

Review

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Review

# Genetically Determined Syndromes Associated with an Increased Risk of Glioma - The Use of Photodynamic Therapy (PDT)

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**Abstract:** In this review, we have included current information on the use of photodynamic therapy in the treatment of gliomas. We mainly focused on the discussion and regarding the use of photodynamic therapy in patients with genetically determined syndromes that are associated with an increased risk of glioma. The review also uses information on genetic syndromes that are associated with an increased risk of glioma.

**Keywords:** brain tumors; photodynamic therapy; genetically determined syndromes

## 1. General Information about Brain Tumors And other CNS Cancers

Brain tumors and other tumors of the central nervous system (CNS) are a significant problem associated with significant mortality and morbidity at all ages. They are the most common group of cancers diagnosed in children aged 0-14 and the second most common cancer in the age group 15-19. Most of these tumors are malignant (3.55 per 100,000), the most common of which are glioma, embryonal tumors and germ cell tumors. In turn, pituitary gland tumor is the most common among non-malignant brain tumors and other CNS tumors, occurring at a frequency of 2.6 per 100,000. In all adults (over 20 years of age), benign lesions are more common (22.38 per 100,000) than malignant lesions (8.5 per 100,000) [1,2]

Brain tumors and other CNS tumors constitute a very complex and extensive group of tumors. The classification according to The 2021 WHO Classification of Tumors of the Central Nervous System includes 12 main groups: 1. Gliomas, glioneuronal tumors, and neuronal tumors; 2. Choroid plexus tumors; 3. Embryonal tumors; 4. Pineal tumors; 5. Cranial and paraspinal nerve tumors; 6. Meningiomas; 7. Mesenchymal, non-meningothelial tumors; 8. Melanocytic tumors; 9. Hematolymphoid tumors; 10. Germ cell tumors; 11. Tumors of the sellar region and 12. Metastases to the CNS [13].

## 2. General Information about Gliomas

Primary brain tumors constitute approximately 5-10% of all cancers, of which 40-50% are gliomas. [4,5] Tumors of glial origin are divided into oligodendroglioma, ependymoma, astrocytoma, heterogeneous forms and mixed forms. [4] 40–90% of brain gliomas are malignant, depending on the age group of patients. [4] Glioblastoma multiforme (GBM) accounts for approximately 49% of malignant brain tumors, along with primary central nervous system (CNS) lymphoma (7%), malignant forms of ependymomas (3%) and malignant forms of meningiomas (2%). [6] GBM is the most frequently diagnosed and the least prognostic cancer of the central nervous system [4,7].

Already at the moment of diagnosis, it is assigned stage IV, and the average median survival, using current treatment techniques, is several months (average 12-18). [4] There are primary and secondary forms of glioblastoma multiforme. The primary form, which occurs most often after the age of 55, is characterized by a rapid clinical course and a structure typical of GBM from the beginning of growth. The secondary form of GBM usually affects people under 45 years of age, and the transformation time from a lower-grade glioma to a more malignant form may take up to 10 years. [8] According to the WHO classification, GBM belongs to Adult-type diffuse gliomas, which is a subtype of Gliomas, glioneuronal tumors, and neuronal tumors. [3]

### 3. Genetically Determined Syndromes that Are Associated with an Increased Risk of Glioma

The vast majority of gliomas are sporadic. It is estimated that only about 5% of gliomas are familial, which may indicate a hereditary mechanism. Of these, only a small percentage of gliomas are syndromic, which means that gliomas occur in cancer predisposition syndromes. [9,10]

It stands out among the syndromes predisposing to the development of glioma:

