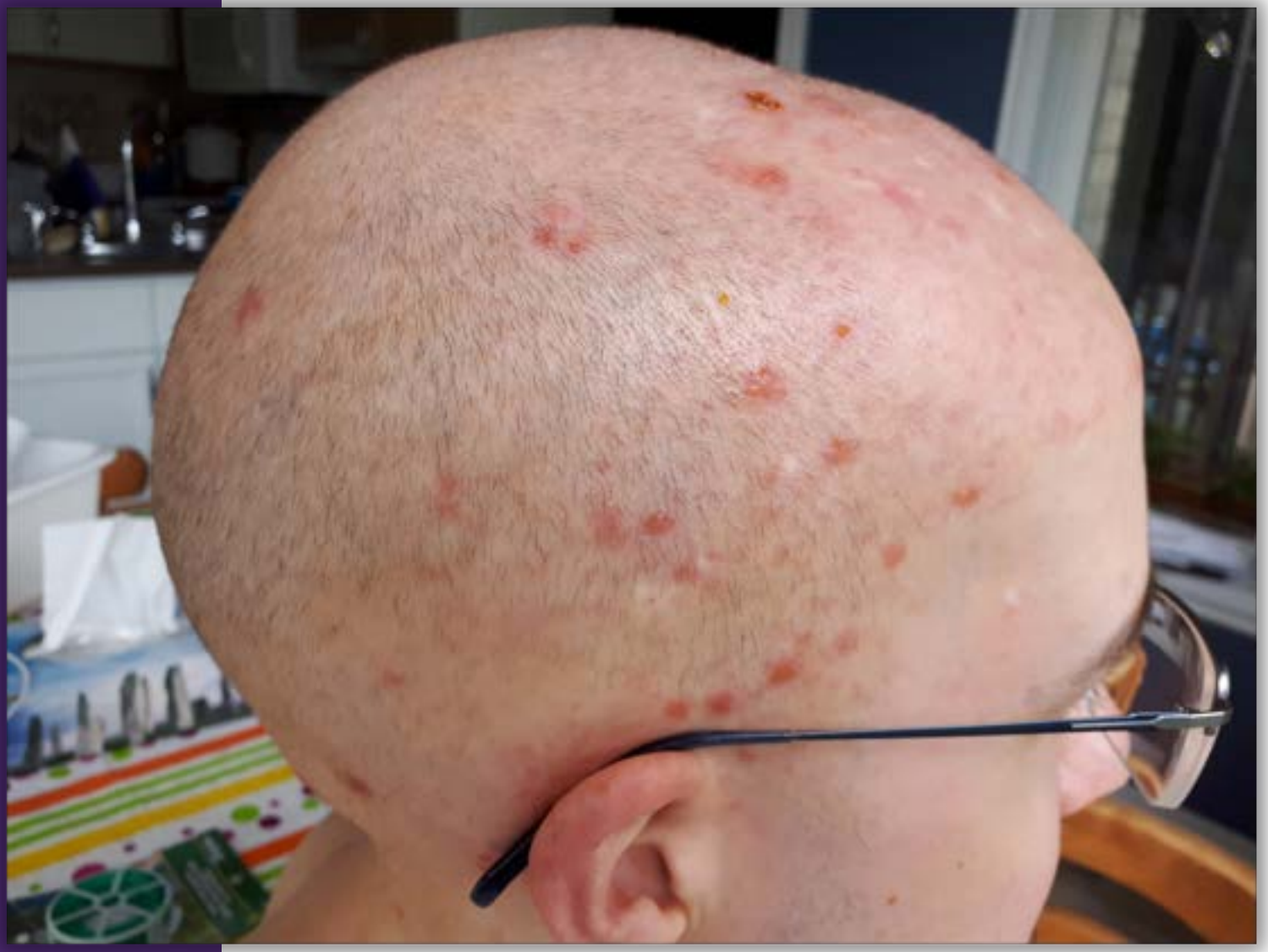


After 6 weeks of treatment with topical 5-FU.

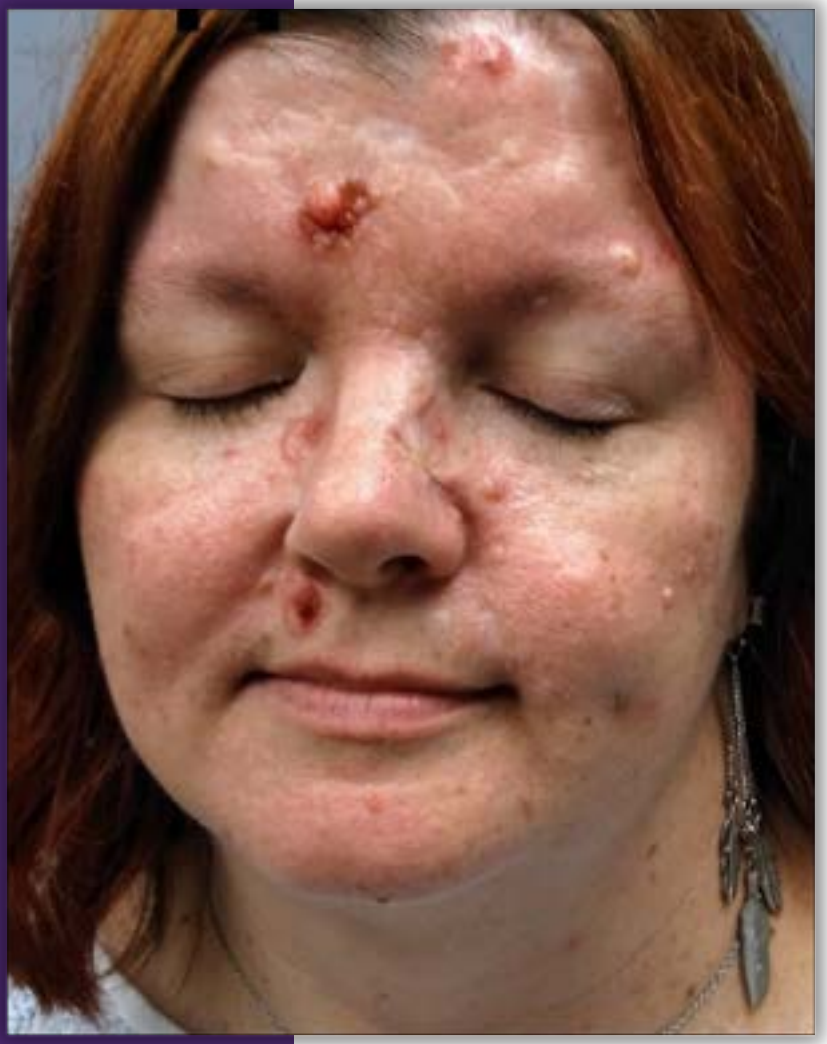




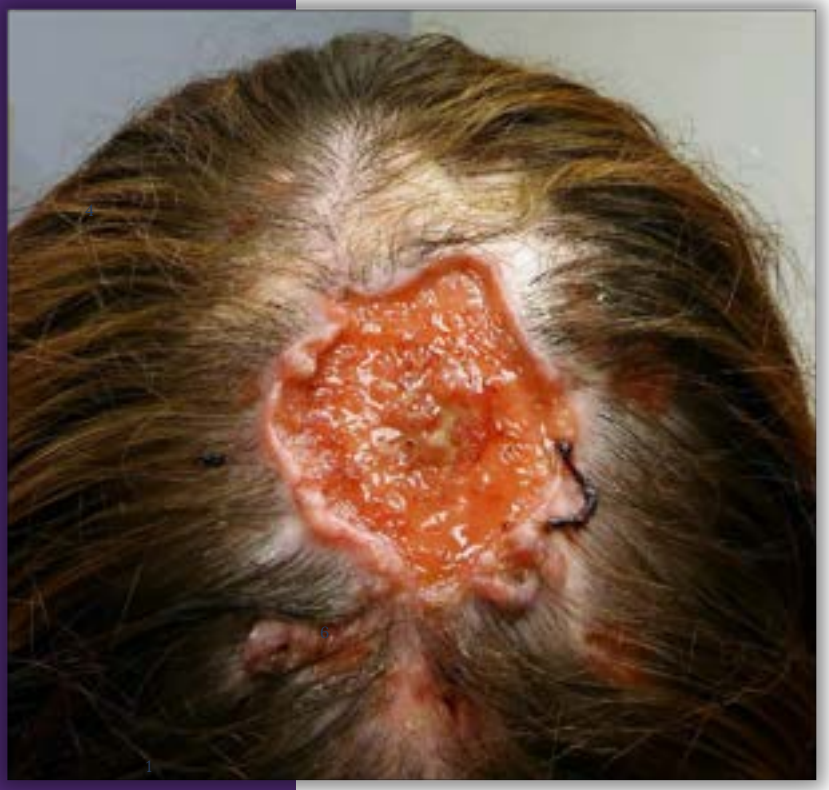
8-year-old boy after undergoing 6-weeks of daily application of topical Imiquimod for multiple BCCs.



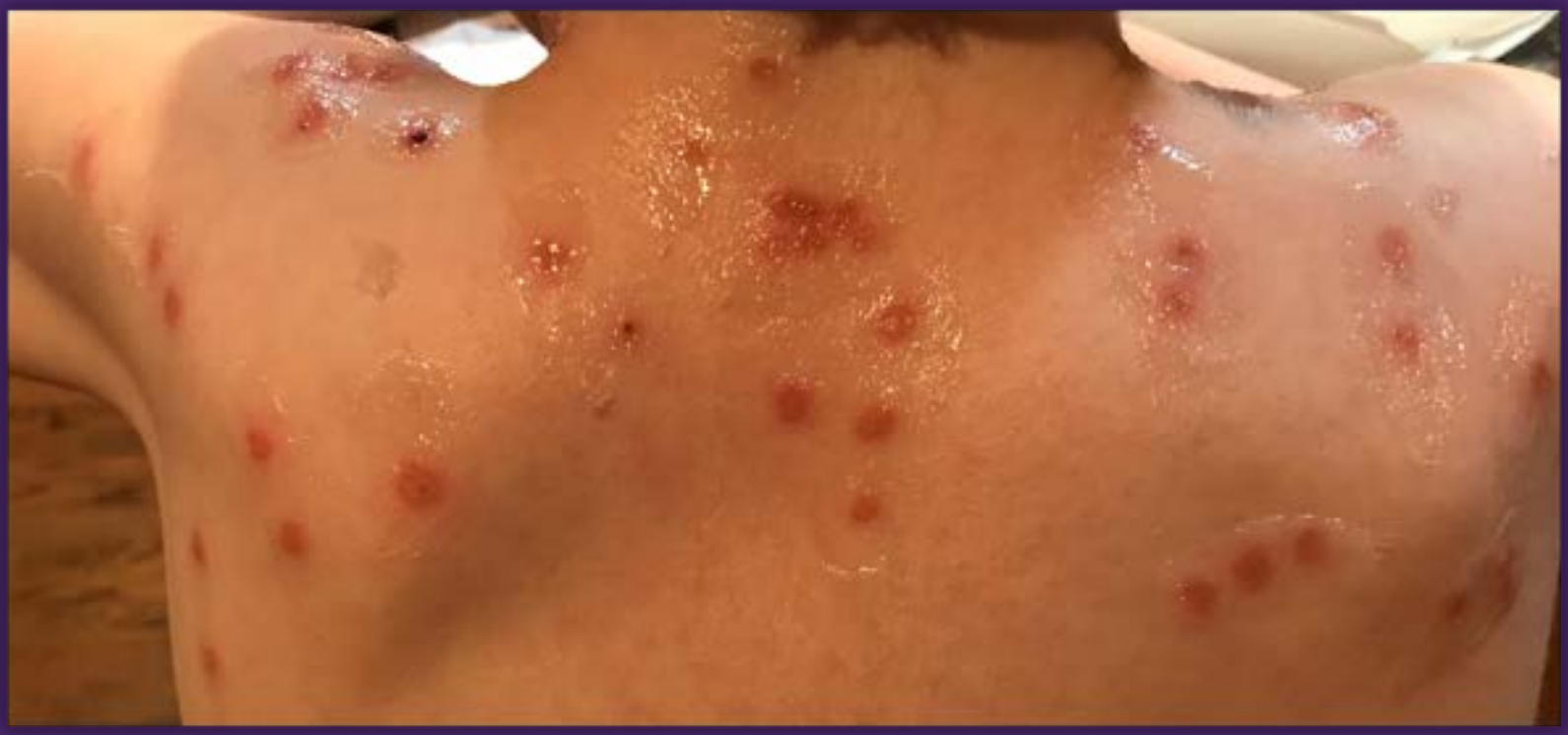
24-year-old male during PDT treatment of multiple BCCs on scalp. This was his 4th PDT treatment since age 7.

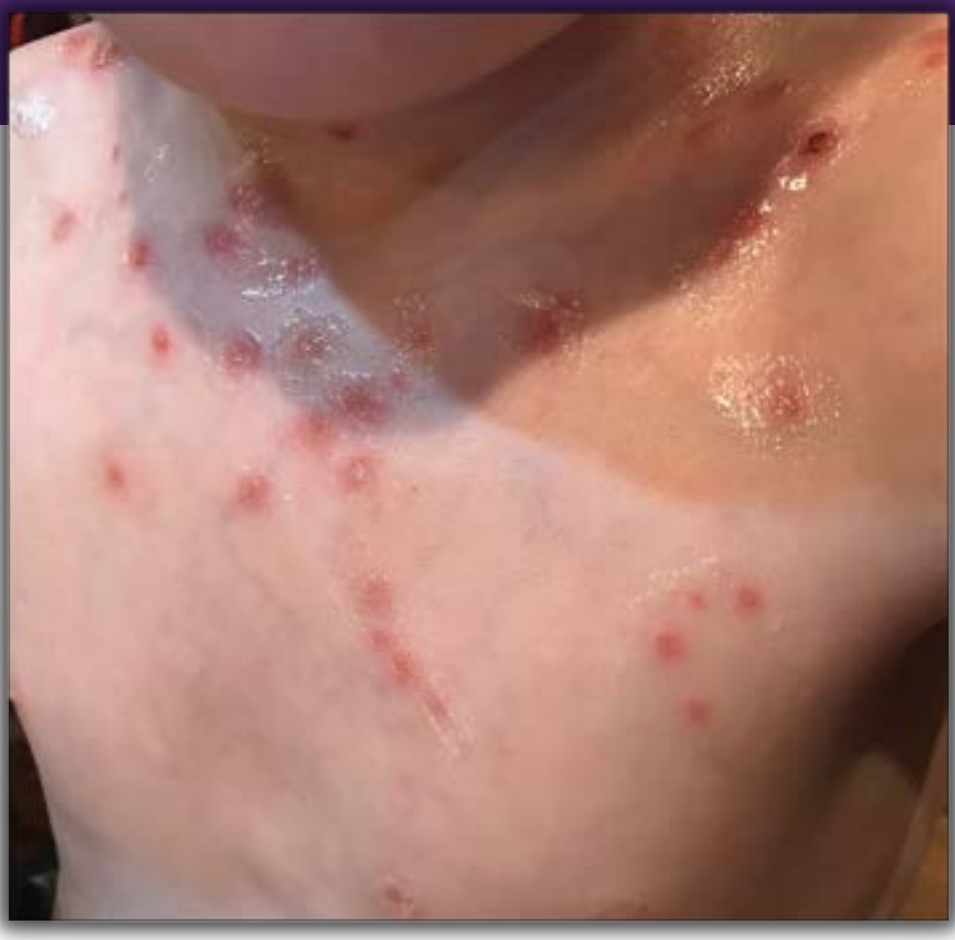


Woman in her 20's with multiple untreated facial BCCs along with disfiguring scars from prior BCC surgery.

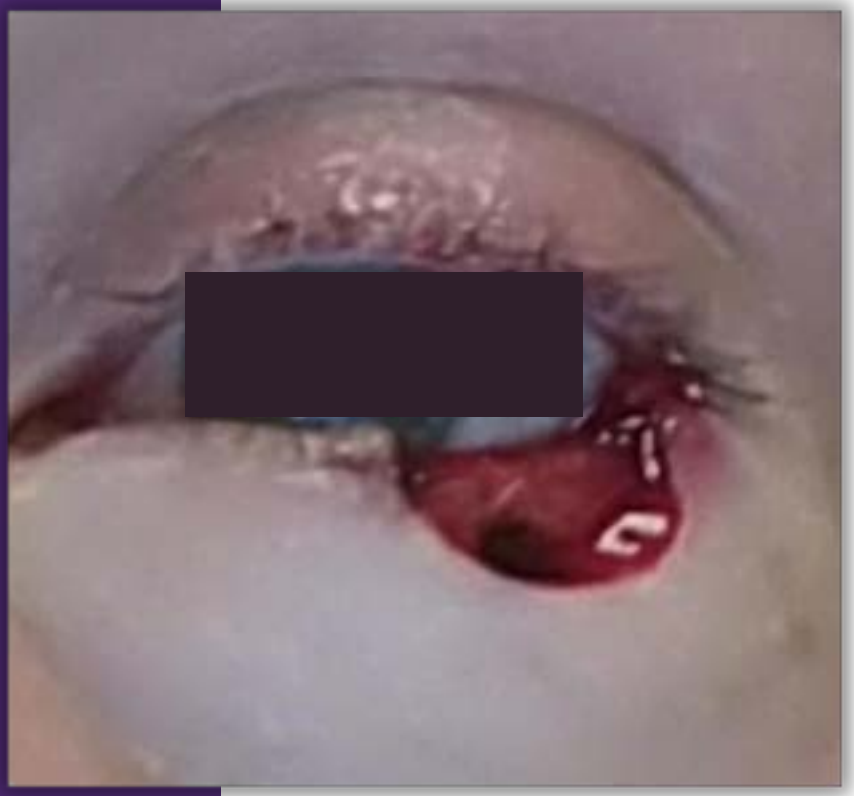


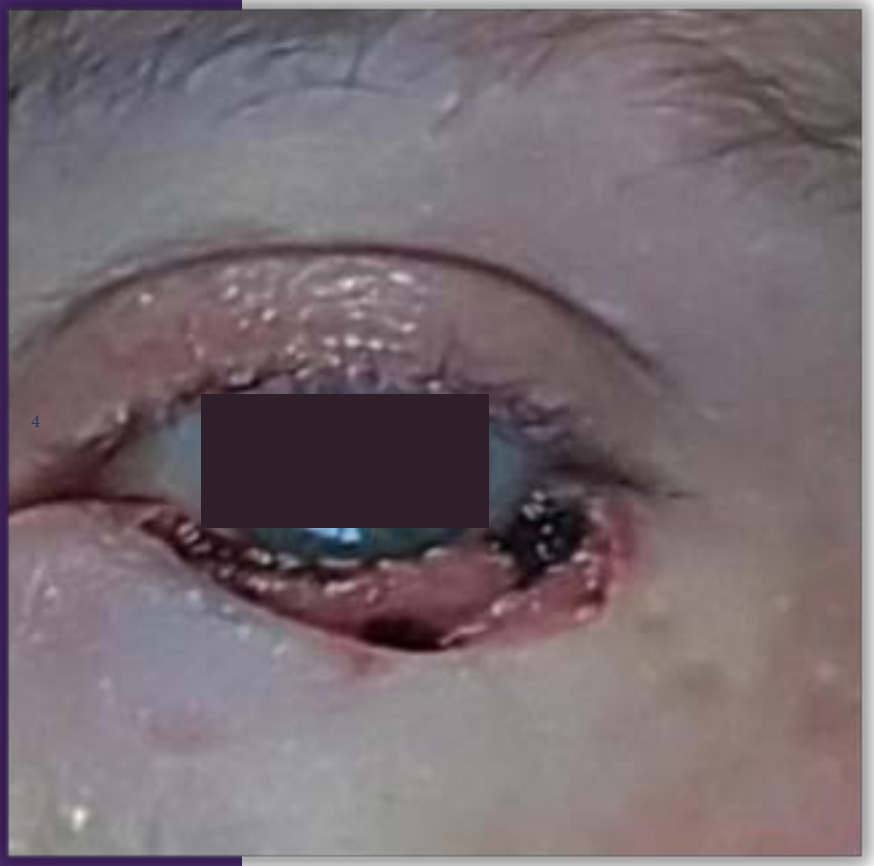
Same woman with a large, untreated BCC on scalp.