3.1. Li-Fraumeni band (LFS), [9–13]

3.2. Lynch syndrome (HNPCC), [9–13]

3.3. Selected neurocutaneous diseases:

3.3.1. Tuberous sclerosis syndrome (*Tuberous Sclerosis Complex*; TSC), [11–13]

3.3.2. Neurofibromatosis:

3.3.2.1. Neurofibromatosis type syndrome 1 (NF1), [9–13]

3.3.2.2. Neurofibromatosis type syndrome 2 (NF2), [9–13]

3.3.3. Von Hippel-Lindau syndrome (VHL). [11,13]

#### 3.1. Li-Fraumeni Band (LFS)

Li-Fraumeni syndrome is a rare disease inherited in an autosomal dominant manner. It was first described by Li and Fraumeni in 1969 [14]. LFS is a cancer predisposition syndrome associated with a high risk of malignant tumors. This risk, over the lifetime of a person affected by LFS, is at least 70% for men and at least 90% for women. [15] According to other authors, the incidence of developing at least one cancer at the age of 30 is 50%, while at the age of 70 it is close to 100%. [14] There are five types of cancer to which these patients are particularly vulnerable: adrenocortical carcinomas, breast cancer, central nervous system tumors, osteosarcomas, and soft-tissue sarcomas. [14,15] It is necessary to confirm all three classic clinical criteria to confirm LFS: (1) proband with sarcoma diagnosed before the age of 45; (2) a first-degree relative diagnosed with cancer before age 45; (3) a first- or second-degree relative diagnosed with cancer before age 45 or sarcoma diagnosed at any age. An additional diagnostic criterion, but not required, is the demonstration of a heterozygous germline pathogenic variant in TP53, which occurs in 60-80% of patients. [14,15] In 40% of patients with a phenotype similar to Li-Fraumeni syndrome (Li-Fraumeni-like - LFL), the presence of harmful TP53 mutations was confirmed. These mutations are located mainly in the DNA-binding domain. It has also been shown that mutations in the cell cycle checkpoint gene CHEK2, without detectable TP53 mutations, may also predispose to the development of LFS or LFL in some families. The literature also indicates that mutations in POT1 are associated with the development of several types of cancer in LFL families. [14]. The incidence of brain cancer up to the age of 70 is 6% in women and 19% in men. Approximately 10% of LFS patients will develop a glioma (astrocytoma or glioblastoma multiforme) [15,16].

#### 3.2. Lynch Syndrome (LS)

Lynch syndrome (LS; otherwise known as Hereditary nonpolyposis colorectal cancer - HNPCC syndrome) is an autosomal dominant disease, the essence of which is the loss of function in one of four different genes encoding mismatch repair proteins. [17] LS is caused by the presence of pathogenic germline variants (PGV) in any of the 4 DNA mismatch repair (MMR) genes, MLH1, MSH2, MSH6 and PMS2, or deletions in EPCAM. [17–22] The consequence is the potential

development of cancers related primarily to the digestive tract and gynecological organs, i.e. large intestine (CRC) and endometrium (EC). [17,19,20,22,23] Lynch syndrome is the most common form of hereditary predisposition to colorectal cancer. It affects approximately 3% of patients with colorectal cancer and approximately 2-6% of patients with endometrial cancer (according to various sources). [22,24] The lifetime risk of developing colorectal cancer in patients affected by LS is 50-80%, and endometrial cancer is 40-60%. [23] These patients also have cancer of the upper urinary tract, hepatobiliary tract, small intestine, ovary, skin, pancreas and brain. [21,24] The first case report of the family, later called "Family G," dates back to 1913, when Dr. Aldred Scott Warthin, a pathologist at the University of Michigan, noticed a distinct susceptibility to developing certain types of cancer.

Then, in 1966, cases of two large families suffering from colon, stomach and endometrial cancer were described by Dr. Henry Lynch, after whom the syndrome was named in 1984. There are Lynch I and Lynch II syndromes, which, unlike the first syndrome, are characterized by additional tumors apart from the colorectal cancer. A little later, the term "hereditary non-polyposis colorectal cancer" (HNPCC) was proposed, which suggested a lack of connection with the classic form of familial adenomatous polyposis (FAP). [21] The diagnosis of LS is based on the Amsterdam and Bethesda criteria, related primarily to the history of cancer in the patient and his family. Cancer diagnosis is performed using two techniques. Using immunohistochemistry, the expression of MMR proteins can be examined, while molecular biology methods are helpful in determining the occurrence of microsatellite DNA instability. [22] There are three varieties of Lynch syndrome, i.e. Turcot's syndrome, Muir–Torre syndrome and constitutional MMR deficiency (CMMR-D) syndrome, which may occur simultaneously in one patient. [23]

### Gliomas in LS

Lynch syndrome is associated with a four-fold increased risk of brain tumors, primarily the development of glioblastoma multiforme. Type I Turcot syndrome predisposes to the development of gliomas and astrocytomas, and type II Turcot syndrome may cause medulloblastomas. Muir–Torre syndrome and CMMR-D syndrome are also characterized by a higher incidence of brain tumors, including gliomas, compared to the general population. According to research, among patients suffering from Lynch syndrome, 14% of families were diagnosed with primary brain tumors. The most common histological subtype was glioblastoma multiforme (56%), followed by astrocytoma in 22% of cases and oligodendroglioma in 9%. The median age at diagnosis was 42 years. [23] For the prevention of central nervous system and brain tumors in people with LS, no additional monitoring beyond an annual physical/neurological examination beginning at age 25–30 is currently recommended. [25] Temozolomide (TMZ) is recommended as a standard treatment option for gliomas, and it works by inducing DNA damage through guanine and adenine methylation. This process initiates a futile cycle of mismatch repair, causing lethal double-strand breaks leading to checkpoint activation and apoptosis. Given the dependence of the effectiveness of TMZ and other alkylating agents on the repair of functional mismatches, MMR-deficient cells are inherently more resistant to their effects and may survive at the cost of extensive mutagenesis. Preliminary studies indicate potential resistance to TMZ in cells from glioma patients. [19] Further research is needed to find the most effective treatment.

### 3.3. Selected Neurocutaneous Diseases

Neurocutaneous diseases include primarily tuberous sclerosis syndrome (TSC) and neurofibromatosis type 1 (NF1) and also neurofibromatosis type II (NF2) or von Hippel-Lindau disease (VHL). All of them can develop cancer, mainly in the central and peripheral nervous system, including glioma. [26,27]

#### 3.3.1. Tuberous Sclerosis Syndrome (TSC)

Tuberous sclerosis syndrome is an autosomal dominant neurocutaneous disease that was first mentioned in 1880-1900. The relationship between changes in the brain and skin symptoms on the

face was then described. At that time, a characteristic triad of symptoms was also described - Vogt's triad: sebaceous adenoma, epilepsy and mental retardation, which is a loose definition of TSC. [27,28] The incidence of TSC is 1 in 6,000-10,000 live births. [27,28] Tuberous sclerosis syndrome is caused by a mutation in the TSC1 or TSC2 gene, which occurs de novo in 80% of cases. Among these cases, mutations in the TSC2 gene are observed approximately 4 times more often than mutations in TSC1. It was noticed that the frequency of both types of mutations is the same among familial cases. [27,28]

### Gliomas in TSC

Patients with TSC are at increased risk of developing tumors of the central nervous system. Cortical tubes, usually in the form of benign hamartomas, which are detected in 95% of patients, are the most characteristic neuropathological and pathognomonic feature of tuberous sclerosis of the brain. They show dysplastic neurons along with eosinophilic giant cells of mixed neuronal lineage. Subependymal nodules are also hamartomatous lesions located along the walls of the lateral ventricles. Subependymal giant cell astrocytomas are slow-growing tumors that are the most common brain tumor in patients with TSC. They are found in approximately 6-14% of patients, usually in the first 2 decades of life. Neuroimaging studies and the presence of hydrocephalus are used to differentiate a giant cell subependymal astrocytoma from a subependymal nodule. To prevent the development of subependymal giant cell astrocytoma, it is recommended to perform follow-up MRI examinations every 1-3 years. Treatment of brain tumors in the course of TSC is mainly based on surgical resection of the lesions and targeted therapy using mTOR inhibitors, e.g. everolimus. Surgery, as the therapy of choice, is necessary in the event of symptoms related to the mass of the tumor, such as obstructive hydrocephalus, swollen papillae, increased intracranial pressure, but also when radiological progression of the tumor is noted or when new focal neurological deficits appear. Everolimus has been shown to be effective in patients with subependymal giant cell astrocytomas associated with TSC. This therapy is recommended in patients who are not good candidates for surgery or in cases of asymptomatic disease with a constantly enlarging lesion.

Further research is necessary to prove the preliminary results of treatment. [27]

### 3.3.2. Neurofibromatosis (Neurofibromatosis Syndrome types 1 and 2; NF1 and NF2)

Neurofibromatosis is a neurocutaneous disease characterized by the development of tumors of the central or peripheral nervous system, including the brain, spinal cord, organs, skin and bones. There are three types of neurofibromatosis, the most common of which is type 1 (NF1), accounting for 96% of cases, type 2 (NF2) is diagnosed in 3%, and schwannomatosis (SWN) in <1%. [29]

#### 3.3.2.1. Neurofibromatosis Type 1 (NF1)

Neurofibromatosis type 1 is caused by a mutation in the NF1 gene, which is located on chromosome 17q11.2. [27,29] There are over 500 known mutations in the NF1 gene. [27,29]