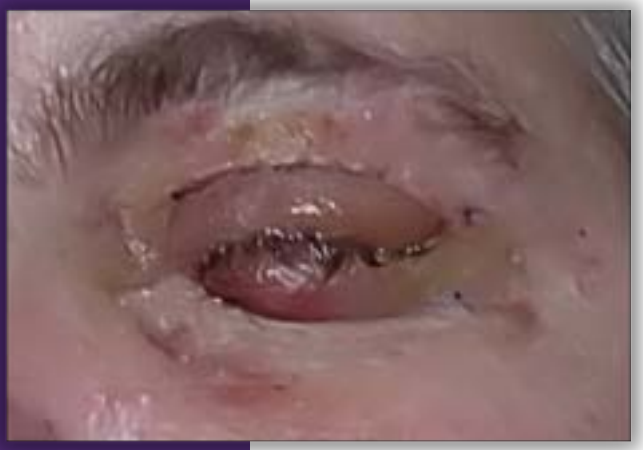


9-year-old boy two days after having 139 BCCs removed under general anesthesia.
There were more to be removed from scalp, neck, and arms but dermatologist felt that further excisions were intolerable at that time.

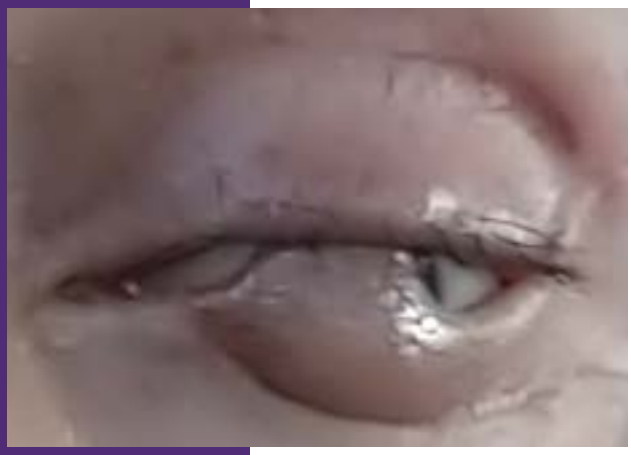


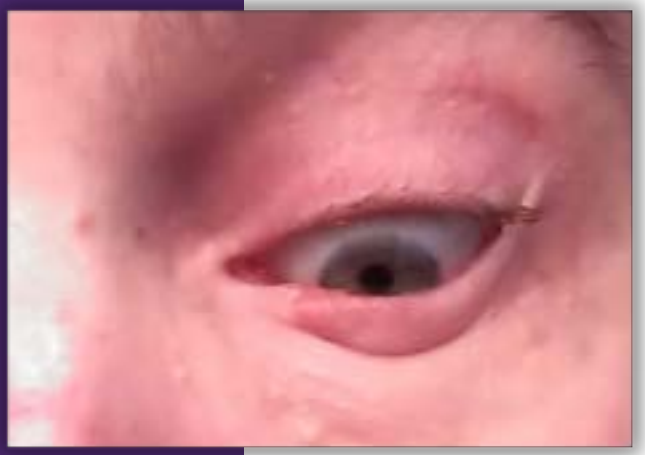


Defect after two (on top) and five cuts (on bottom) during Mohs surgery of 52-year-old woman with Gorlin syndrome.



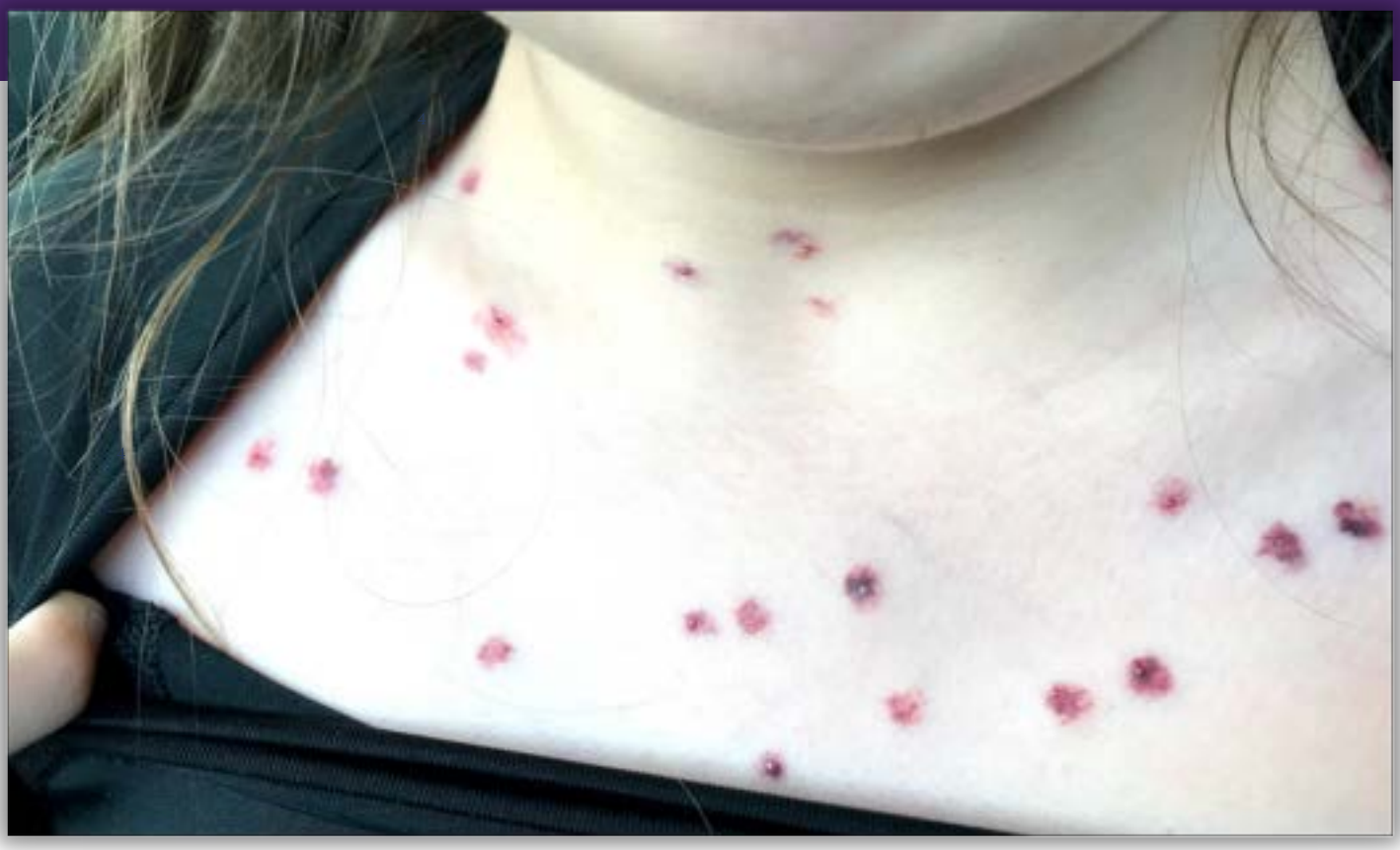
Surgery to repair defect necessitated eye being sewn closed for 12 weeks to heal. This significantly impacted daily life for her, as well as her husband and family.



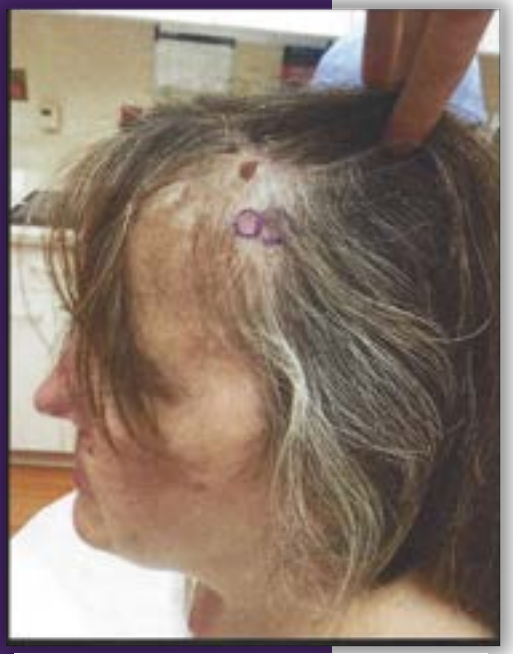


It resulted in permanent loss of muscle function of lower lid in that it does not move down as far as that on the right.

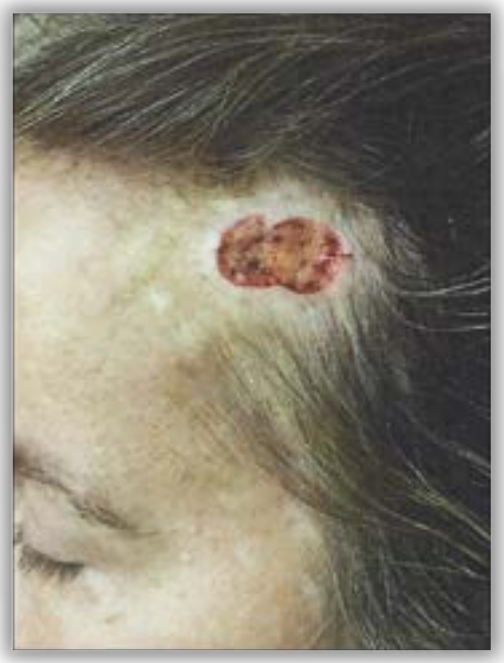
8-year-old after undergoing PDT (top) and laser ablation (bottom) of multiple BCCs.



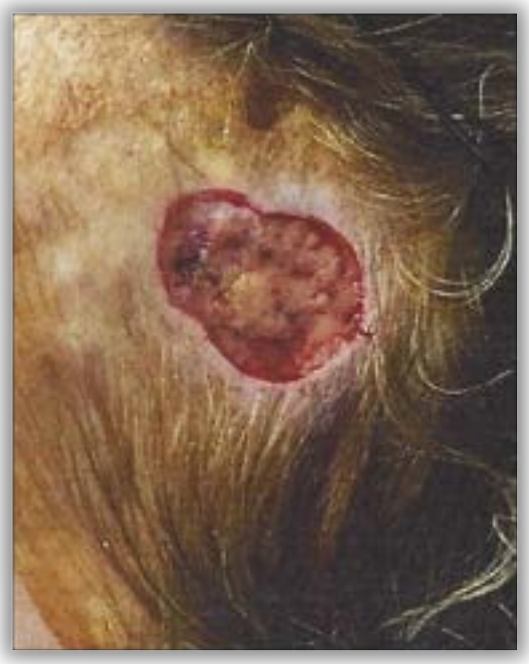
A long day... Patient departed 9 hours after arriving for 3-hour drive home.



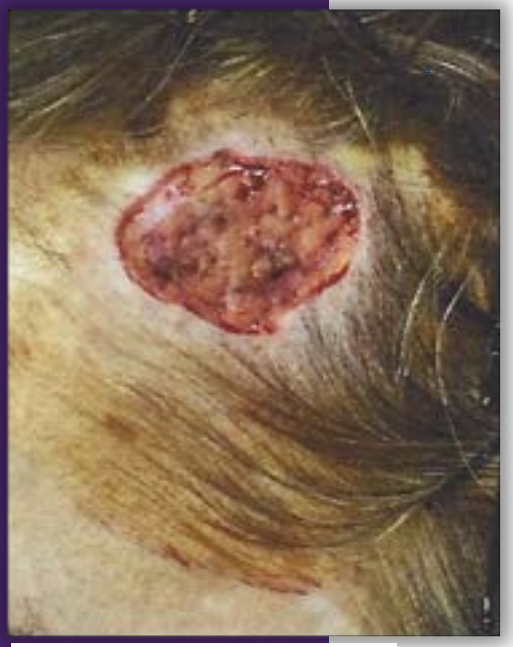
Pre-op. June 2020.



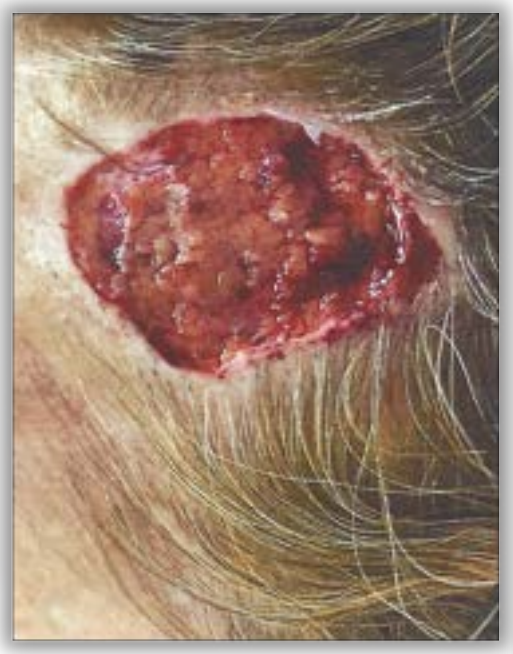
Mohs after 1st cut.



After 2nd cut.



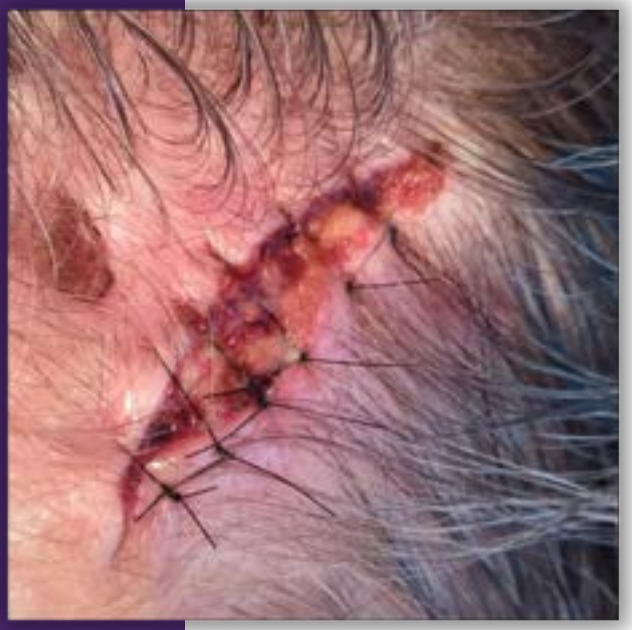
After 3rd cut.



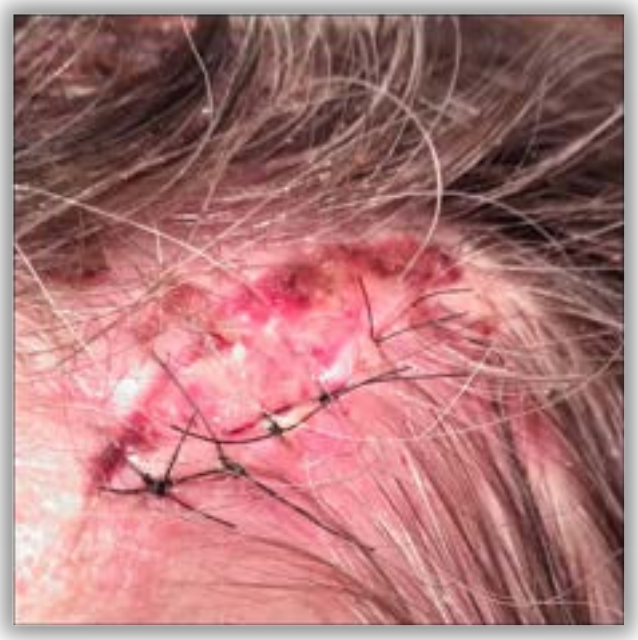
Clean after 4th cut.

Wound closed.

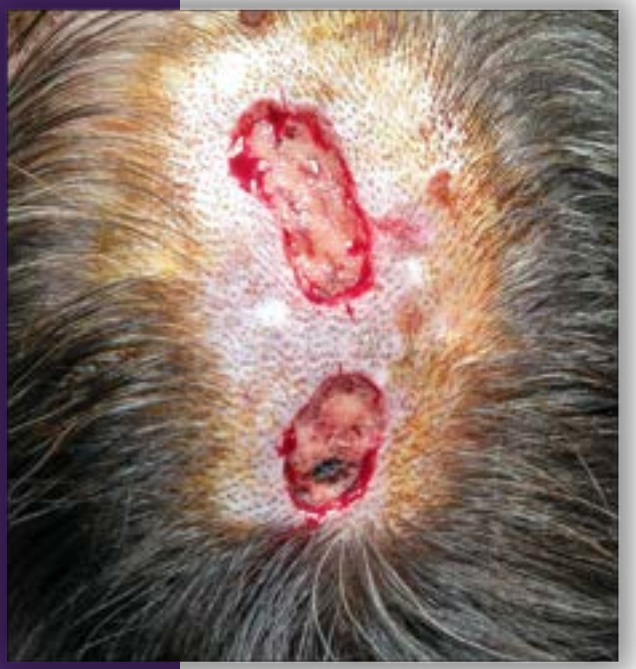
Same patient.



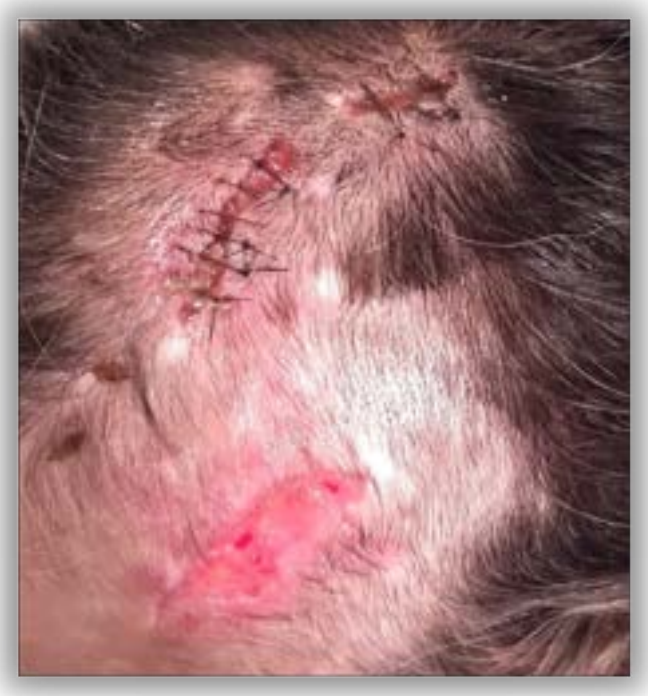
Post-op day 3.