In 90% of cases, these are point mutations, while deletion of a single exon or the entire NF1 gene is responsible for the remaining 5-7%. [29] The neurofibromatosis type 1 gene encodes neurofibromin, which is a protein that activates Ras-GTPase, thereby interrupting Ras signaling. NF1 protein deficiency results in hyperactivation of Ras, leading to subsequent activation of many important pathways. Neurofibromin is produced in neurons, oligodendrocytes and Schwann cells and other types of non-neuronal cells. The non-functional protein affects the growth of neurofibromas along nerves throughout the body. [27,29]

### Gliomas in NF1

Neurofibromatosis type 1 is associated with an increased risk of developing many types of cancer, including those affecting the nervous system, which constitute a significant proportion of malignancies. The most common intracranial tumors include optic gliomas, diagnosed in 15-20% of patients with NF1, and brain stem gliomas. It is believed that these tumors have a milder course than

in patients without cancer predisposition syndromes, which may even regress. Most of them are asymptomatic and do not require treatment or biopsy. The main therapeutic method for tumors not related to the optic pathway is surgery, which is unfortunately limited due to the possibility of regrowth of the lesion. For patients with optic glioma, the treatment of choice is conservative treatment with follow-up imaging or chemotherapy with carboplatin and vincristine, and surgical resection is used for tumors that have an atypical appearance, are associated with hydrocephalus, or are associated with complete loss of vision in one eye. In patients who have progressed after using other therapeutic options, radiotherapy is recommended, but is limited due to the fear of the development of a secondary tumor or malignant transformation. The possible effectiveness of targeted therapy directed at the pathogenic molecular pathway of neurofibromatosis type 1 is indicated, but there is still insufficient research on the most effective therapeutic strategy. Diagnostic MRI screening is not recommended in asymptomatic patients. [27]

### 3.3.2.2. Neurofibromatosis Type 2 (NF2)

Neurofibromatosis type 2, like schwannomatosis, originates from Schwann cells and leads to an increased susceptibility to the development of tumors of the nervous system. [27]

#### Gliomas in NF2

The most frequently observed lesions in the central nervous system are bilateral vestibular schwannomas, which occur in 90-95% of patients under 30 years of age. Also characteristic are intramedullary and extramedullary tumors of the spine (63-90%), intracranial meningiomas (45-71%), and neuromas of other cranial nerves (24-51%). [27] Currently, there is no most effective therapeutic option for patients with NF2. The most important goal of treatment in patients with NF2 is to preserve hearing function and improve quality of life. [27] The simultaneous occurrence of multiple intracranial tumors indicates the advantage of conservative treatment. [27] Additional treatment is usually necessary when neurological changes occur and there is a risk of brain stem compression, hearing loss or facial nerve dysfunction. [27,29] Surgical intervention is the primary treatment method, but there is a high probability of tumor regrowth. Radiosurgery is being used more and more often, but it may be associated with vestibular dysfunction and trigeminal neuropathy. Malignant transformation after using this method is very rare. [29] The use of radiotherapy may contribute to the secondary development of cancer, therefore its use is not recommended in patients with NF2. [27] Recent research reports the benefits of using targeted therapies that target the molecular pathways that control cell growth. The latest reports indicate the monoclonal antibody bevacizumab as the first-line drug in the treatment of rapidly growing vestibular schwannomas. [27,29]

### 3.3.3. Von Hippel-Lindau Syndrome (VHL)

Von Hippel-Lindau syndrome (VHL) is a multi-system autosomal dominant disease that predisposes to the development of benign and malignant tumors of the central nervous system and visceral organs [27,32–34] In approximately 80% of cases, VHL is hereditary, and in 20% of cases the mutation occurs de novo. [34] The most characteristic type of cancer for VHL, developing in approximately 50% of patients, is hemangioblastoma, which originates from the blood vessels as a benign lesion. This tumor may occur both in the central nervous system (CNS hemangioblastoma; CNS-H) - in the brain and spinal cord, as well as in the retina (retinal hemangioblastoma; RH). Depending on the location, it may cause different symptoms. Retinal hemangioblastomas may present with loss of vision, cerebellar hemangioblastomas with headaches, vomiting, gait disturbances or ataxia, and spinal hemangioblastomas and related syrinx with pain. Typical kidney diseases are cysts and renal cell carcinoma (RCC), occurring in approximately 70% of patients with VHL, which is the main cause of mortality. [33,34]

Typical symptoms of VHL also include pheochromocytoma (PCC), which may cause hypertension or be asymptomatic, and changes in the pancreas (pancreatic neuroendocrine tumors

or cystadenomas), inner ear and genital tract (cysts and/or cystadenomas of epididymis and cysts and/or cystadenomas of broad ligament). [33,34] Due to the genotype-phenotype correlation and the incidence of PCC, VHL is divided into type 1 and type 2. Type 1 VHL is caused by truncating mutations or exon deletions. It is characterized mainly by the occurrence of RH, CNS-H, RCC, with a low risk of developing PCC. Type 2 VHL, characterized by PCC, is caused by a missense mutation. Type 2 is divided into three further subtypes (2A, 2B and 2C), differing in the incidence of CNS-H, RH and RCC tumors. [32–34] The diagnosis is based on the diagnosis of tumors characteristic of this syndrome in patients with or without a positive family history of VHL. [27]Glejaki w VHL

The most common lesions in the central nervous system in people with VHL are undoubtedly hemangioblastoma. Available studies show that these patients may also develop low-grade or pilocytic astrocytomas, while glioblastoma multiforme is extremely rare. [35] Surgical resection is recommended for the treatment of CNS tumors. The use of targeted therapies is under research. [33,34] Screening to detect VHL-related tumors at an early stage of development includes frequent general physical and neurological examinations, regular dilated eye examinations, audiological evaluation, CNS and systemic imaging, and laboratory tests. [32]

#### 4. Non-Syndromic Familial Gliomas

These cancer susceptibility syndromes are associated with only a small minority of familial gliomas, suggesting the presence of additional predisposing genes.. [9]

#### 5. The Future in the Treatment of Gliomas - Photodynamic Therapy (PDT)

##### 5.1. General Information About Photodynamic Therapy

Photodynamic therapy (PDT) is a new, still researched therapeutic method whose action is based on the interaction between dye, light and oxygen. [36,37] The first literature reports, presented about 100 years ago by Raab and von Tappeiner, concerned the influence of selected dyes on cell death under the influence of light. Additionally, it was noticed that in the absence of oxygen, the reaction does not occur. [36–38] In 1913, the German scientist Meyer-Betz reported that hematoporphyrin, a first-generation photosensitizer, increases the skin's sensitivity to light. [37]

In turn, in 1990, Kennedy et al. used the photosensitizer 5-ALA and visible light, confirming the effectiveness of PDT in the treatment of basal cell carcinoma. The complete response rate was up to 90%. [36] PDT involves the intravenous, intraperitoneal, local or oral introduction of a photosensitive chemical - a photosensitizer (PS), and then its activation with light of an appropriate wavelength, which usually coincides with the longest absorption band of the photosensitizer and is approximately 600-800 nm. [39–41] An oxidative reaction occurs, resulting in the formation of reactive oxygen species (ROS), which in turn leads to cell death. [39,40] The anticancer effects of PDT include: direct cytotoxic effects on cancer cells, damage to the microcirculation causing local ischemia, and stimulation of the immune response against the cancer. [39,40] The greatest advantages of photodynamic therapy are the safety of its simultaneous use with other methods: surgery, radiotherapy and chemotherapy, as well as the selective effect on selected (cancer) cells, which significantly reduces the risk of side effects. [39,42,43] Photodynamic therapy is used in the treatment of many diseases of various systems and tissues. It is commonly used in dermatological diseases such as keratosis, skin cancer and melanoma. PDT has also been shown to have an effect on the treatment of many types of solid organ cancers: esophagus, lung, prostate, breast, head and neck, biliary tract, urinary bladder, pancreas, cervix, brain and others. [44]

##### 5.2. Photosensitizers (PS)

Photosensitizers (PS), as substances necessary to carry out photodynamic therapy, should have certain features. An ideal photosensitizer accumulates only in tumors, has low activity in the absence of light and does not remain in the body for long. Since there are difficulties in selecting an appropriate substance that meets all the above criteria, based on the research conducted so far, photosensitizers have been divided into 3 generations, taking into account their molecular properties