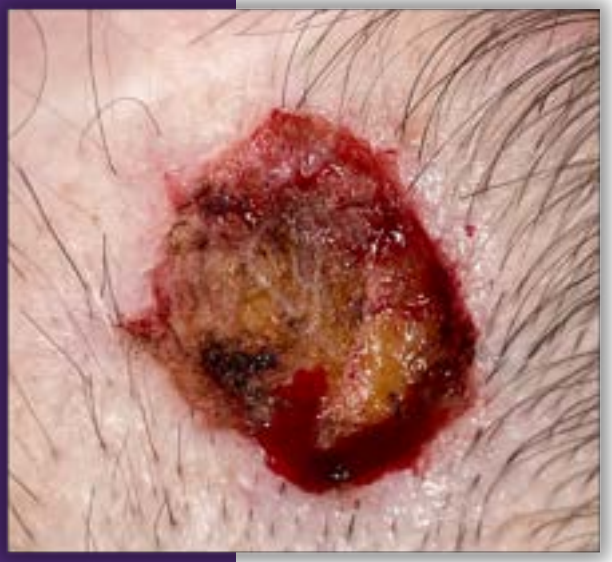
Post-op day 10.



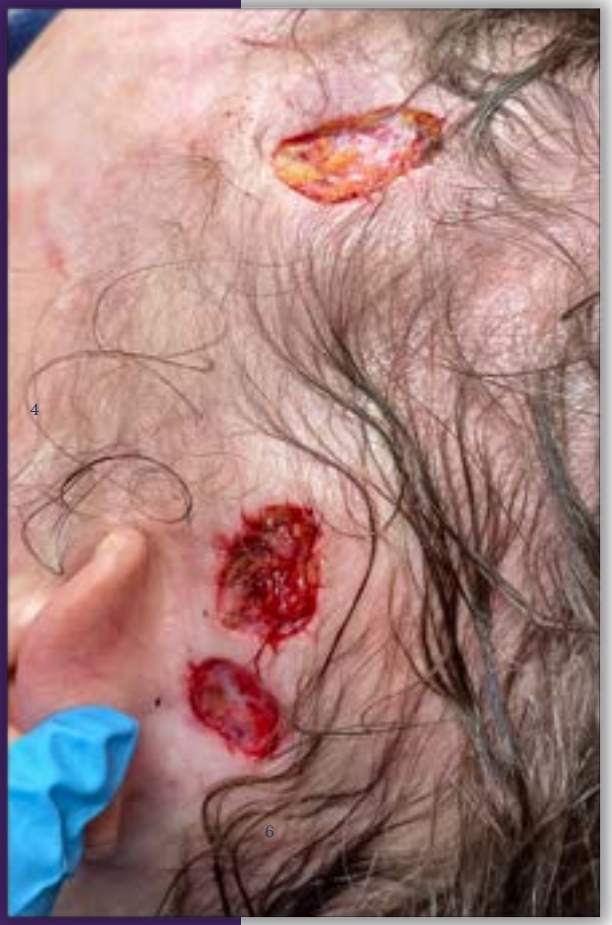
2nd Mohs procedure in 10 days – after 4 cuts.

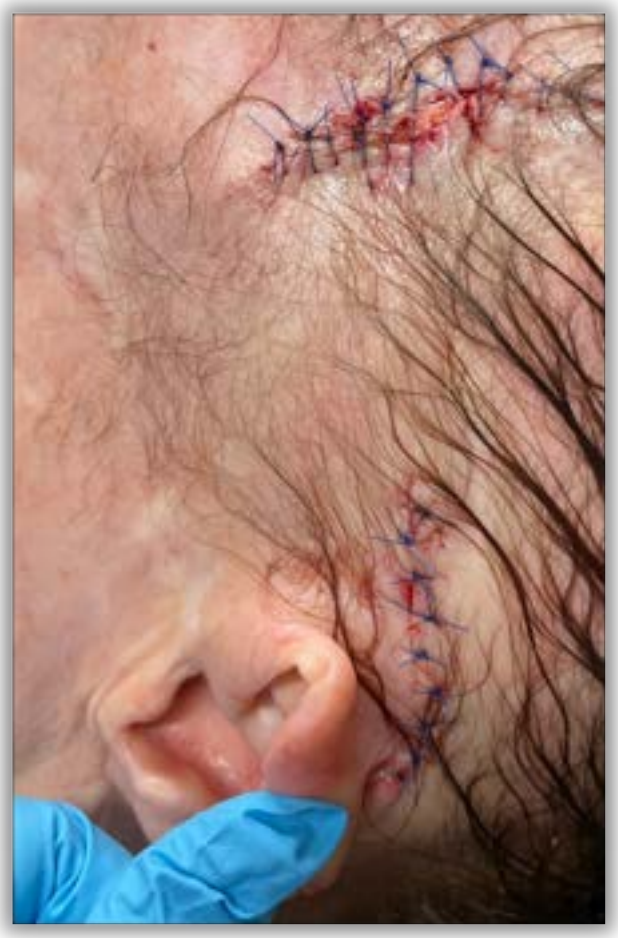


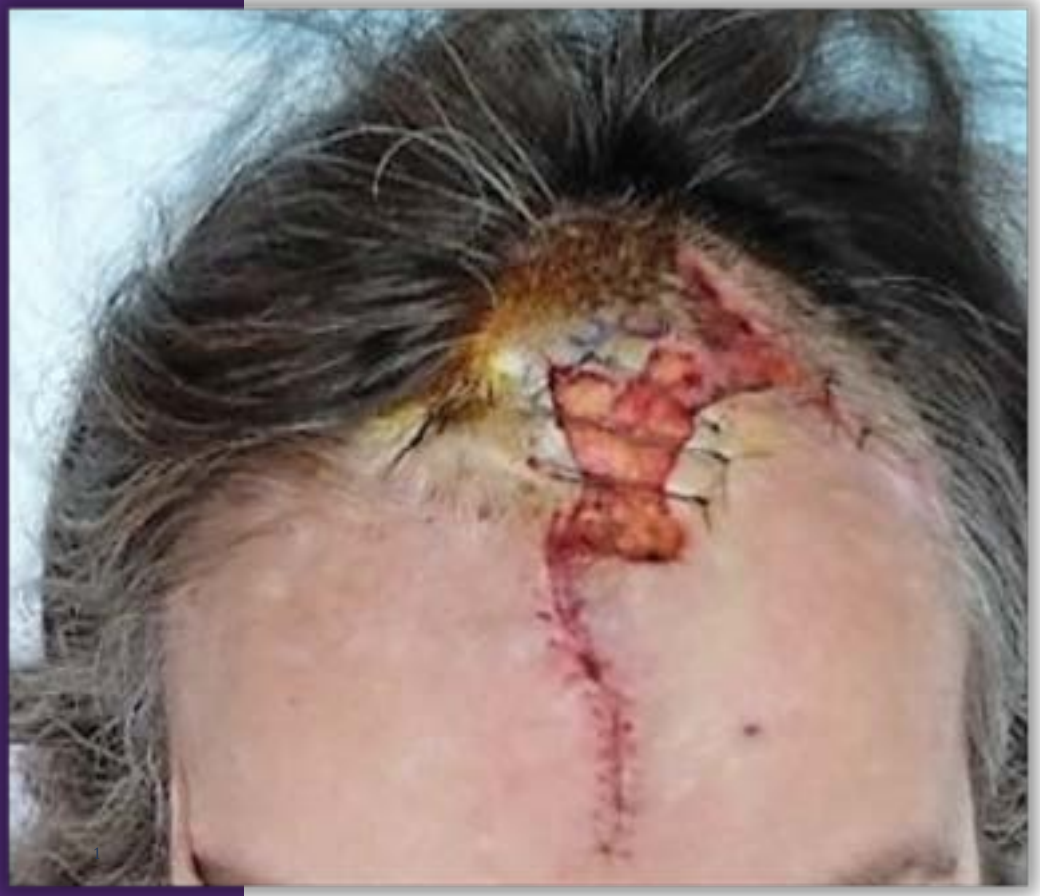
17 days post-op 1st Mohs, and 7 days post-op 2nd Mohs.



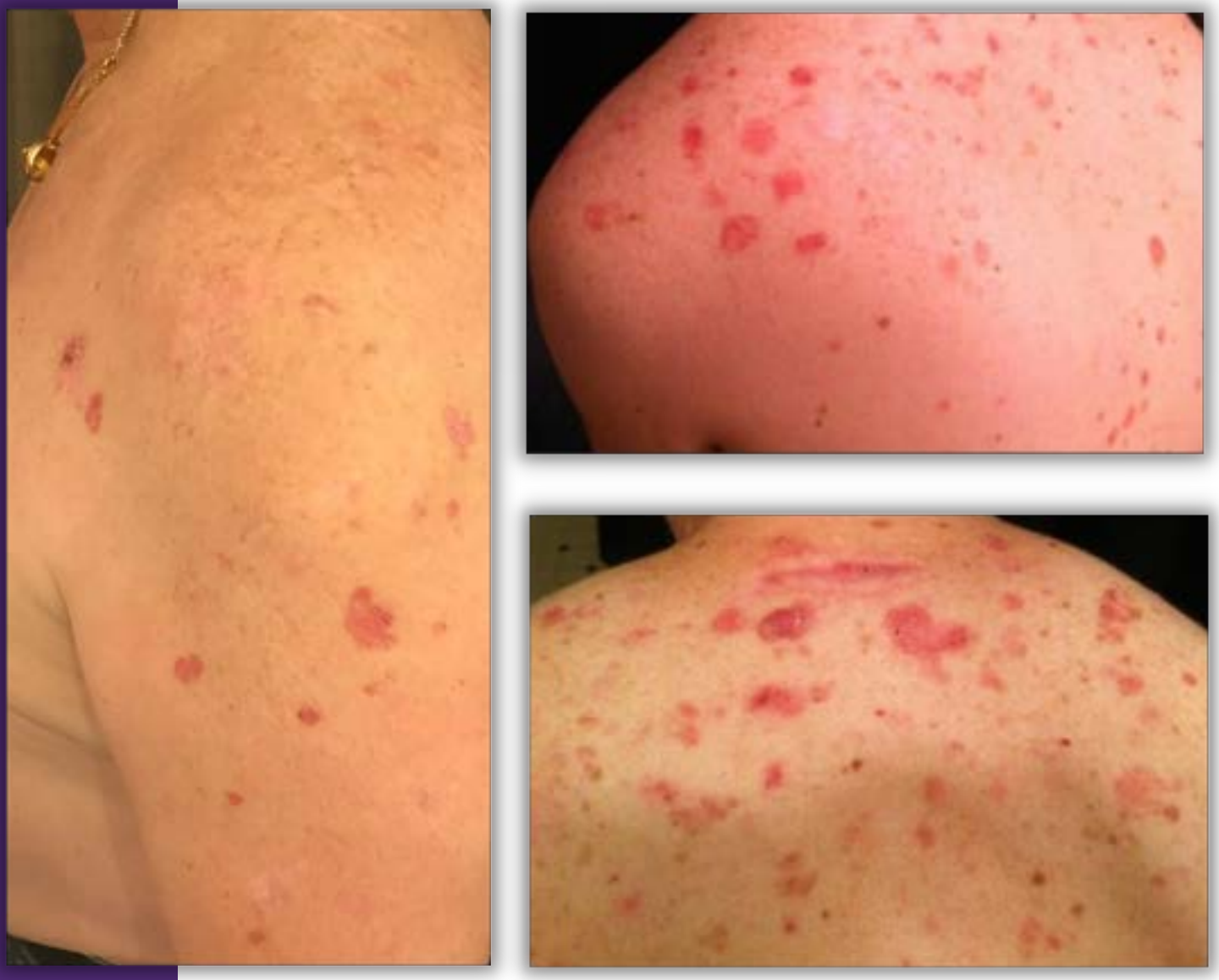
Two separate Mohs procedures. These individuals found sleeping and wearing glasses to be challenging for over 6 months.





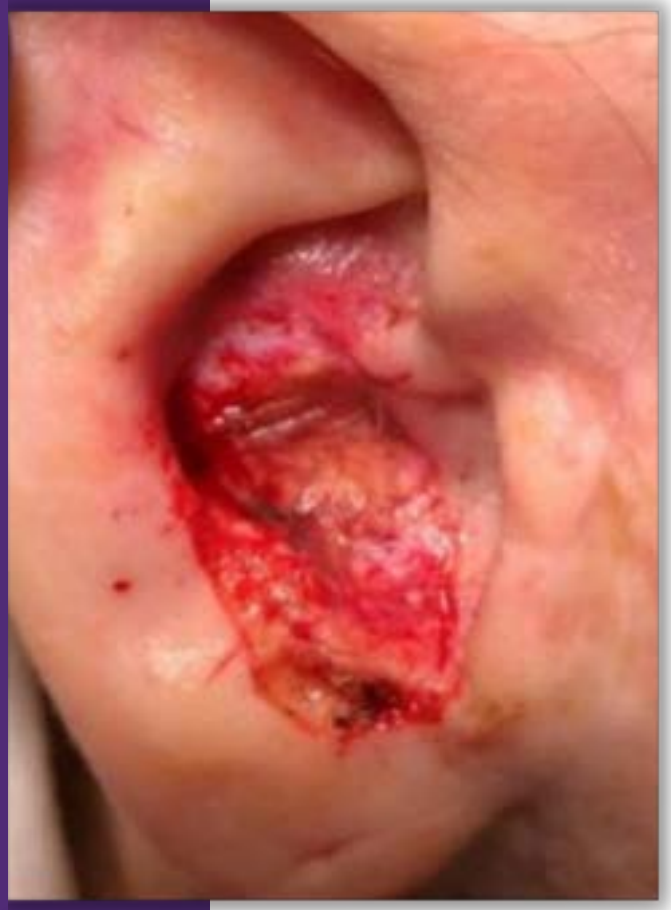


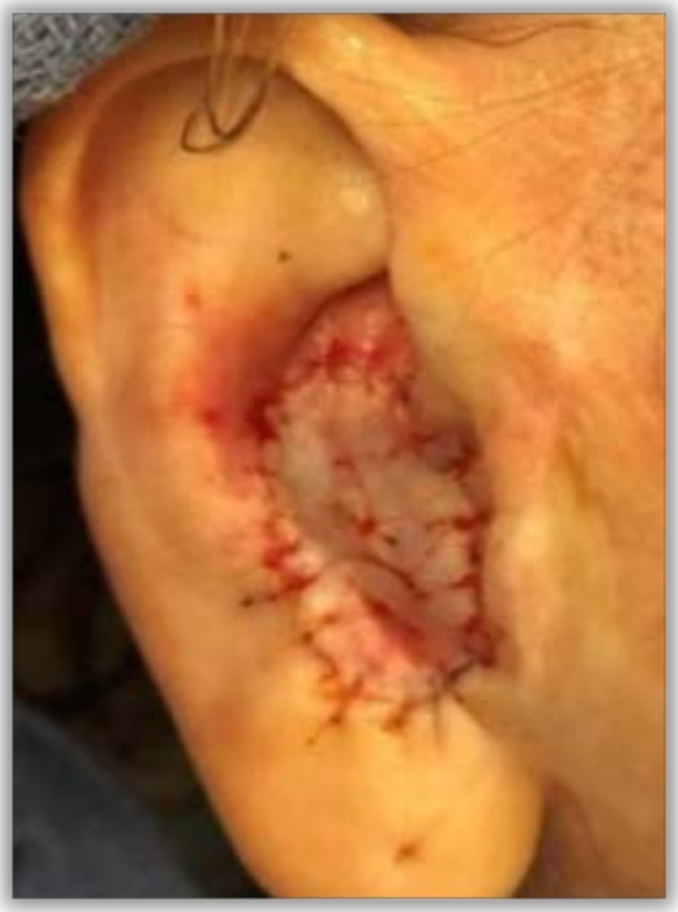
Extensive closure of Mohs defect. Due to its size, it was not possible to completely close. Borders were not clear and further treatment was required.

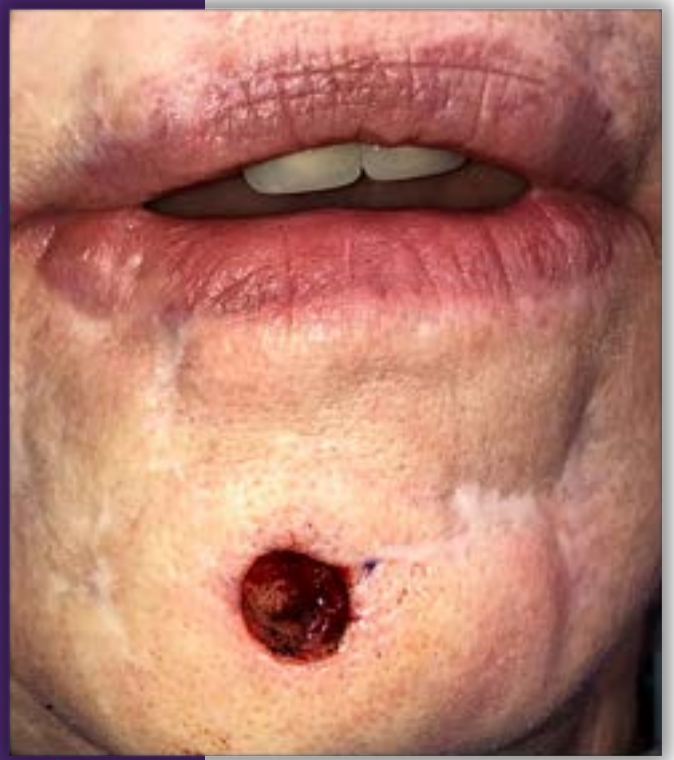


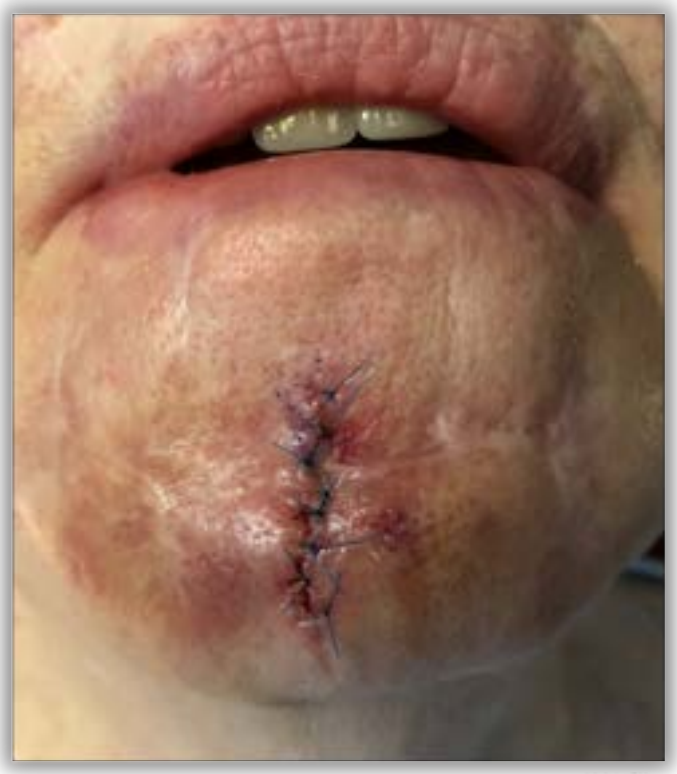
Multiple BCCs on the back and arm of three men.

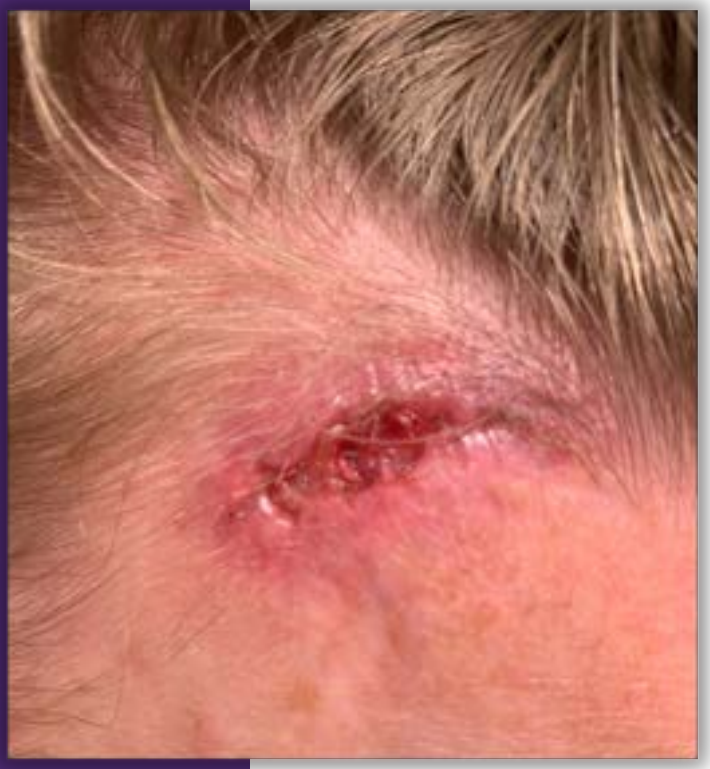
Patients with breakthrough disease while on hedgehog inhibitors may require Mohs procedures for treatment of resistant lesions.



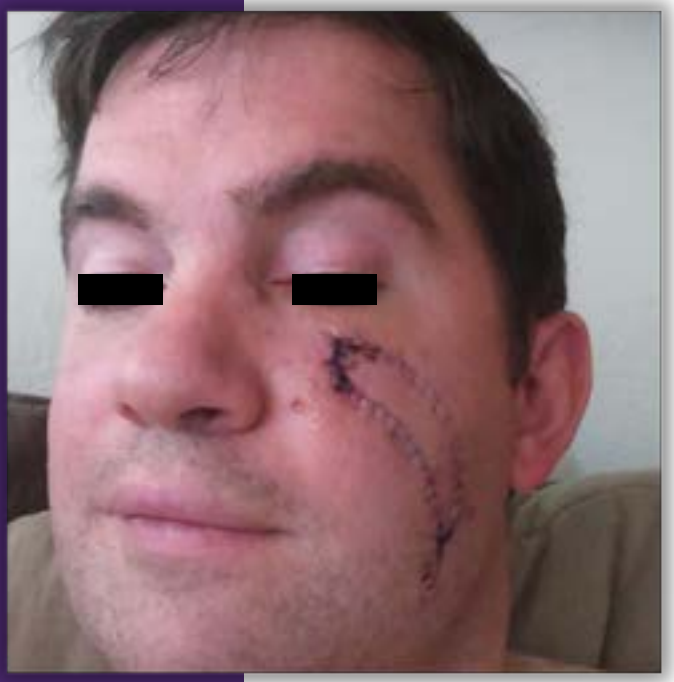


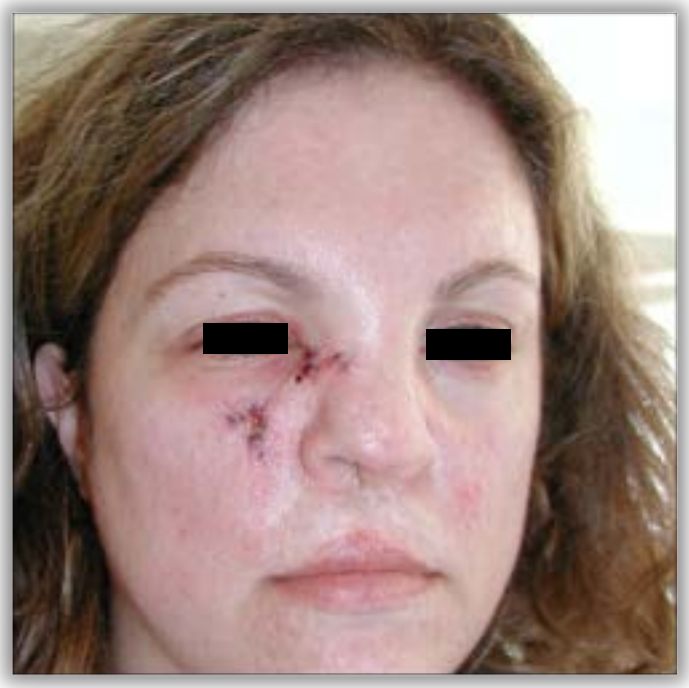




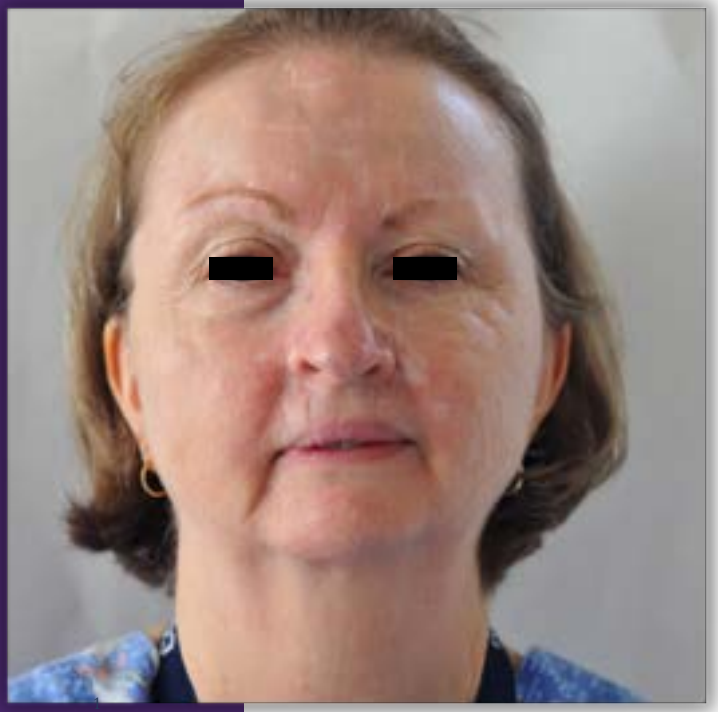


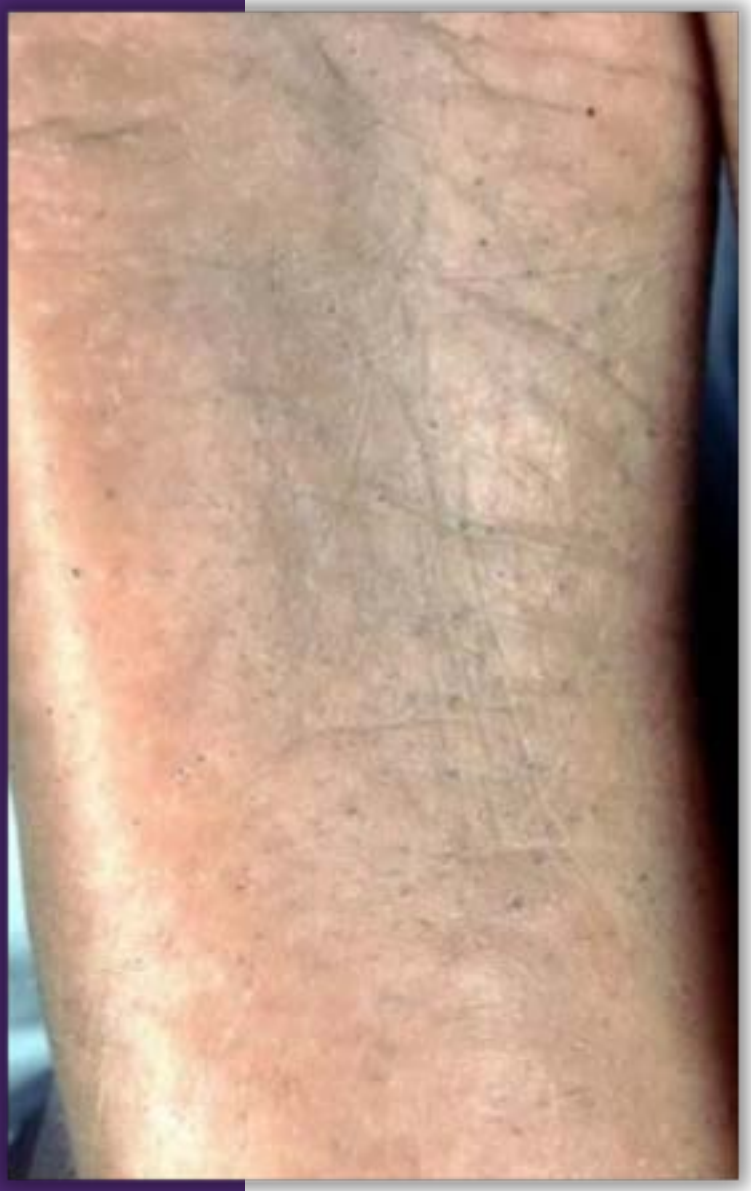
Individuals in their 20's already showing significant BCC burden and scarring. The woman below with sutures on the cheek and right side of her nose had a cleft lip and palate repaired as an infant. Cleft lip and palate are manifestations of Gorlin syndrome.

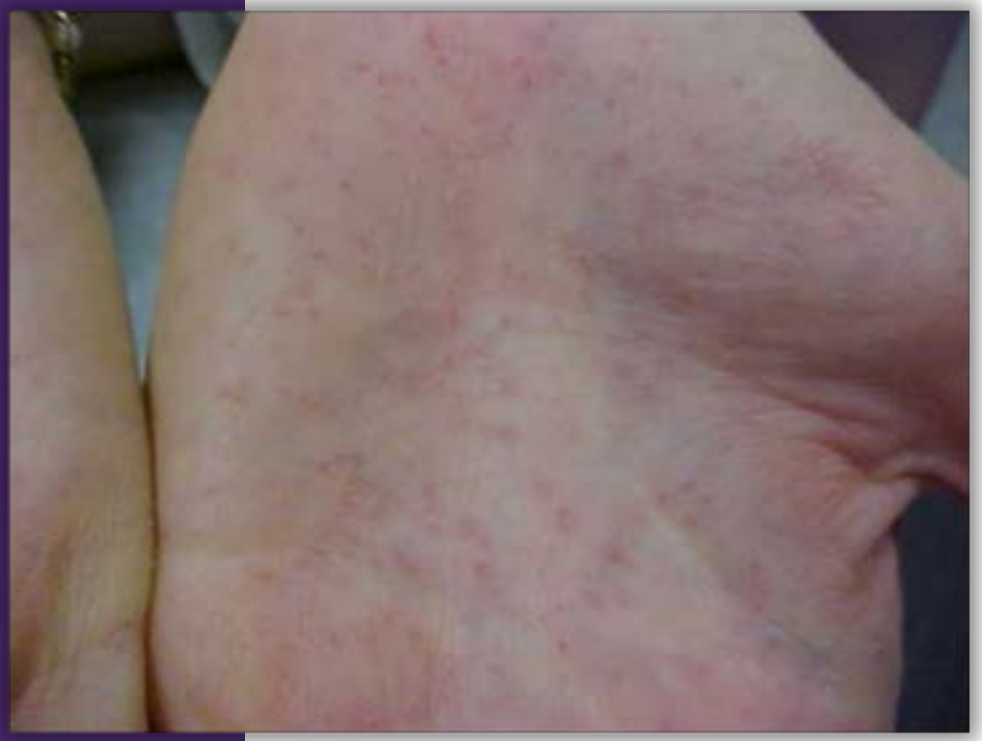




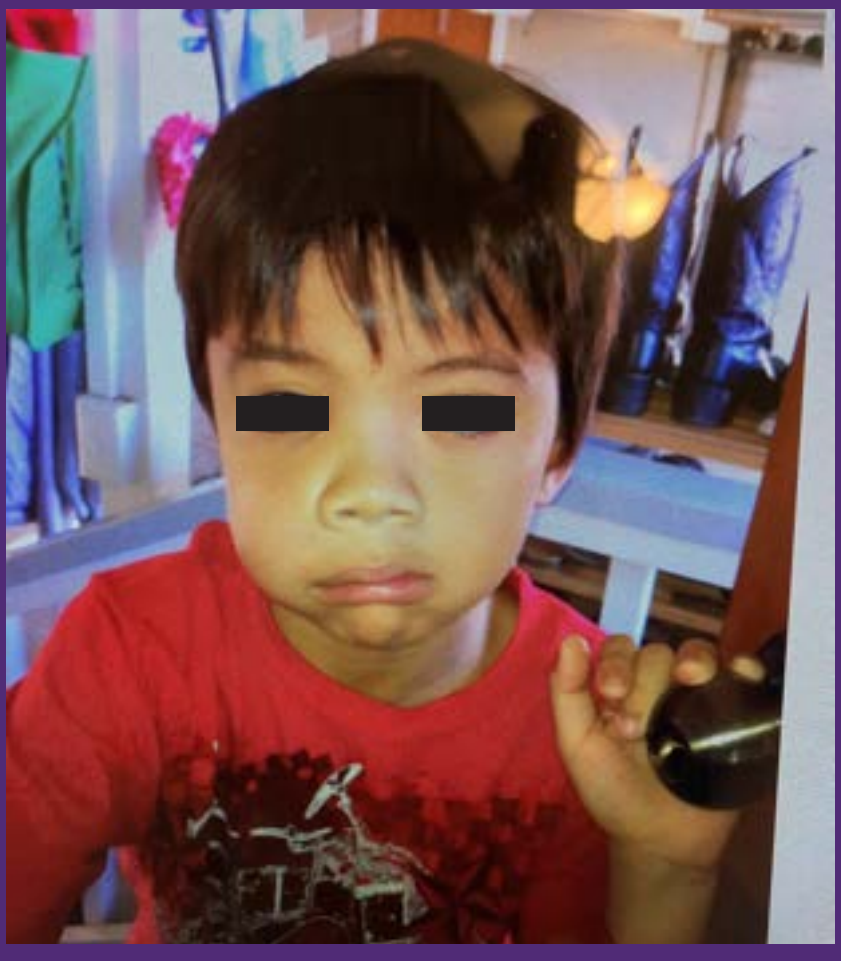
Permanent disfiguration & scarring from years of BCC removal treatments.



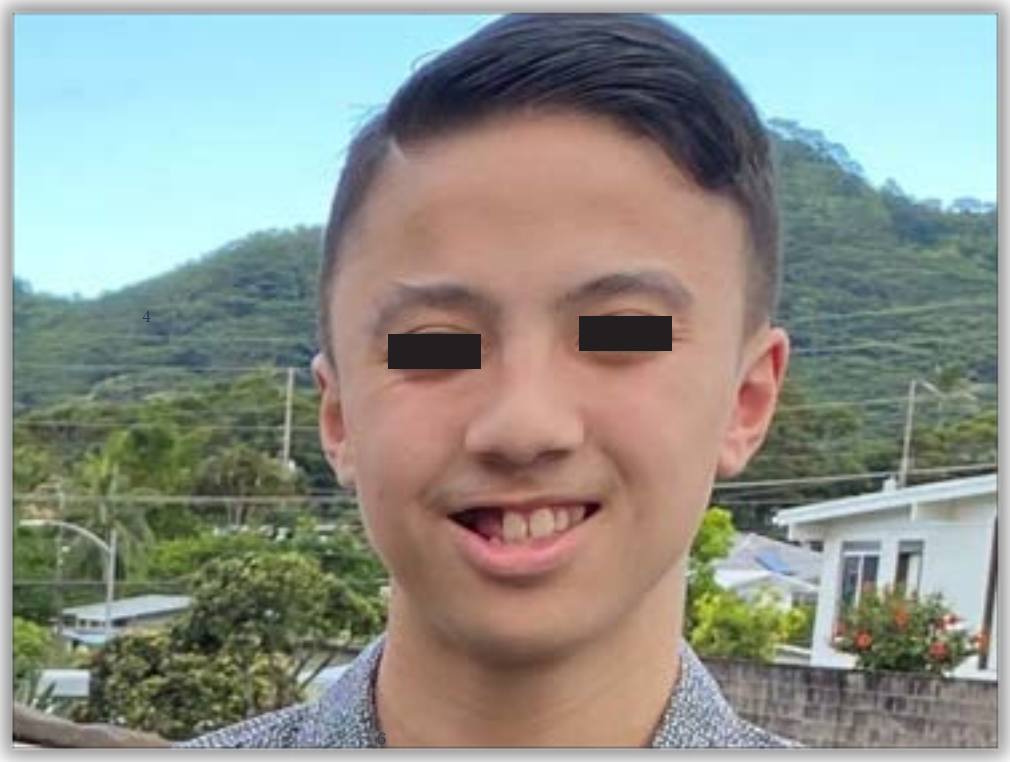




Pits on the palms and soles are unique to Gorlin syndrome.



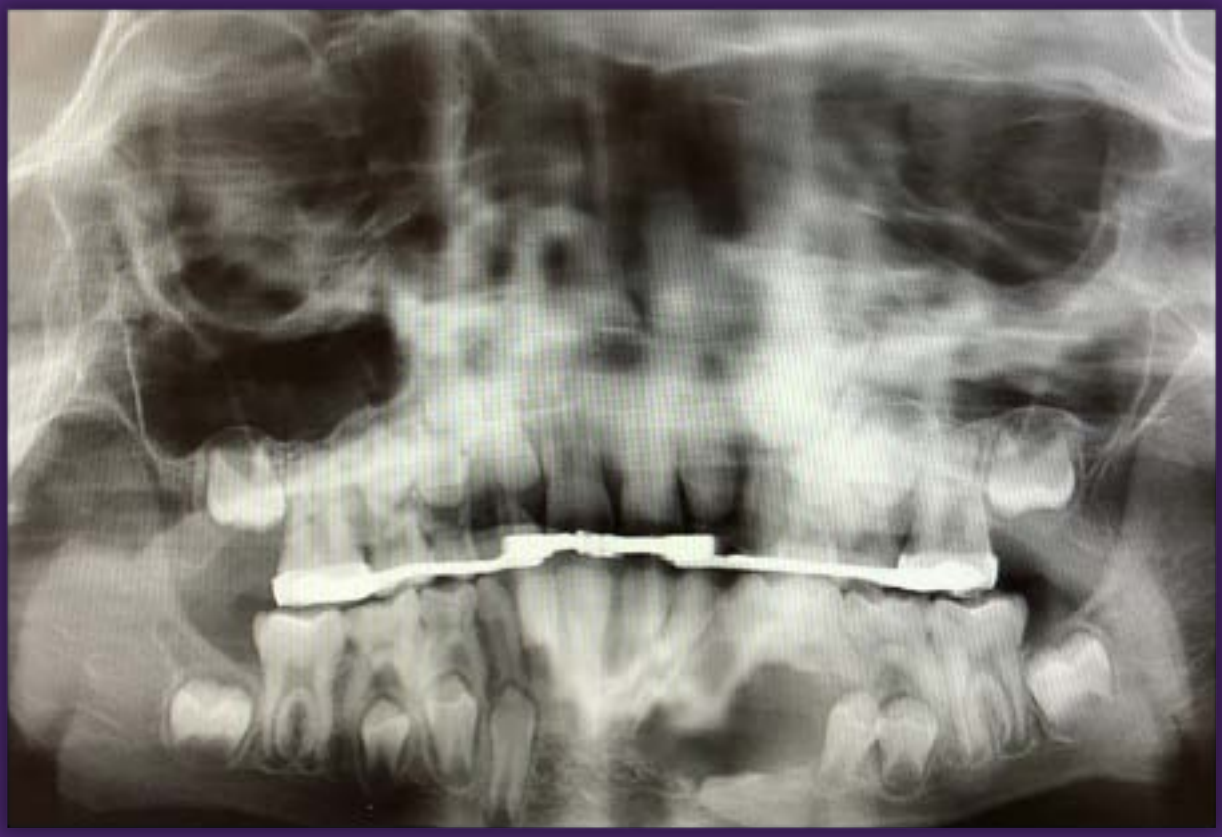
7-year-old one day after removal of right maxillary OKC.