(Table 3). First generation photosensitizers are naturally occurring porphyrins that are characterized by skin sensitivity and poor absorption at 630 nm. These features significantly limited their use in many diseases, which is why second-generation photosensitizers were distinguished, characterized by better parameters related to light absorption in a specific area of the spectrum and greater selectivity towards cancer. In turn, third-generation photosensitizers include nanoplatforms, genetically modified systems and carrier-bound systems. These substances show even greater cytotoxicity towards tumor areas. [37,41,45] The most thoroughly researched and most frequently used is 5-aminolaevulinic acid (5-ALA). [43,45]

**Table 1.** Division of photosensitizers into generations and their examples [37,41,45].

| Generations of photosensitizers | Examples of photosensitizers                                                                                                                                                                                                                                                                                                                                                                                   |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1st generation                  | Porfimer sodium (Photofrin)<br>Hematoporphyrin derivative (HpD)<br>Dihematoporphyrin ether [AND]                                                                                                                                                                                                                                                                                                               |
| 2nd generation                  | 5-Aminolaevulinic acid (5-ALA)<br>Benzoporphyrin derivatives (BPD; Verteporfin)<br>Purlytin<br>Foscan<br>Lutex<br>9-Acetoxy-2,7,12,17-tetrakis-( $\beta$ -methoxyethyl)-<br>porphycene (ATMPn)<br>Zinc phthalocyanine CGP55847<br>Naphthalocyanines (NCs)<br>Talaporfin sodium (mono-L-aspartyl chlorin e6, NPe6,<br>TS; Laserphyrin)<br>Boronated porphyrins (BOPP)<br>Temoporfin (m-THPC, Foscan and Foslip) |
| 3rd generation                  | Metallation<br>Expanded metallo-porphyrins<br>Metallochlorins/bacteriochlorins<br>Metallo-phthalocyanines<br>Metallo-naphthocyaninesulfobenzo- porphyrazines (M-<br>NSBP)<br>Metallo-naphthalocyanines                                                                                                                                                                                                         |

5.3. The Use of Photodynamic Therapy in the Treatment of Gliomas

The treatment of gliomas, due to their very poor prognosis, has been the subject of discussion since the 1980s. Current therapeutic methods, such as surgery, radiotherapy, chemotherapy or targeted therapy, do not bring the expected results. [42,45] The current therapeutic standard includes surgical resection combined with radiochemotherapy. [45] The first research results using photodynamic therapy in the treatment of gliomas bring promising results. It was noticed that the use of photodynamic therapy in combination with surgery prolongs the patient's survival time compared to tumor resection alone. [42,46,47] Muller and Willson showed that the median survival in patients who additionally received PDT was 11 months, which means an extension of survival by 3 months compared to patients who did not receive this therapy. [48] In turn, from the results presented by Schwartz et al. shows that in the group of patients with unresectable, newly diagnosed glioblastomas who, in addition to radiotherapy and chemotherapy, were also treated with PDT, a significantly longer median time to disease progression was found, which was 16.0 months compared to 10.2 months in patients who underwent resection. surgery, radiotherapy, and chemotherapy, and

3-year survival of 56.0 vs. 21.0%. [49] In another study, Folgat et al. described patients in whom standard treatment could not be implemented due to the location of the tumor or other contraindications. Photodynamic therapy, radiotherapy and chemotherapy were used, achieving prolonged overall survival (over 24 months) in 10 of 16 patients. [50] Despite the encouraging first research results, some limitations related to photodynamic therapy should also be noted. Resistance to PDT is the main problem that specialists have to face. This may be due to, among others: from the development of cellular resistance or the occurrence of many biological barriers, such as technical limitations of light delivery, insufficient accumulation of the photosensitizer in the tumor, as well as limited transport of the photosensitizer to the area of postoperative resection. [42,43] Further research is needed, focusing on improving light delivery mechanisms and optimizing workflow.

#### *5.4. The Use of Photodynamic Therapy in Patients with Genetically Determined Syndromes that Are Associated with an Increased Risk of Glioma*

The current treatment standards for sporadic gliomas include, in addition to surgical resection, radiotherapy and chemotherapy. These methods may contribute to DNA damage, which in turn may result in the development of secondary cancers, to which patients affected by the above genetic syndromes are predisposed. Due to the rarity of the described syndromes, there is no data on the use of photodynamic therapy in these patients, which requires conducting appropriate research. [12] Taking into account the targeted treatment of cancer, organ-sparing technique and low systemic toxicity, PDT seems to be a method bypassing the problems occurring when using currently recommended procedures, therefore it should be the future of the treatment of these diseases.

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