Now 15, the same boy four months after surgical removal of recurrent OKC in right maxilla. Thus far, he has had 9 surgical procedures to remove OKCs and lost 6 permanent teeth.

11-year-old on her way home from having four OKCs surgically excised. Now 14, she has had nine OKCs removed since age 9 and has lost 2 permanent teeth. Since birth, she has had 11 surgical procedures for a variety of Gorlin[6] syndrome manifestations including hydrocephalus, strabismus, and hundreds of BCCs.

Since his first surgical procedure to remove an OKC at the age of 9, he has felt self-conscious about doing an open mouth smile. Other manifestations thus far include macrocephaly (wears his hair down on his forehead to hide this), hydrocephalus requiring VP shunt, scoliosis, and Sprengel deformity of shoulder blades.



Left Mandibular OKC.

One day post-op.

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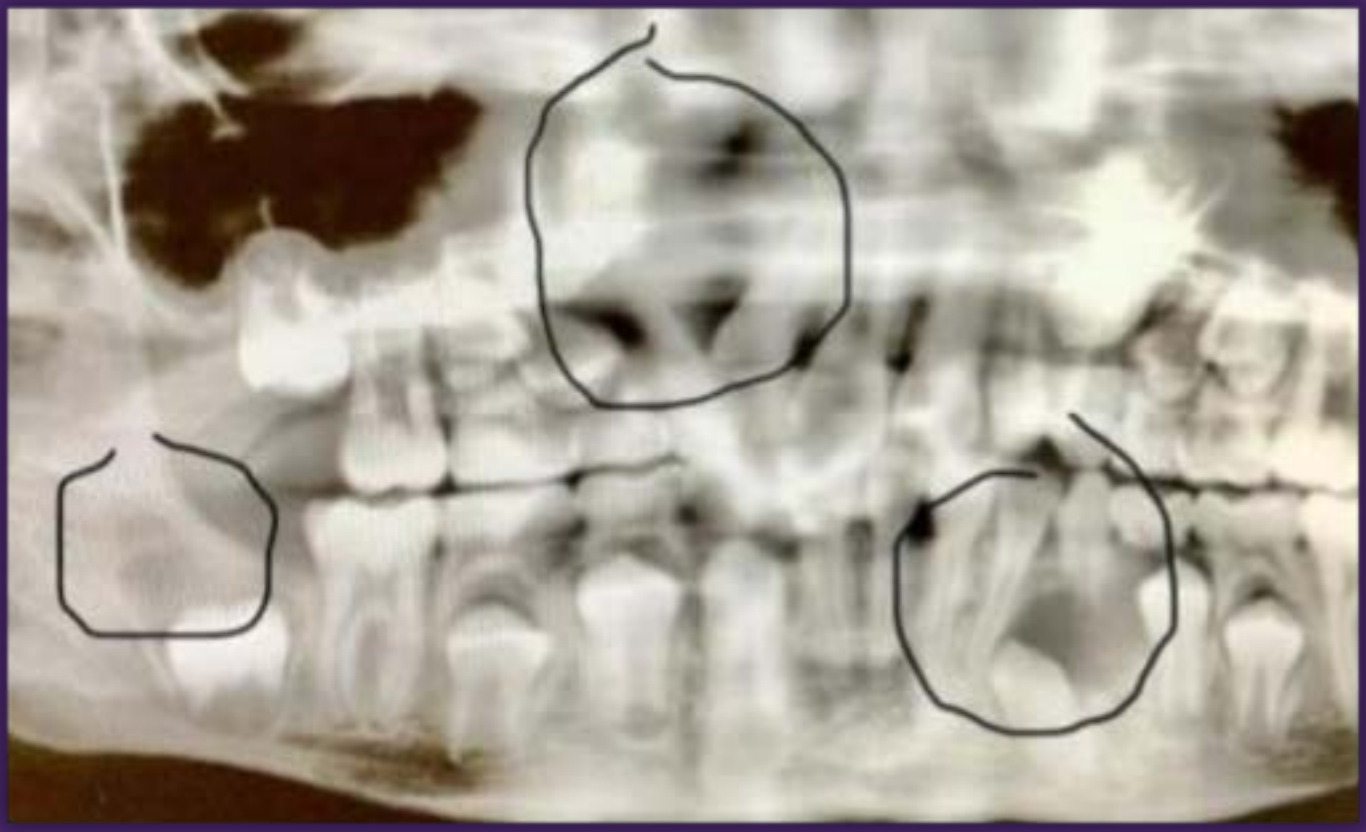
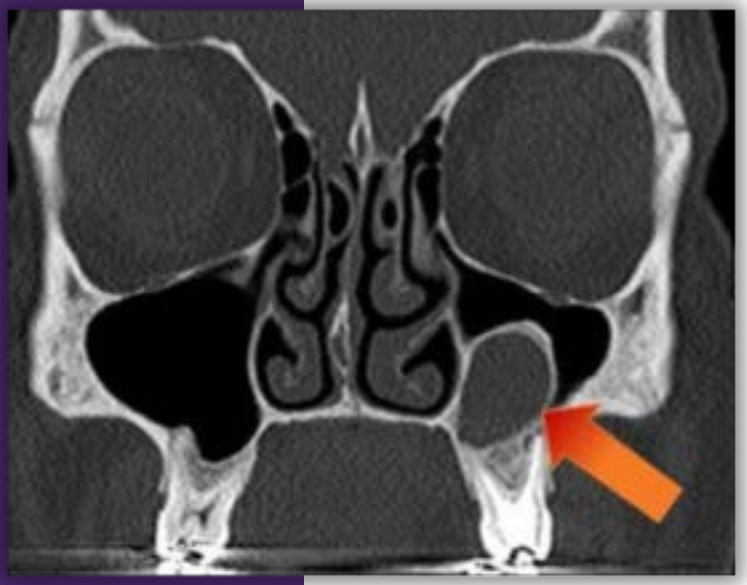


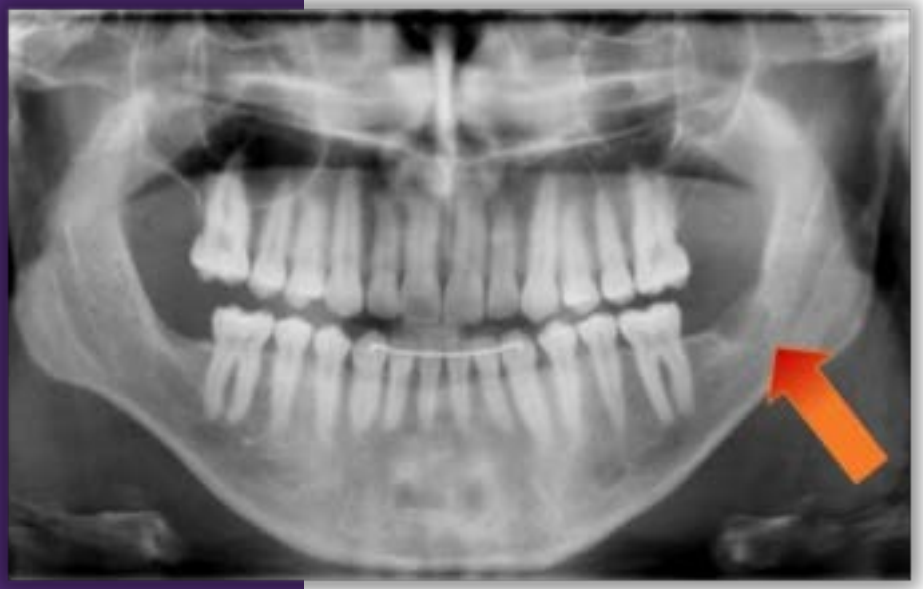
18 months later he had a recurrence of the left mandibular OKC along with two others.

One day post-op.

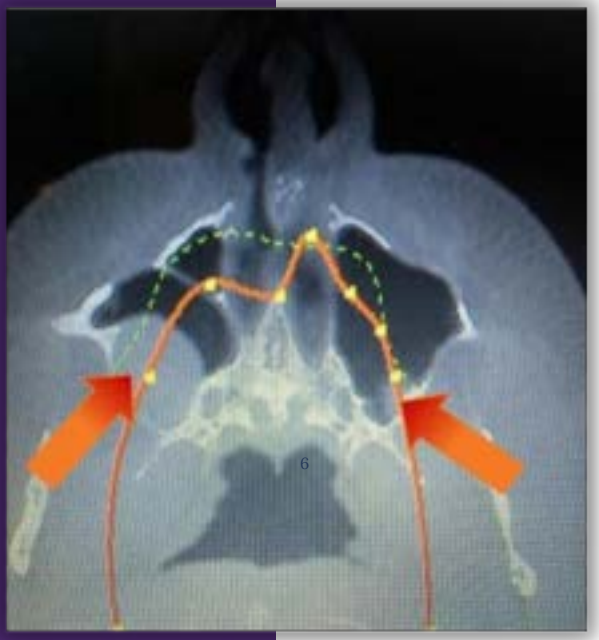
Other manifestations thus far include over 150 BCCs removed, cranial synostosis, cerebral ventriculomegaly, macrocephaly, bilateral hyperopia, hypertelorism, hypotonia, growth anomalies due to low growth hormone levels, strabismus, trichotillomania/ anxiety, ADHD (inattentive).



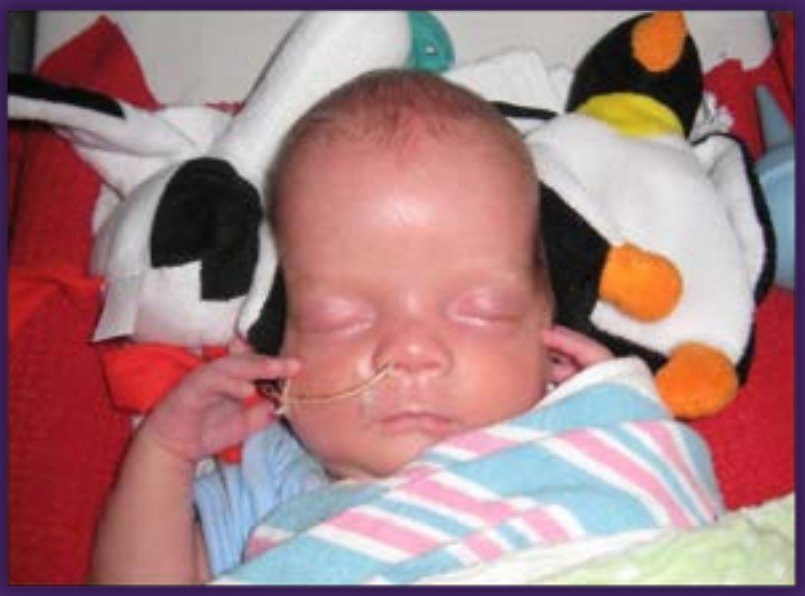
18-year-old with OKC in left maxillary sinus.



21-year-old with recurrent OKC in left mandible. Two sets of braces set the family back financially.



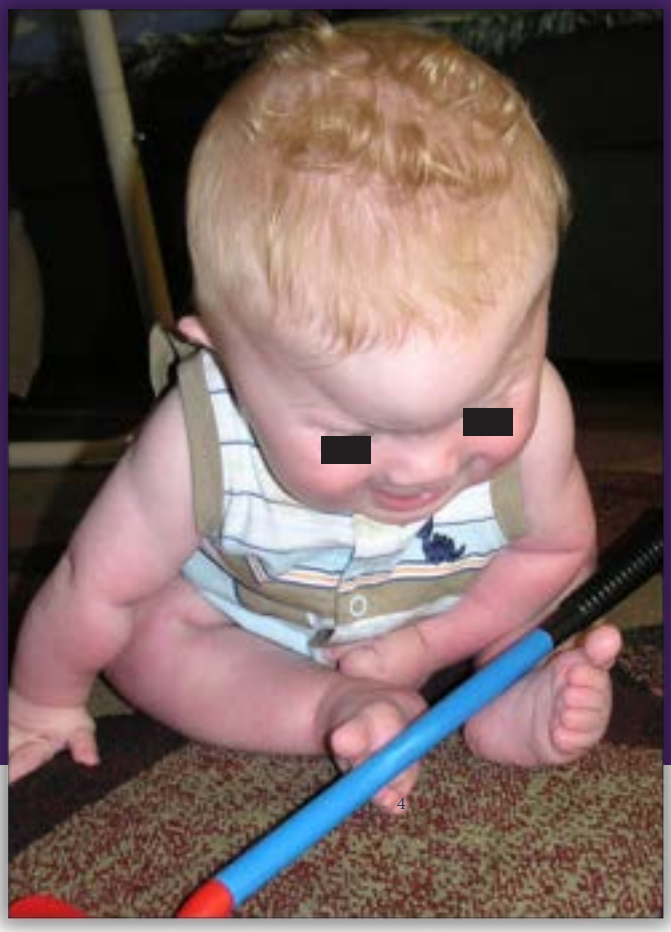
17-year-old with recurrent OKCs in right & left maxillary sinuses.

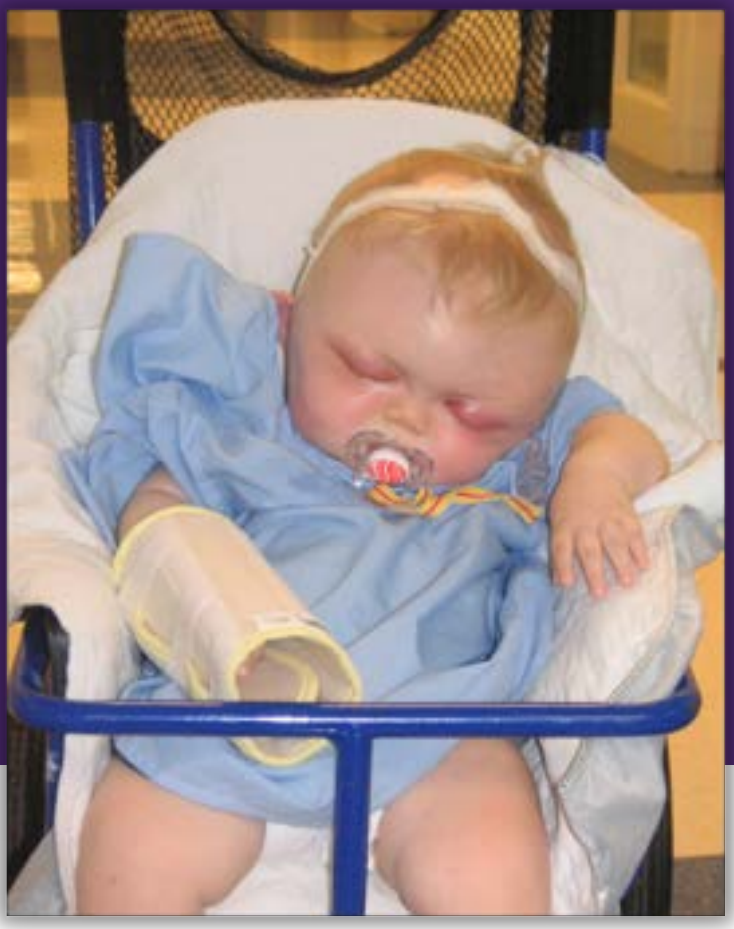


Individuals with hydrocephalus or ventricular asymmetry that required surgical intervention.

Twin boys. Mom, who has Gorlin syndrome, knew immediately that one son did as well based on his head size.

Individuals affected with Gorlin syndrome who have had cleft lip and or palate.





On left, 7-month-old prior to surgery for cranial synostosis. On right, one day after surgery. Post-operative skull infection necessitated a month-long hospital stay and a 2nd cranial surgery. Infection was in the skull and required insertion of a PIC line to administer IV antibiotics for an additional 2 months after hospital discharge.

L to R: Waking up from surgery to remove medulloblastoma, undergoing chemotherapy, requiring oxygen for support during chemotherapy. Now 5 years old, he has had had general anesthesia 20 times for Gorlin syndrome related manifestations including cleft palate and fetal rhabdomyoma on a rib.
Other manifestations have included macrocephaly, enlarged brain ventricles, torticollis, motor and speech delays necessitating regular Physical and Speech Therapy.

Appendix 6: Comments Submitted Online

An online comment submission portal was open for two weeks before and four weeks after the Gorlin syndrome EL-PFDD meeting in order to allow as many voices as possible to respond to the Meeting Discussion Questions presented in **Appendix 3**.

The comments submitted through the online portal are presented below. Respondents are identified by their first name only. Comments are sorted by the respondent and then in the order that they were submitted. The comments were edited slightly for grammar, spelling and punctuation and those that did not address the meeting discussion questions were removed. Selected comments and excerpts were included in the main body of the *Voice of the Patient* report above.

Lornna - four comments submitted

Lornna (Submitted September 25, 2021)

For OKCs, we continue to deal with the significant impact of them recurring. My 15-year-old son has lost four adult teeth (pic. submitted) due to Gorlin syndrome. Because he is still growing and the nature of Gorlin syndrome, it's likely he may never be able to replace those missing teeth. His oral surgeon, orthodontist and prosthodontist have told us that we will need to wait until he is an adult before we can consider reconstructive surgery with the possibility of dental implants. In the meantime, my son has a partial which he never uses because it is very hard to get used to and uncomfortable to wear. The orthodontist has filled the missing teeth in his Invisalign with fake teeth for aesthetics and to prevent his permanent teeth from shifting, which is what he currently wears.

For BCCs, we have tried several topical medications, photodynamic therapy (hives) and invasive procedures. We are not too sure which is the best therapy for him as he has numerous BCCs from head to toe which makes him a very complex case to manage.

For me, as a parent of a teenager who has Gorlin syndrome, I am trying to teach him the importance of med adherence to minimize and keep the BCCs under control. Anyone with a teenager will tell you that is very difficult to do. Reminding him to apply the creams and sunscreens everyday is a huge challenge. We live in Hawaii where the sun almost always shines bright and we are surrounded with beautiful beaches to enjoy. Since being diagnosed with Gorlin syndrome, our family has settled for going to the beach early in the morning and leaving by 10 am to avoid the damaging effects of the sun. Because of Gorlin syndrome, my son is at a higher risk of developing more BCCs throughout his life. Please help us find a cure or better treatments for Gorlin syndrome!!

Lornna (Submitted September 25, 2021)

Because Gorlin syndrome and its manifestations can affect multiple organs in our bodies, managing and staying on track of our health can become a huge burden in our lives. In addition, it can eventually affect one’s mental health.

I remember when my son had his first OKC removed at age 7 and we thought this was just an isolated occurrence. Since then, he has had recurrent OKCs and refuses the anesthesia before a medical procedure as he attributes feeling "weird" upon waking because there were so many people standing around him taking pictures of what was described as a very large tumor for his age. His oral surgeon will prescribe an anti-anxiety, Ativan before his procedures but he is partially awake and aware of what's going on during surgery. Next time, if the OKC recurs, his surgeon said that he will likely need to perform the surgery in the operating room vs in office. As a parent, I will need to figure out a way to make my son feel comfortable and accept the anesthesia for surgical procedures.

Lornna (Submitted October 8, 2021)

Fear of never finding a cure and worrying if my son will ever be able to manage this complex syndrome

Lornna (Submitted October 8, 2021)

Q. What are you currently doing to manage Gorlin syndrome symptoms?

A. For OKC's: My son has had multiple surgeries to remove a recurrent OKC. For the most recent one done in January, his oral surgeon used gauze with 5-FU cream on it to pack the site once the tumor was removed, then stitched it up and had us come back in 24 hrs to remove the gauze. Learning that this is a treatment used for OKC's through Dr. James Swift, I had suggested for our doctor to reach out to Dr. Swift for more guidance on doing the procedure. I will always wonder if this had been done earlier, if it would have saved my 15-year-old son from losing his 4 teeth, which is very significant when he smiles (see photos **in Appendix 5** above) and will now need reconstructive surgery when he is an adult. Until then, he will need to live the rest of his teenage years with a huge gap in his smile. As a parent, it breaks my heart every time I see him as I'm reminded of the scar that Gorlin syndrome has left and that there will potentially be many more to prepare for!

Kelly - one comment submitted

Kelly (Submitted September 27)

1. Preventing sun exposure. This has an enormous impact on a young boy's mind, body and soul.
2. Jaw cyst surgery-once per year he bravely goes under the knife with full anesthesia. Our doctor is spectacular, but it is terrifying and a painful recovery none the less.
3. Sprengel's shoulder reparation surgery. Five hours in surgery at Hopkins at age seven. Spent Thanksgiving and three more weeks in the hospital, trying to sit up and feel a little better.

John J. - one comment submitted

John J. (Submitted September 27, 2021)

The worst part of Gorlin syndrome is that it never goes away. Regardless of the number, length and extent of the diverse types of procedures and treatments one undergoes, it always returns. Cancers and tumors recur. The syndrome comes back, attacks and forces one to surrender

more tissue, teeth, bone or hair. There is no détente, no victory, no final resolution, just a continuing battle to minimize the losses. But the losses keep accumulating.

My first keratocystic odontogenic tumor was removed in 1962 when I was four years old. Yet, the syndrome was not identified as my problem until two decades later when I was 24.

Since I am a mutation, my family had no experience with the syndrome. The oral surgeon who treated my tumors (removing several from 1962 to 1975) in Portland, Oregon did not see a connection to a bigger issue.

It was a middle-aged barber who first noticed what he thought could be a skin cancer on my neck in 1982. He told me to see "Student Health" since I was a student at the University of Virginia. A dermatologist at the University Medical Center removed the lesion. The pathology lab identified it as a basal cell carcinoma. My dermatologist reviewed my case with another dermatologist, but they did not ask me any questions about syndrome-related issues. Just a few weeks after the dermatology treatment, I was seen by the Otolaryngology Department (ENT) for a pain in my upper right jaw. An x-ray revealed a shadow. They asked me about any history of cancer or infection in my jaw. Even though it had been at least seven years since the last tumor removal, I told them about my history. At that time, I called them cysts.

An ENT resident noticed the fresh scar on my neck and asked what happened. I told him about the basal cell cancer. He suggested the connection between it and my tumors, and the ENT doctors referred me back to dermatology. They found more cancers and ordered x-rays which identified other symptoms of the syndrome.

Since 1982, my body has been burned, cut, scraped, frozen, x-rayed, lasered, and electrodesiccated. There are scores of scars from my shins to my scalp. The normal adult mouth has 32 teeth. After decades of ENT and oral surgery, I have 18 teeth remaining.

Beyond the scars, I have lost hair from various treatments, including Mohs. Most recently the cancer was biopsied and confirmed to be in my ears. To avoid having pieces of my ear cartilage removed permanently, I went on Erivedge (vismodegib). I took it for over 12 months, lost all my hair, and the lesions on my ears went away.

I experienced side effects from Erivedge which were painful and exhausting. After I stopped taking the capsules, some of my hair came back but it is very thin and sparse and I can no longer grow a beard. The most disappointing thing is that the lesions on my ears came back and my cartilage is again vulnerable to permanent removal. There is no end to this battle.

The decades of wounds, scars, lost teeth, pain of Erivedge and other treatments, lost hair, lost beard, have all created an overall fatigue within me. I miss my hair, eyebrows and beard which helped to cover many scars. My son now has the syndrome and faces the same pain, loss and never-ending battle.

Please help. In its random, relentless, sometimes slow but never-ending way, the syndrome slowly disfigures and wears us down over time. Any treatments or medications that could reduce or prevent the lesions and/or tumors with fewer side effects would be helpful. Targeted topical treatments could be a major improvement. Any medications with fewer side effects would be beneficial since it would relieve one from the stress of using them repeatedly. It is extremely hard to undergo the prolonged pain and difficulty of current treatments while knowing the benefits are only temporary and the symptoms of the syndrome will come back again, and again, and again.

Nancy - one comment submitted

Nancy (Submitted September 27, 2021)

Diagnosed in 1964 with BCCNS, I had 100s of BCCs, several cysts, 2 bifid ribs, scoliosis, four wisdom teeth that turned out to be cysts growing. The only way to stop BCCs and cysts at that time was surgery and grafts. In 2011, I participated in Genentech's Erivedge research program. Within 3 months of taking that pill, the cancer in my left eye was completely gone and then for 4 years = no bccs, cysts or surgery until that pill stopped working. Creams did not work on me. Novartis came out with Odomzo, and that too worked on me for 4 years and stopped. I am now 79 years old and back to surgery. Please understand the importance of continued research for this lifetime disease.

Joan - one comment submitted

Joan (Submitted September 30, 2021)

I am thankful for the drug Erivedge, no doubt. But I am still plagued with recurring basal cell carcinomas that the drug doesn't treat. I must still seek surgical means to eliminate these lesions. In fact, I am scheduled in a few weeks to have Mohs surgery on my cheek, where I have a biopsy proven Basal Cell Carcinoma which developed so unlike my other ones, that I didn't recognize that it was a skin tumor. This disease, Gorlin syndrome, is devastating to the people it affects. I have undergone over 117 surgeries that took me into the operating room in an outpatient facility as a result of this disease. My face and scalp reflect those surgeries- I have virtually no hair on my scalp due to many skin grafts and my face- well, my one eyelid that has suffered the worst of the surgeries -despite the best efforts of a plastic surgeon- doesn't close all the way so I must treat for dry eye issues. My tear duct was sacrificed as a result of extensive basal cell carcinoma involvement, so tears are continually running down my cheek. I have no control over that. My nose is an asymmetric mess due to multiple surgeries on the skin and cartilage. There's no tissue near by to rebuild it because all the skin tissue has the potential to develop basal cell carcinomas. Recurrence of the skin tumors is a constant worry for me.

Sherry - one comment submitted

Sherry (Submitted September 30, 2021)

My son has Gorlin Syndrome. He is 25 years old and has had for years and will into the future have many doctor's appointments and surgeries. It takes so much time out of his life to just keep up with doctor's appointments (oral surgeon, dermatologist, ophthalmologist, urologist,

etc). We have trouble finding and keeping doctors, especially any doctors that know or understand Gorlin syndrome.

He lost his first out-of-college job because of Covid and is struggling to get a job that pays better than minimum wage. He will no longer be on his parent's insurance within the next year! He is a college graduate and a capable and loving man. I fear, but try not to believe, that he has trouble landing a job because he has a different appearance. I lose sleep nearly every night worrying about him and his future. How can he live, go to the doctor, have surgeries, recover, pay his medical bills, and keep a job?

His main issues are chest wall deformity, severe scoliosis, and OKCs in his jaw. In the last year his surgeon thinks he saw something in his nasal passage so had scans done. And another doctor who was seeing him about pain in his neck due to scoliosis saw nodules on his lung. They insisted on another CAT scan (he should be getting less radiation, not more). Then we got a message via MyChart saying "good news, don't worry because we don't know what we see but the odds of a person in his age group having a malignant tumor is low". I could have told you that without a CAT scan. Please help us! I try to shield him by paying his bills for him. I wake up every night thinking about my worries for him.

I worry of course about the jaw cysts. He's had four surgeries, lost teeth, and has a titanium plate in his face. The surgery and recovery take time. All his life, summer vacations have been a good time to have surgery but I worry what he will do in the future.

I am so hopeful that there will be something that can safely and reliably stop the jaw cysts/tumors from recurring.

Kathy - one comment submitted

Kathy (Submitted October 1, 2021)

I would like to see little or no side effects of Erivedge as my most severe side effect for me are leg cramps. Regardless of the time of day or evening I take Erivedge I get really, really bad leg cramps at 3am. It keeps me awake for at least an hour. Could there possibly be another drug that would still work as a hedgehog [inhibitor] to rid my body of BCCs? I can deal with the hair loss but my anxiety level goes up when I take Erivedge and lingers with me for the 2 or 3 months I’m on it.

Brian

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I guess my biggest complaint is the bleeding. I have at least 40 BCCs on my face with about 100 on my shoulders and back. They bleed a lot! If I rub my nose a few will start bleeding, or if someone rubs or grabs my back I start bleeding. I wear black shirts so people don’t see my blood stained shirt. My bed sheets and bed are always bloody from me rolling in my sleep. It is also very hard to get a job or to meet new people with all the BCCs.

My second complaint is that I grew up with no enamel on my teeth, so I started losing teeth at a young age. They just started breaking. I looked like a crackhead in my teens. Couldn't eat very well.

Kyle - one comment submitted

Kyle (Submitted October 3, 2021)

I am 31 years old and inherited the syndrome from my dad. I was about eight years old when my first jaw tumor was removed. Later, in high school, I was in the ICU overnight in recovery after four tumors were removed from my upper jaw. They were very painful. I have also had multiple basal cell cancers removed. Each procedure is painful and makes me nervous. Yet, the symptoms keep coming back and I have to go through it all over again. Each time there is a surgery there is also swelling and pain, and the risk of infection or other complications. My dad recently had an internal blood infection after a basal cell cancer surgery on his right forearm. He had to spend a night in the hospital on IV antibiotics. There has to be better alternatives for treatment.

Michael - one comment submitted

Michael (Submitted October 3, 2021)

When my beautiful bride had her first Mohs surgery to remove a BCC, I was completely caught off guard and horrified at the result. A small spot, that looked like a bug bite, ended up with a four-inch suture line snaking across her face. Despite trying to keep her head raised at night and apply ice packs, the swelling grew large and painful. I tried to stay positive for her, but it is heartbreaking to watch and I felt so angry and helpless. She tried to explain that small spots are often larger than they look with "roots" beneath the skin. That the surgeon had to do this in order to make the result look better, but that made no sense to me. After seeing the results of countless surgeries, I do understand now. Some results are better than others. There has to be another way...

Maria - three comments submitted

Maria (Submitted October 3, 2021)

When my son was 12 years old, he had already had several OKC surgeries. At a check-up, multiple cysts were discovered in his upper jaw and sinus. The doctor explained the LeFort procedure that he wanted to do - breaking my son's jaw beneath his nose and basically cracking his head open like an egg in order to get the best access to clear the cysts. I was horrified and begged for another option. The surgeon was gently stern with me saying that if it was his son, this is the way he would want it done.

The surgery went very well according to the surgeon, but the recovery was incredibly difficult. Lots of pain medication, and my son's face and mouth were horribly misshapen by swelling. He could only have liquified food. It took 8 weeks for life to resemble normal.

Maria (Submitted October 8, 2021)

Affected son is 30 years old. He does not practice sun protection. Loves to be outdoors. He has not had any BCC diagnosed yet, which is unusual, but it is a helpless feeling to be unable to "protect" him.

Maria (Submitted October 29, 2021)

Obviously the focus of the PFDD is drug-related treatments, but I wanted to share an additional impact of why a variety of options are so very important.

I see a Mohs surgeon who is also trained in plastic surgery. One of my first rude awakenings was that "plastic surgery" is not what it looks like on TV. Surgeons do their best to pull, stretch, and patch skin into the holes that remain, often cutting out healthy skin to make the repair better cosmetically, so a small spot of cancer results in a huge defect. During a Mohs surgery on my face when I was in my late twenties, my surgeon informed me that the best skin to graft onto the face is located behind the ear....

"BUT I'm not going to use that today because you have a long road of surgery and repairs ahead of you."

This reality hit me hard.

Surgical repairs can stretch and pull skin which affect facial/body structures. You can end up with hair growing somewhere it shouldn't be, or no hair where you need some. Ears are at high risk. The nose and lips are usually the center focus of a person's face, unless surgery has moved or disrupted them, making them an eye sore (pun intended). Eyelids are high value real estate. That's correct -- we have to evaluate our skin like property when determining how to use or repair it.

Miriam - three comments submitted

Miriam R. (Submitted October 4, 2021)

I have Gorlin syndrome, my dad has it, and so does my older brother. I see all the scar, scabs, pain, and time my dad has dealt with because of Gorlin syndrome. He gets choked up, and feels guilty, every time I mention a new biopsy I had. His has gotten worse with age, and so has mine. This affects me emotionally, physically, financially and professionally. I worry, is how I look now as a woman in her mid-20s going to be the best I ever look, with the clearest, kinda scarred body? My dad and brother are on Erivedge. They've lost hair and sense of taste, but it seems to work for them. My dermatologist recently asked if I've thought about freezing my eggs so I can go on it, or participate in another trial. Do you know what it's like to have to think about going through an egg freezing process as a single, 3 job-holding, 20 something year old with hopes of traveling, getting a Masters, and more? I don't want to have to go through egg freezing alone (emotionally, physically and financially), but if I don't, I risk the potential of not being able to have kids in the future. Most people also don't take Erivedge for decades. If I start now, am I stuck with symptoms or running out of options down the road? What will happen after that then? It occurred to me, well if whatever I take works, maybe I won't grow up with more and more scars all over my body, but will I have hair? Will I be able to find a spouse and not be as worried they will stop loving me due to all the scars, or lack of hair? If what I take doesn't work,

will that exclude me from other trials or being able to switch to other medicines? Dealing with this condition is extremely expensive, even with insurance. Insurance companies rarely budge when it comes to covering costs for procedures/surgeries, especially when it doesn't have a usual protocol. This condition isn't usual, and there isn't a protocol for younger people with it, so what? I have to wait until I get older to be able to be more proactive about things, because I can't afford to do things now, but at the expense of the condition potentially harming me all those years I couldn't do anything? Additionally, how am I supposed to be proactive in monitoring my condition, and taking care of it, when the only plans available to me are high deductible, with bad co-insurance. I work multiple jobs, so no time off or overtime, etc.? Why does getting stitched up after surgery have to cost an additional several hundred dollars? I've been told it's because insurance thinks it's not part of the main procedure. But, for many of these surgeries, if the person asks to forgo stitches because they can't afford it, medically, wouldn't it be frowned upon due to the increased chance of infection from exposed skin? Insurance thinks stitches are optional, so we pay the price. That's not right. I've usually tried staying away from participating in these kinds of things because this condition already steals enough of my time, energy, etc, but I need hope, backed up by science, that I won't become a seriously scarred, deformed, child-less, broke woman because something out there didn't change about how we treat and overcome this condition.

Clara - one comment submitted

Clara (Submitted October 4, 2021)

My Gorlin syndrome test came back many years ago that mine was created in utero and they named it a mosaic gene! There is no family history of it. Also, my children and grandchildren do not have it! Unfortunately for me I have suffered with many of the symptoms many of you describe too!

The most painful one for me was ongoing nerve damage done via OKC in my whole mouth. Pain and burning all the time! And many leg cramps that caused terrible falls and injuries throughout my body! I am living in fear and continue to worry about not being able to take care of my body's daily needs. Hope that is helpful!

Sarah - one comment submitted

Sarah (Submitted October 4, 2021)

I am my daughter's caregiver. So far, she has not had a BCC, she has had jaw cysts. What I want to impress upon the FDA members is that even though my daughter has not had a BCC (yet) - We live with an underlying fear of what is to come. I have read about how much others have suffered taking the medicines that are currently available. They have written about the excruciating muscle cramps, the difficulty dealing with side effects. I don't want anyone, let alone my daughter, to suffer. I'm dreading what may/will come from dealing with BCCs - pain, scarring, fear, disfigurement, time off work (job loss), time where she may not want to leave the house, and worries about health insurance.

Meanwhile, she diligently protects her skin from the sun - hope against hope that will help. She has to limit some activities to minimize sun exposure, select jobs that don't require being outside, has to fight feeling depressed and at times she feels isolated.

My hope is future prophylactic medicines will be 100% effective without debilitating side-effects.

Sasha - one comment submitted

Sasha (Submitted October 4, 2021)

I feel at war with my own body.
I was diagnosed with Gorlin syndrome at the age of 12, having had six jaw cysts and a cataract all related back to this syndrome. Annually having to go to at least four doctors wondering if they will find something and having to debate with them over whether the radiation from an x-ray is necessary. Questioning if that is just a pimple or is that something I should be worried about. Hoping that the sunscreen and sun protective clothing I have had to invest in actually does what it advertises. Ensuring and limiting the outdoor errands and activities I do per week are necessary because of the risks of this syndrome even at the cost of seeing friends and family.

There is a constant fear in the back of my mind of what the future will hold with this syndrome and how much money I have in my bank account for possible medical expenses. Choosing to not have kids for fear that I will pass this on. The medications available for this syndrome right now, from what I've seen, are intense and makes me fear what else I will lose if and when I take them. I have already lost out on being able to live my life without constant fear. What can the medical community do for us?

Toby - one comment submitted

Toby (Submitted October 4, 2021)

I'm the 5th person in my family with Gorlin syndrome/BCCNS. Although treatments and procedures are less arduous than what my grandfather, mother and uncle endured, this disorder still results in severe disfigurement, especially to one's face, causes a lot of "down time", as one recovers from these various surgeries and blistering, scabbing, bleeding, erosion from various creams such as Aldara [Imiquimod]and 5-FU. The jaw cysts are a random occurrence for me, but I had a huge jaw cyst that developed in late February 2020, as soon as the Covid-19 lockdowns started, my 2nd cyst in 69 years, necessitating numerous visits to oral surgeons, endodontists and the regular dentist under extreme conditions. I had to pay for the expensive x-rays, because the oral surgeon wasn't aware that Gorlin related jaw cysts are covered under Major Medical-not regular dental insurance coverage. (I wasn't aware until I attended the Gorlin webinar this summer.) Nobody dwells on life altering events that one cannot control, but I was a flight attendant for 26 years with a major airline, and I have spent much time and money paying for plastic surgery when I thought I would have a better cosmetic outcome removing facial basal cells. Most dermatologists don't operate with a light touch. Getting the cancer out is their main goal-not sparing one's appearance. Mohs surgeons take

extra skin I cannot afford to give up. All those small holes, stitches, white scars from liquid nitrogen, skin grafts and electric needle sites, add up. Theatrical makeup can cover some scars-but skin grafts are usually pretty visible. My uncle and mother had so many surgeries, grafts, radiation burns, etc, that they seldom went out in their later years. People stare at oddities.

I would like to see laser treatments, which have proven to be less disfiguring, be made available to those with multiple basal cells. I approached a laser specialist in our area, 10 years ago, and he turned me down. Actually - he laughed. More money to be made from beauty procedures than in the treatment of facial basal cells. Dr. Orit Markowitz, a dermatologist at Optiskin Medical and assistant professor of dermatology at Mt Sinai Hospital, in NYC, has established a method for diagnosing, measuring and clearing many skin cancers in just one appointment. She uses a virtual biopsy via Reflectance Confocal Microscopy. It takes snapshots of skin at 30-fold. Immediate diagnosis. To circumvent surgery, she uses Optical Coherence Tomography, which measures a tumor's depth, giving her a blueprint of what and how much to remove. This all accurately measures a tumor's margins, which reduces unnecessary cutting. Depending on the case, Dr. Markowitz often completes her non-invasive protocol with laser therapy to remove the cancer, using non-ablative devices like pulsed dye or thermal resurfacing lasers. Studies published in CUTIS found that when compared to surgery, non-ablative treatment for BCCs had an improved cosmetic outcome. This treatment is at university medical centers-not your dermatologist's office. So far, it isn't covered by insurance, as it's considered to be in an investigational phase. Doctors need to be trained how to use this. She has been doing this protocol since 2008. Isn't it time to fast track this treatment, which is better than anything I have seen or heard about in years? This is quick-not weeks and months of downtime. It works and it's less scarring. Forget messy creams/gels, that eat away the skin cancer, horrible drugs that make one sick and their hair to fall out, or skin grafts and reconstruction surgeries and nasty adhesions around one's eyes! More people have this most common form of skin cancer than any other, so there are patients galore who would come for treatment, not just BCCNS/Gorlin syndrome folks. You need to think big and bring BCC treatment into the 21st century, on par with proton beam therapy and such.

Paul - three comments submitted

Paul (Submitted October 5, 2021)

I am aware that the FDA does not set pricing on medication or the cost of insurance, but they need to be made aware of the stress that is created when trying to figure out how folks can afford the cost for the few medications out there or the price tag to have BCCs removed every three months. This needs to be addressed!

Paul (Submitted October 5, 2021)

What role if any does the FDA have in developing how clinical trials are performed, and when developing protocols? Do they utilize possible participants to review or provide input? I have participated in clinical trials where even after the trial I was never told if I was on the medication or the placebo.

Paul (Submitted October 8, 2021)

The way and intensity in which Gorlin's manifests itself has a direct effect on how we choose to live our lives. The impact we have on others who have the condition is so important, we want to protect but at the same time encourage them to live their lives to the fullest.

Dan - three comments submitted

Dan (Submitted October 5, 2021)

I wanted to shed light on experiences more than specific symptoms, to put you in the mind of a typical BCNS patient.

I am not a cancer survivor. That is what I told my friend who worked for the American Cancer Assoc. and wanted to have me walk with other cancer survivors in a parade. I am not a survivor. How can I be a survivor when I know every six to eight months I have to endure having five more skin cancers removed that were not there six months ago. I have done that for 40 years and until there is a cure will continue to every year I am still alive. I am not sure many people understand the psychological pain to a disease like BCNS. You are having surgeries pretty much every year from the time you are like 10 years old. So many facets of this syndrome are brutal. Too many to go into here but for starters, as a kid (and adult) you have jaw cysts which if they don't know you have BCNS they are constantly taking pano's of your face which is the worst thing you can do to someone with BCNS. Then you get the basal cells and you are constantly getting "numbing" shots when getting them removed. Ever have a shot on the tip of the nose, the lip, near the eye? It is not fun, especially when you have a doctor that doesn't go out of their way to reduce the pain of that shot. That alone has me driving three hours to Houston vs having the doctors I had who said your body will start to convulse to get rid of the pain. So I trek three hours to Houston every six months and need my wife with me as I can't drive back after surgery. She gets to see a doctor rip flesh from my face over and over again. I sit there on the table praying they say they got it all. Instead, I have the back of my ear now the top of my ear. I have had more than 1000 stitches on my face alone. Luckily, I have a great Mohs surgeon so people can only see maybe 1/3 of the scars. Sadly, I see them all. It is a toll. A 50-year-old man, lying on a table, tearing not from the pain but just knowing I am in a fight I can never win.

Dan (Submitted October 5, 2021)

What advances are being made with CRISPR, gene modification, or new drugs that would have minimal side effects with great results?

Dan (Submitted October 8, 2021)

Pain from needles is not a needle or nerve problem. It is a doctor problem. I drive 3 hours to my Mohs surgeon in Houston because he can give me shots in the nose or lip without pain. I had top dermatologists in California tell me the pain will be severe and your body will convulse from pain. It is almost malpractice what these doctors will continue to do when there is a way not to have this pain.

Mimma - two comments submitted

Mimma (Submitted October 5, 2021)

The symptom that impacts me the most is the profusion of basal cells throughout my body. The various modes of extraction impact my movements shortly after they have been removed (ex. Can't bend down or go out for a few days when scalp and head are impacted). I have so many that I get them removed every 2-3 months. I'm taking 20 mg of Accutane and 1000 IU of Niacinamide daily. I've been told that this helps suppress some of the basal cells but I'm not sure it's helping since they're still coming out. Dry skin is the biggest negative side effect, but can be tolerated.

Mimma (Submitted October 8, 2021)

I was part of the last PellePharm study and we counted 30+ BCCs on my face. PDT, topical creams, etc. have not worked and anything other than Mohs, will cause them to reoccur. Need to find something that is less invasive and painful to help decrease the BCCs.

Connie - one comment submitted

Connie (Submitted October 6, 2021)

My 32-year-old daughter was diagnosed with a medulloblastoma when she was 15 months old. She had two years of chemo followed by radiation to the whole brain and spine at the age of three. She has multiple meningiomas, ovarian fibromas, and multiple basal cell carcinomas. Just last week we had a very astute Physician's Assistant suggest that she may have Gorlin syndrome. We are amazed that despite all the excellent medical care that we have received at Children's Healthcare of Atlanta, Emory University, Mass General and Johns Hopkins, no one has put the pieces of the puzzle together until last week. Just relieved that we now have a diagnosis and can move forward.

Ronnie - one comment submitted

Ronnie (Submitted October 6, 2021)

Gorlin's syndrome impacts my life and the life of my family every day all day. Scheduling surgeries, recovering from surgeries, the anxiety of more surgeries, time off from work, deformities, pain and the pain of our loved ones who suffer, as well. Staying out of the sun...without suffering and losing life's precious gifts. The out-of-pocket costs i.e. (if one is lucky to have the funds) for car window UVA/UVB tinting. Keeping up with all of the appointments and tests.

It would be beneficial to have a drug or a cream/gel to use that didn't have severe side effects. To have treatments that would enable all of us to live a life with less anxiety and to present our better selves to the world around us.

Erika – one comment submitted

Erika (Submitted October 7, 2021)

There seems to be always something growing on a Gorlin syndrome patient. The weeks or months between symptoms being diagnosed should be a relief. Instead that reprise is just the

waiting room for more cutting, draining or burning. It's a constant cycle, a riptide of anxiety, fear and resentment.

You no longer fall on the floor crying and demanding life to stop when you hear "we found a tumor". Because this is your life. There are always things growing. Our child has had four surgeries over six years on her jaw. She is eleven years old and I am pretty sure as I write this there are two more things growing in her jaw. We see the doctor next month.

She's had a bunch of skin cancers burned, cut and frozen off. She is so used to hospitals she rates them by popsicle and Jell-o selection.

In my mind, there is a huge chasm in having a “viable” treatment option that is used once in a lifetime versus a "viable" treatment option when it's actually repeat maintenance. These "viable" treatments can be brutal, disfiguring and psychologically exhausting.

Manually draining a jaw cyst with a syringe on a daily basis for months is viable, if it is a once in a lifetime thing. Having your jaw rebuilt once in a lifetime may be viable, losing a few adult teeth once in a lifetime may be viable. Having your eyelid rebuilt after skin cancer removed is viable, once in a lifetime. There is only so much skin, so much cutting, draining and burning that is viable. The thing is, it is never a once in a lifetime thing with Gorlin syndrome, it's your lifestyle. Waiting, finding, draining, cutting, repeat. "Viable" treatments for Gorlin syndrome patients need to be on another level and the whole population will benefit.

We have to figure out how to shrink the tumors, cysts and BCCs and stop them from coming back. “Viable" treatments are needed, more humane treatments are needed. My hope is that with your help we can break the cycle of “viable” but oftentimes brutal and disfiguring treatments. Thank you for your time.

Barbara J. - one comment submitted

Barbara J. (Submitted October 7, 2021)

Family members:

1. Basal cell cancers and other skin abnormalities that require monitoring, topical treatments and surgery, jaw cysts that require surgery, scoliosis.

2. Loss of teeth, scarring, bleeding and deterioration of skin tissue, general movement, going out in public.

3. Observation, topical treatments, surgeries; went through an experimental round of anti-cancer treatment that led to permanent hair loss but skin lesions appeared following end of the treatment; lesions continue to appear, often multiple; skin degrading in many areas.

4. Surgery is invasive, topical ointments have low to moderate success.

AB - one comment submitted

AB (Submitted October 7, 2021)

My name is AB and I am in my 20's. Over the next four weeks I will have Mohs three times on at least 11 BCC's. When I was 11, I had what we called a "surgical summer" with an operation to remove a calcified ovarian fibroma that was the size of a grapefruit, a month later, two jaw cysts had to be removed, followed by a surgery to remove multiple BCC's. Until there is a cure, I wish there were topical treatments that would shrink and prevent my skin cancers without an ugly irritated reaction.

Narcisa - one comment submitted

Narcisa (Submitted October 7, 2021)

I'm a mother of a 3-year-old girl who was diagnosed with Gorlin syndrome when she was two.

I'm begging you to please find a treatment, medicine or cure for her and those who have this condition as well. It hurts to see how my daughter, since a young age, has to go through different surgical procedures in which she suffers.

The whole family suffers from seeing her in these conditions. Patients with Gorlin syndrome should be a priority right now, I'm begging you to please understand them.

Barbara O. - two comments submitted

Barbara O. (Submitted October 8, 2021)

My daughter has been living with Gorlin Syndrome since 1989. The doctors that did the OKC told me they had gotten it all and that it would never come back. It has come back in spades. She has had hundreds of surgeries, including brain surgery. So any treatment that can and will help anyone with Gorlin syndrome should be tested and approved.

Barbara O. (Submitted October 8, 2021)

My daughter has had Gorlin since she was small. A lot of people don't understand what it is like to be afraid to go in and wake your child up for school, afraid she might be dead due to another colloid cyst in her brain. The doctors at Mayo Clinic told me that we were lucky to find it when we did or she could have died in her sleep. Or to hold your child when they are taking packing out of their sinus cavity. This syndrome is not something you can just put a bandage on. She had 9.5 hours in a Mohs surgical chair yesterday only to be told she could not get clean margins. Let the Doctors work on finding a new way OR an old way to work with this syndrome.

Jenni - one comment submitted

Jenni (Submitted October 8, 2021)

1.) Of all the symptoms that you experience (or your loved one experiences) because of Gorlin syndrome, what are the 1-3 symptoms that have the most significant impact on quality of life?
1.) Bcc's treatments and prevention technique's
2.) Mental health
Psychosocial effect on individual affected and loved ones.

Mental health of affected

3.) Time required for appointments, procedures, and recovery for affected and loved ones.

2.) How do these symptoms impact specific activities that are important to you? As a person affected with multiple BCC's any daytime outdoor activity has to be thought through- from clothing, sunscreen, head and scalp protection, is there shade, can shade be created, how much time outside especially if sunny and hot, etc… If recent procedures whether Biopsy, ED&C, or Mohs any in water events are out of the question.

3.) What are you doing (or what is your loved one doing) to help treat Gorlin syndrome, and how well are those treatments working? Treatment of BCC's is seeing a dermatologist every 3-4 months for biopsies, and ED & C, with Mohs to follow up for any of those areas needing Mohs.

4.) What are the most significant downsides to those treatments? Pain, time, disfigurement.

John - five comments submitted

John (Submitted October 8, 2021)

1) Congenital Cataract, Osteoarthritis, Jaw Cysts

2) Prohibits me from several activities common to/normal for non-affected people; numerous hospital appointments are often difficult to reconcile with daily work schedules

3) Numerous surgeries, several per year, for every year of life

4) that none, not one, is a "cure", just a needed "fix" of a current manifestation

John (Submitted October 8, 2021)

Much talk is on the individual manifestations, yet cumulatively:

2) Impact - the constant and continuous doctor appointments, tests, surgical procedures, recovery, etc. impacts employability, especially as one gets older. Yes, there are legal requirements for a boss/employer to provide reasonable adjustments and accommodations for this, as it is classified as a disability. Yet they rightfully have to consider that impact on doing the job, the team, the service/product being provided, etc. and at some point it would understandably be too much to keep one's job.

John (Submitted October 8, 2021)

2) IMPACT involves not only the person but also treatment - these manifestations are often many and simultaneous. Multiple surgical procedures may be required, and clinicians and patients face difficult decisions that may mean going ahead with one and delaying others. There might be so many doctor appointments, tests, procedures, etc. that likewise, one has to juggle which to attend and which to delay, if possible. As these are ongoing, there is never a "rest" from any - one's impact may subside a bit, but others remain or come to the surface. And, manifestations last a lifetime - there is no point at which one grows out of this, or emerges from a phase of this.

John (Submitted October 8, 2021)

STUNNED that the "brain tumours" option had so few ticks by it in terms of what people want for treatments. Yes, the bcc's are so hard, so often, so damaging, so disfiguring - BUT, whilst they damage skin and appearance, brain tumours damage so, so, so much more.

Agree "the medical community" needs to know about this disease, but that community is made up of individuals, and realistically, there's only so many rare diseases that any individual can be aware of at any time....but we, ourselves, need to "be" the education we think they need.

John (Submitted November 4, 2021)

As a patient with Gorlin Syndrome, I have NEVER had a month of my nearly 60-year-long life without having to go to a doctor or hospital for something due to the syndrome - until the pandemic! During the pandemic, health services rightfully diverted resources to COVID, "routine" and "non-emergency" procedures and visits were suspended. For the first time in life I had a few months of not having to see a doctor or hospital, and it blew my mind that this is what it would be like for "normal", non-affected people. I thought how horrific must this condition be that it takes a pandemic to give you a break from it.

Sandra – one comment submitted

Sandra (Submitted October 8, 2021)

One of the main challenges of my granddaughter having Gorlin syndrome is the fact that she has to wear sunscreen all the time, and I have a hard time finding one that is safe. Innately we go to the organic products, but those are not always the safest as well. We struggle trying to find products such as sunscreen, lip balm, etc. that don't have carcinogens and harmful properties. What is the FDA going to do about this and why have we not already banned Titanium Dioxide in all our products, not just candy and sunscreen? The UK has banned it for many years now, this cannot be a concern you brush off. Please explain what you are going to do and how that will impact us?

Another concern is the fact that all the doctors are not educated enough on the signs, symptoms, and a lot of times they have no idea what it is until I explain it to them. They tend to brush each situation off as no concern, but if you put them all together, it is a concern, and most definitely to find out that all these years we likely have all been living with it. How can we change that together?

Another real concern is the real nature of being a child and not being able to go out and play like the others. Also looking different from others, and on top of that having to miss school a lot for doctors appointments. How can we innovate together to reduce the need for these visits and the impact they have (depression, anxiety, feeling so different, and left out)?

A huge challenge today for the children and the caregivers is the cost of clothing, hats, and sunscreen that is outrageously expensive. We need to have these things (of great quality) that are more easily accessible to everyone, not just the rich. How can we change this?

Let's try to reduce the amount of doctor visits, the need for a parent to take off all the time and not be able to hold a job due to all of the doctor visits. The worry, costs, and on top of that having to read every ingredient and educating themselves on all of it?

Suzanne - one comment submitted

Suzanne (Submitted October 8, 2021)

It’s surprising to me how few dermatologists, even ones who have Gorlin syndrome patients, tell their patients about clinical trial availability. I have found out about every one I have participated in on Facebook, including one my dermatologist was participating in! How can we get doctors to keep their patients informed?

Nichole - one comment submitted

Nichole (Submitted October 8, 2021)

Hello, my name is Nichole and I am 42 years old. I was diagnosed with Gorlin syndrome at eight years old. Immediately after I was diagnosed I lost my top three front teeth due to jaw cysts. This was followed by a lot of bullying in school by being called toothless. I didn't have any front teeth until I was about 22 years old. Since I was 15, I have also been going to a dermatologist every six months to have skin cancers removed. Some visits are worse than others. At first I was stressed and scared, and now I feel like I have gotten used to it. Why should I feel that way? Why should I feel like it's another ordinary day walking in and getting 25-100 shots to have skin cancer removed? Or even to be put under to have jaw cysts removed and waking up wondering if you lost anymore teeth as a result. When I was 35 years old I was forced to have a hysterectomy. That was the scariest surgery ever! My decision to have children was being taken away but I was put under not knowing what was going to happen to me! I had massive cysts on my ovaries and the doctor said if I can't save my ovaries then no need to save anything else. This is what I have dealt with living my life. But it's still sometimes scary living with Gorlin syndrome as you don't know what's next. This summer I found a lump in my side. After several appointments and a biopsy, it was determined it was skin cancer. Since when does skin cancer grow under the skin as a lump?!? When I had my biopsy, it was hard for me to lift so who knows what it will be like after the lump is removed. Normally I like to get things taken care of right away. But I'm also a full-time nanny and take care of babies. I don't like asking my families for many days off. So I scheduled the surgery to remove the lump the day before Thanksgiving. I'd rather take away time from my family than time from my job. I hate feeling this way and I hate how I think about things. Why can't I be fine like everyone else is my biggest question. It's been hard. I have hated growing up with this, and if there's a medicine to help cure or make it easier then it may have saved my life. I say saved my life because I have eaten away my emotions from dealing with all of the trauma. Sacrifices, and bad news I have gotten due to the syndrome thus classifying me as morbidly obese. I hope one day it becomes better for all of us. Because the pain and hurt I felt with this syndrome as a child is still there, especially when I'm the only one in my family with it.

Gareth - one comment submitted

Gareth (Submitted October 8, 2021)

PTCH2 is not a convincing Gorlin gene.

Patricia - six comments submitted

Patricia (Submitted October 8, 2021)

Most of the medical challenges that our Gorlin Warrior has had to deal with are side effects from the medulloblastoma brain tumour when he was four years old. Radiation treatments to save his life led to another life-threatening tumour (osteosarcoma) 15 years later. This late-effect tumour has had a VERY significant effect on his quality of life and daily living and independence.

Patricia (Submitted October 8, 2021)

Our Gorlin Warrior has tried most of the available treatments for 100's of basal cell lesions since the age of 6. Every treatment has left scars and disfigurement. All Gorlin syndrome patients need better options.

Patricia (Submitted October 8, 2021)

There needs to be a better way to diagnose the lesions, the status/stage of them, the depth of them, as a way to decide on appropriate and effective treatments.

Patricia (Submitted October 8, 2021)

Some people have different presentations of different types of bcc lesions.

Patricia (Submitted October 8, 2021)

It is another stress for us that in some cases we have to be the ones that educate our medical providers about this condition.

Patricia (Submitted October 8, 2021)

There need to be more clinical trials accessible for Canadian patients.

Miriam S. - two comments submitted

Miriam S. (Submitted October 8, 2021)

She’s great! But no mention that those drugs are only for adults not for pediatrics.

Miriam S. (Submitted October 8, 2021)

I won’t be able to get back on the phone but I wanted to emphasize that because concern of the unknown as one who lives with the syndrome as well as parenting all children affected with the syndrome the unknown is the most difficult whenever there’s an issue. Doctors are very quick to blame the syndrome thinking there might be a magical doctor who can treat it without finding a solution. A parent has to be able to decipher between what’s treatment and what’s just bogus for experimental use. The amount of travel and cost as well as time. My kids are very

positive and don’t have the negativity associated with the syndrome as I’ve always made sure to be positive and by leading by example.

About teaching our children as they get to adulthood. I always send an invite to their appointments to make them aware and for my oldest now that he is over 18. I’ve been next to him as he calls or writes to the doctors so that when it comes time that I can’t be there with him every second he knows how to call talk and verify that what they are saying makes sense and he can feel confident in the plan

Another point is of substance abuse awareness due to the syndrome. I have a sibling who has struggled with it for many years and one of the main reasons for not being able to kick it before it was too late was due to having a syndrome no doctor would get in trouble for prescribing.

Trudy - three comments submitted

Trudy (Submitted October 8, 2021)

The most significant downside for me, living with Gorlin syndrome, is currently a general lack of hope for management of this syndrome changing anytime in my lifetime. As you know there is currently no cure and that would be the biggest game changer. Figure out a way to synthesize our missing/mutated protein/gene. That would be our world changer, which we have earned no matter how rare this disease is! I understand standard immunotherapy is not an option because it would have to follow the germ line to be impactful to us. However, I am unimpressed thus far with the approved chemotherapy treatments for this syndrome. They can shrink cysts and carcinomas and prevent surgery while a patient remains on them AND the drug remains effective, but also come with most of the general chemo side effects? Those side effects would be fine if they came along with a cure, but they come along with just a delay in surgery. That's it! I know there have to be better options. I'm not interested in settling for such harsh side effects or organ damage that we risk with some of the topical options. Better is out there! So, for now I'll remain vigilant with self checks. I'll have surgery every two months because if I don't this disease will become unmanageable really quick (and I already have 11-14 skin cancers removed every 2 months). I'll use my vacation days solely for Gorlin syndrome appointments so I can maintain employment to finance this relentless disease. I'll deal with trying to disguise myself enough to get home from the surgical appointment because we can look pretty battered, which can be dignity crushing, and I'm not interested in looking like a "cancer patient." I'll deal with the pain of showering and bandaging myself for weeks afterwards because this disease is never ending, so asking for help went out the window decades ago. I'll continue to be creative in contorting myself to try and rest somehow, which can seem impossible when inevitably I'm cut in locations like my right arm, my back, my forehead, and the left side of my scalp during one visit, leaving no side of my body uncut. I'll deal with worrying about what is next (will my brain be impacted by the calcification of the falx? Am I overlooking a tumor in my brain, spine, or heart?), and what else am I overlooking because doctors depend on me to point things out to them with this disease due to their lack of experience/exposure. I'll deal with or at least acknowledge the depression from the lack of a light at the end of this genetic tunnel and surrendering to my choice of not living my dream of procreating because I wouldn't wish this on my biggest enemy. It's mentally a struggle for me at

times, although we're survivors so it probably doesn't appear that way externally. However, I definitely would not be okay knowing I passed this on, because after all it's autosomal dominant so one "bad" gene is all it takes and nobody gets away with having the mutation and not having physical manifestations of it to some degree. So, I'll ask you to please join our team of warriors and demand better on our behalf, demand more sustainable, and more curative treatments, and refuse to accept anything less. A cure is out there. It might not be where the money is, but we deserve a better quality of life regardless of profit. I appreciate your efforts!

Trudy (Submitted October 8, 2021)

Treatment overall is difficult because this is an overgrowth syndrome (overall physical size, head size, relentless basal cells, jaw cysts, benign epidermoid cysts, milia, etc.), and because so many organ systems are involved. So anytime there's a medical issue the question: is always is it Gorlin syndrome-related or do we go down a rabbit hole for something non-related to Gorlin syndrome and hope for a successful outcome?

Trudy (Submitted October 18, 2021)

Not to minimize anyone else's experience with different types of cancer, but I've always thought a huge differentiator between Gorlin syndrome and most other cancers is that this is a life sentence. There is no light at the end of the tunnel, whether good or bad, in the form of remission or death in the near future. Gorlin syndrome is unrelenting. So, correcting our genetic mutation is really the only true light at the end of the tunnel that anyone could provide us because I know I get tired of being strong or being a warrior. And I really don't want to take on harsh side effects of a medication to treat symptoms, without offering a cure, along with managing Gorlin syndrome. We need a resolution that restores hope and overturns our life sentence.

Cindy - four comments submitted

Cindy (Submitted October 8, 2021)

I have Gorlin syndrome, as does my daughter and grandson.

I was diagnosed at age 20. First jaw tumor at age 13. First Basal Cell at 22.

Last tumor at age 62.

Fear of continuing cancers, having had 200+ on me now. Fear of getting other cancers due to us missing the tumor suppressor gene. Emotional stress, worrying not only about myself, but my daughter and grandson (age 7); already he has a jaw tumor.

Cindy (Submitted October 8, 2021)

I am fearful of the severe side effects of the oral drugs: cramps, hair loss, taste loss, etc. The topical drugs leave open sores for weeks.

Get tired of doctor appointments, having to use vacation hours for appointments and recovery time. Planning surgery during school breaks... no "real" break for Gorlin patients. It is a snowball effect...affects everyone else in family.

Cindy (Submitted October 8, 2021)

Gorlin patients will most likely never be in remission... our BCCs will come back. Jaw tumors come back - Just had one at age 62. Ongoing worries and fears.

Cindy (Submitted October 8, 2021)

Yes, sometimes our treating doctors don't listen to us the more experienced Gorlin syndrome person.

DB - one comment submitted

DB (Submitted October 8, 2021)

I've had multiple cysts removed, carcinomas, and been on a drug study. When I was younger I was bullied for my symptoms like my "Jimmy Neutron" head and other symptoms. The biggest surgeries for me were when I was in the 6th and 7th grade I had two tarsal coalitions removed that allowed me to move and run properly.

Kaylene - two comments submitted

Kaylene (Submitted October 8, 2021)

Three of the most challenging manifestations that I have dealt with as a result of Gorlin Syndrome are Basal Cell Carcinomas, Odontogenic Keratocystic Tumors, and a cardiac fibroma. I was diagnosed when I was two (I am now 22), and all three of these manifestations have had such a huge impact because they are time consuming to manage and also affect my cosmetic appearance. Throughout my life, I have been viewed as an outcast due to my cosmetic differences in comparison to my peers, which also affects my social-emotional well being at times. Although I have learned to cope with all of the stares and bullying that are associated with being a young person with this condition, this condition has not only resulted in physical but has also had an impact on my self-esteem and self-confidence.

One of the most difficult times in my life in regard to the emotional burden that this disease has had was when I was on the medication Erivedge. Although I was glad to not need countless Mohs surgeries, the hair loss associated with this medication had a huge impact on how I viewed myself and how the world viewed me. In the future, I hope that the social-emotional impacts that this disease can have are considered when determining what treatments would be best, especially in regard to the cosmetic effects and pain of treatments.

Kaylene (Submitted October 8, 2021)

One of the most significant downsides to the current treatments are the side effects and the cost of the treatments that are available. As a patient with Gorlin Syndrome, I am constantly faced with medical expenses (copays for specialists, medications, etc.), and many drug companies are not open to sharing the cost of these medications when patients are given the opportunity to participate in a clinical trial. This leads to patients only having a short-term solution to a long-term problem, especially if the medication ends up not being accessible.

I have encountered medication inaccessibility firsthand through my experience of a copay being changed when I was on a hedgehog inhibitor. The cost of my medication went from free to thousands of dollars a month. Although this treatment was effective, it eventually became inaccessible to me since I am a young college student with a rare disease that is already so costly.

Anthony - one comment submitted

Anthony (Submitted October 8, 2021)

I will echo what the prior caller discussed. It is easy for a young person to avoid getting treatment in lieu of social events or avoid the wound/scarring to get dates, etc. They may also think that the uncertain future provides a license to partake in harmful activities, such as drugs and excessive alcohol. Parents often have a difficult time in deciding whether or not to give a longer leash in many situations in agreement that their child does perhaps have an uncertain future and maybe should be able to live large while they can. This may not end as the best possible formula. Well, at least it wasn't in my case growing up in the late 70's and early 80's!

Sandy - one comment submitted

Sandy (Submitted October 8, 2021)

Ann nailed it when she was talking about going undiagnosed. It's probably best if I put it in bullet formation.

- Our family is very private and doesn’t talk about issues, only drink. Not having access to doctors for so many years has impacted almost everyone in my family, including myself.
- We all have been diagnosed with 9% scoliosis but never returned to check again.
- My mom had rickets and had her legs broken as a child, she was in pain her whole life, she had her spine replaced piece by piece.
- My oldest brother died from a heart attack at age 26, they never explained how or why that happened.
- My other older brother had a cyst on his aorta that was benign, but they still removed it and he has had multiple back surgeries and deals with teeth and mouth issues.
- I personally have been in debilitating pain with my knees and legs for almost 6 years, every time I go to a doctor, and I've been to one in 5 states now, they say, it may or may not be arthritis, meniscus tear, now they say I'm bone on bone.
- When I was 14 I had huge ovarian cysts that had to be removed along with one of my ovaries. I have since been dealing with fibrocystic breast disease.
- My two youngest kids had six wisdom teeth removed.
- My dad and I were both told we were allergic to the sun from the cysts we developed, mostly in the form of the bumps on our feet and hands that occur.
- My dad has had three recent cancer surgeries, basal cell, and the only reason he hadn't before is because he refuses to go to the doctor. My mom just passed so I made him go.
- My oldest son has always had a sense of immortality and stays up to this day banging his head on the wall not knowing how to deal with it.

- My dad and I were told we have Reynaud's disease, lupus, rheumatoid arthritis, but of course nothing was ever done about it, but using steroids. I took myself off of those and changed my diet, and I haven't been diagnosed with those again, but it's not like I have been too forthcoming as everything has always been talked down, nothing to worry about, just stay out of the sun. My sons have horrible sores that come and they pop them or remove them by themselves, and dealt with it by using drugs.
- Thank goodness they are both sober now for many years, and I have had them in with therapists, but still no one has addressed all of these things.
- They did diagnose my 31 year old son with trichotillomania, a form of OCD because he pulls out his hair, has high anxiety, panic attacks and since he was four has had this overwhelming fear of dying and that something was wrong.
- I am often times considered weak at work because they say I am "soft". I am not, I just don't like confrontation that leads to anxiety and panic attacks.
- It is very, very typical for us to have so many of these symptoms and I'm wondering now if we do actually have it.
- Thank you all for sharing.

Bob - one comment submitted

Bob (Submitted October 8, 2021)

Not to diminish the medical burdens of having Gorlin syndrome, but the mental and emotional burden is never easing and never ending.

Kathlyn - one comment submitted

Kathlyn (Submitted October 8, 2021)

I agree we are cancer livers not survivors.

A good deal of the medical community spends more time with potential survivors (leukemia, lymphoma etc.) than us because 1. They know little about Gorlin and 2. They don't see the constancy and impact of our cancer in the same way.

Elizabeth - one comment submitted

Elizabeth (Submitted October 8, 2021)

Finally going to a conference in my 30's helped me feel like I wasn't alone. While there I was talking with a woman in her 20's and mentioned that seriously if she ever needed someone to talk to, to please reach out to me, and her mom sitting next to her who didn't have the syndrome said "thank you! I'm glad to know she can talk to someone who also has this as I don't have the experience and haven't lived with it." That mom gave her daughter the "permission" (if you will) that she can reach out and talk to others, because with all due respect we are never cancer free. We also don't at times have others to lean on as we aren't in the nearest hospital's cancer ward.

Lauren - one comment submitted

Lauren (Submitted October 8, 2021)

Gorlin syndrome, aka basal cell nevus syndrome, has affected four generations of my family, and counting. Each of us must put our lives on hold over and over for more cyst removals, more cancer surgeries, only for more spots to appear within the year. It has prevented me from wanting children of my own, and surely had physically and financially limited my loved ones from many opportunities. The only drugs we have come with side effects, arguably worse than the symptoms, with results that do not last. Please help.

Jen - one comment submitted

Jen (Submitted October 8, 2021)

The stent for our daughter saved her from getting her jaw cracked and losing teeth -- Dr. Bonnie Padwa at Boston Children's Hospital recommended and did this surgery after the first oral surgeon wanted to break her jaw and remove the cyst immediately. For our child, shrinking the cyst made for a less dramatic oral surgery and recovery. But we are blessed that she has only had the one cyst so far, and I can imagine having to deal with the stents frequently would be inconvenient and troublesome for children and parents alike.

Craig - one comment submitted

Craig (Submitted October 8, 2021)

I'm 54 and when I was in my early twenties I would dream of better treatments beyond procedures/surgeries/reconstructive surgeries (these were my best treatment) for myself and generations to come. Fast forward to my late forties and Erivedge came along and was a miracle for me at the time, along with others. Always dreamt for so long that those children can be kids sooner than later and maybe along the way us older patients will have better opportunities too. Thank you and bless you parents facing these heart wrenching times.

Mandy - one comment submitted

Mandy (Submitted October 11, 2021)

Having Gorlin syndrome, I have always felt different. From having braces for seven years to the constant surgeries. I have so many scars on my body due to all of the surgeries for basal cells. I have tried lotions/creams, oral chemotherapy, and recently immunotherapy. Nothing has worked- I have over 40 spots on my legs, which I'm told surgery is the only way to get rid of them since nothing else has worked. This is very frustrating because I don't want any more scars. I hate to be in a sleeveless shirt or bathing suit because of all of my scars and people seeing them. I have suffered from anxiety and depression my whole life trying to deal with this syndrome. The cost of trying all of these different medications has been astronomical. When there are clinical trials, the criteria is there has to be basal cells on the face. I don't have any on my face and therefore do not qualify for the trials. I wanted to make sure my children never had this syndrome as well, so I went through IVF to conceive. To have my daughter, we paid $60,000. I am thankful for the Gorlin support group on Facebook because a lot of times, they are the only ones who understand.

Katerina - one comment submitted

Katerina (Submitted October 25, 2021)

My son is 13 years old. He was diagnosed with Gorlin syndrome at the age of six after he developed medulloblastoma at the age of 2. Due to craniospinal radiation he received at the age of three, he faced early BCCs, jaw cysts, and at 12 he got grade 2 meningioma on the brain. He was operated on and received medication for one year. Unfortunately, the tumor recurred after one year and he was operated on again in August. He is currently receiving vismodegib, 1 pill daily. We do not know if this will work. The only treatment that works for sure is proton radiation, but due to the syndrome the doctors avoid giving that to him. Did you ever have similar cases, and what medications were used for treatment?

Judith - one comment submitted

Judith (Submitted November 2, 2021)

Last year was the first in over 50 years of yearly surgery that I had without surgery - thanks to medication for BCCs (but the side affects of it are horrible!) In my 65 years, there have only been seven years when I haven't had eye, jaw or skin surgery - so any developments in drug treatment would be wonderful! I'm a school teacher of five to ten year olds. Having had an eye removed and thousands of BCCs off my face, I'm not the most attractive looking person - and my wobbly nose (thanks to all those surgeries) makes me quite witch-like - so there are always a million questions from the children. Every school holiday is spent having surgery - but I'm thankful I have a job that gives me such extensive time to have multiple surgeries. My son struggles to get time off for his surgeries, and often leaves surgery until the pain is overwhelming - and then more damage is done. He suffers from jaw cysts - he has had multiple cysts over the years. He was born with a cleft lip and palate, so his dental/ mouth problems have been very extensive - over 20 operations in his 40 years, and that doesn't include the surgeries for BCCs. My father had the BCCs very severely. His whole body was made up of skin grafts - and I mean his whole body. No ears, and very minimal nose. In his last surgery on his skull, they had a lot of trouble maintaining a blood flow. He had skin grafts over skin grafts - in some spots at least five regrafts. He lived 67 years in pain, and eventually took his own life. I can only imagine what drug development could have done to make his life liveable. And now our 4th generation of Gorlin syndrome starts - and she has a cardiac fibroma. That is one of the worst parts of this syndrome, you just don't know what symptoms you will get. The symptoms are so varied - no one doctor can cover them all, so it is often left to the patients themselves to monitor the condition themselves. Every person with the syndrome in our family has had BCCs and jaw cysts - but at varying degrees and has had very different other symptoms. For example, I had a small eye, my son a cleft lip and palate, and my granddaughter a cardiac fibroma (plus we all have other symptoms). The worst part of this syndrome is that it is never ending - surgery is still the main procedure for dealing with the many symptoms - and just when you think you have all the symptoms you will develop, something else pops up. It is SO difficult to maintain an everyday life. The financial and emotional toll is extreme. Little things like family holidays are virtually non-existent as any time off work is devoted to surgery. My wish for my granddaughter

is to have a life where the symptoms of the syndrome are controlled by drugs - especially the BCCs and jaw cysts, and hopefully new treatments for the cardiac fibroma.

Charlotte - two comments submitted

Charlotte (Submitted September 27)

Muscle spasms from taking Erivedge and Odomzo are the worst. I can't see how any person can endure them. Pain relievers don't work. It hurts my feet to walk, my lower back pain limits time I can walk. Diarrhea is no fun. I've lost some hair that won't grow back, but I'm 71 not a young child, teen or young woman. I don't like having all the scars on my face, body, or a life-time of surgeries or a disfigured, blind right eye- the result of retinal hemorrhage after cataract surgery when I was 26. That sealed my fate to be a single person the rest of my life. Treatment shouldn't be torture. I took Erivedge off and on since 2012. I'm on Odomzo four months after a three-year break from Erivedge just to stop muscle spasms. I vote for research on Gorlin syndrome to continue, but not the torture. Thank you. BTW I have years of surgery photos if you need them.

Charlotte (Submitted October 8, 2021)

Doctors didn't know about Nevoid Basal Cell Carcinoma Syndrome/Gorlin syndrome when I was a young child. The eye problem I was born with: Tiny part of my iris was missing. My vision in my right eye was fuzzy but I could see movement, colors, etc. When I was 26 (1976) the doctor did surgery to remove a cataract in that eye. During the week after my surgery, my retina collapsed in the right eye and it was bleeding internally, so my iris turned from blue to green. The eye shrunk. I was left with a distorted iris and had to wear a prosthetic shell for almost 10 years as that eye gradually returned to almost it's original size. Then the shell wasn't thin enough to work. So, the damaged eye was no longer covered. I knew at 26 I would never marry once they really looked at my eyes, they would lose interest. I have an uneven sternum and slightly larger than normal head. I wore a light back brace for 2 or 3 years as a teen because my posture was bad, but that didn't help. Skin cancer started at 13 but wasn't biopsied until I was 18. After the first removal more started popping up. I'm single, never married, (that also means I never had children) and now 71.