MAJOR CHANGES IN THE 2016 CNS WHO CLASSIFICATION	
CATEGORY	NOTES
Incorporation of genetically defined entities	
Diffuse gliomas	
Medulloblastomas	
New entities, variants and patterns	
IDH-wildtype and IDH-mutant glioblastoma	
Diffuse midline glioma, H3 K27M–mutant	
Embryonal tumour with multilayered rosettes, C19MC-altered	
Ependymoma, RELA fusion–positive	
Diffuse leptomeningeal glioneuronal tumor	

Anaplastic PXA	
Epithelioid glioblastoma	
Glioblastoma with primitive neuronal component	
Multinodular and vacuolated pattern of ganglion cell tumor	
Deleted entities, variants and terms	
Gliomatosis cerebri	
Protoplasmic and fibrillary astrocytoma variants	
Cellular ependymoma variant	
“Primitive neuroectodermal tumour” terminology	
Addition of brain invasion as a criterion for atypical meningioma	

TUMOR PREDISPOSITION IN NEURO-ONCOLOGY

Brain tumors are seen in numerous cancer susceptibility syndromes and approximately 5% of gliomas occur with familial features [1], suggesting that tumor predisposition syndromes are often under-recognized in neuro-oncology practice. Identification of patients with a hereditary tumor predisposition is critical to allow for surveillance and risk-reduction measures for other health risks associated with the syndrome. In addition, there is potential impact on treatment decisions and prognosis.

RED FLAGS. Several "red flags" in a patient's personal and family history should prompt consideration of a hereditary tumor predisposition syndrome.

In the Patient	In the Family
Multiple primary tumors in the same organ, paired organs, different organs, or multifocality in one organ	First-degree relative with the same or a related tumor, or tumor belonging to a known syndrome
Younger age at tumor diagnosis	Two or more first-degree relatives with rare tumors
Rare histology	Three or more relatives in two generations with tumors of the same or related sites
Rare for gender	
Associated genetic traits, congenital defects or other rare disease	
Presence of cutaneous lesions	

FAMILY HISTORY. The neuro-oncologist's family history should include at least first-degree (parents, children, and full siblings) and second-degree relatives (aunts/uncles, grandparents, half-siblings, grandchildren, and nieces/nephews) on both sides of the family (paternal and maternal). For affected family members the following should be documented: type(s) of primary cancer, age at diagnosis, relationship to patient, and lineage (maternal or paternal). Patients should also be asked about any known tumor susceptibility in the family, any prior genetic testing in the family, and family ethnicity. The presence of consanguinity should be also noted to evaluate the risk of an autosomal recessive syndrome.

See the next page for a practical worksheet

Close Relatives			
Relationship to you Father, mother, brothers/sisters, children, nieces/nephews	**Type of Cancer(s)** Please note site where cancer *started*	**Age at Diagnosis**	**Source of information**

Extended Relatives – FATHER'S SIDE			
Relationship to you Grandfather, grandmother, uncles, aunts, half-siblings, cousins, etc.	**Type of Cancer(s)** Please note site where cancer *started*	**Age at Diagnosis**	**Source of information**

Extended Relatives – MOTHER'S SIDE			
Relationship to you Grandfather, grandmother, uncles, aunts, half-siblings, cousins, etc.	**Type of Cancer(s)** Please note site where cancer *started*	**Age at Diagnosis**	**Source of information**

Signs of potential hereditary cancer	
❒ Multiple tumors Examples: brain tumor and personal or family history of brain tumor, sarcoma, breast cancer, adrenocortical, bronchoalveolar, leukemia, colorectal, uterine, ovarian, stomach, biliary tract, pancreatic, urothelial, or sebaceous gland cancers	❒ Rare tumors Examples: adult Lhermitte-Duclos, choroid plexus carcinoma, hemangioblastoma, psammomatous melanotic schwannoma, optic nerve glioma, vestibular schwannoma
❒ Early onset tumors Examples: brain tumor <18 and 2nd primary cancer, signs of NF1, consanguinity, sibling w/ cancer <18, or fam hx Lynch cancers	❒ Related tumors or other findings Examples: astrocytoma+melanoma, SEGA+TSC findings, medulloblastoma+colon adenomas, PNET+ basal cell SC
Include only blood relatives (not set or married-in relatives) Reference: Genetic Counseling and Tumor Predisposition in Neuro-oncology Practice (2015)	

Medical Geneticists and Genetic Counselors

Medical geneticists are physicians trained to evaluate patients for genetic syndromes through medical and family history (often performed by a genetic counselor working with the geneticist), review of systems, and detailed physical examination. Referral to a medical geneticist is most strongly indicated for evaluation of syndromes with dermatologic manifestations or other findings that require physical examination, such as neurofibromatosis type 1 or tuberous sclerosis. In some cases, medical geneticists can provide a clinical diagnosis of a tumor predisposition syndrome when genetic testing is not available or has incomplete detection. Medical geneticists can also aid in the management of patients with tumor predisposition syndromes and are most often employed at academic institutions.

Genetic counselors are healthcare providers with training in genetics and counseling skills, typically at the masters level. Genetic counselors have expertise in evaluating and counseling patients for hereditary syndromes, as well as coordinating and interpreting genetic testing. Advanced practice genetics nurses are also employed at some cancer centers.

A searchable list of genetics providers (by specialty and location) is available from the National Society of Genetic Counselors and the American College of Medical Genetics.

Genetic Testing

Genetic testing is usually most informative when first performed in an affected family member, or the family member with the highest clinical suspicion of the syndrome, rather than on a family member with no clinical manifestations. Genetic testing comes in many forms. Germline testing for constitutional gene mutations is usually performed on DNA obtained from a peripheral blood sample, although buccal sample are available more recently. If a patient has had a recent blood transfusion, germline testing may need to be delayed to allow for heterologous mixtures to resolve over two to four weeks. In patients who have undergone allogeneic stem cell transplant, germline testing is usually performed on fibroblasts instead.

For most syndromes, full gene sequencing and deletion/duplication testing is recommended. Gene sequencing helps detect smaller gene mutations (e.g. point mutations and small insertions/deletions), while deletion/duplication analysis helps detect larger alterations. Mutation detection rates of each technology vary based on the gene and the types of mutations commonly associated with that syndrome. If there is a known mutation detected in a family, then targeted testing for the familial mutation is usually recommended.

Tumor specimens may also be analyzed as part of a workup for inherited syndromes. In some cases, especially in syndromes with a high rate of somatic mosaicism (e.g., neurofibromatosis type 2), genetic testing on tumor tissue may help detect a causative mutation when germline testing on blood or buccal sample cannot. In addition, tumor immunohistochemistry (IHC) can help screen for individuals likely to have a genetic syndrome and help direct which gene to test in the germline, as in the case of CMRD/Lynch syndrome where IHC identifies loss of one of four mismatch repair proteins.

More recently, next-generation sequencing has become clinically available and has broadened options for genetic testing. Next generation gene panels are identifying a higher proportion of hereditary predisposition in patients with certain cancers compared to previous estimates. For example, approximately 10% of ovarian cancer was classically thought to be hereditary; however, gene panel testing now identifies a pathogenic mutation in one of 13 genes in almost 24% of unselected patients [2].

Practical Considerations

- Timing of genetic testing. Depends on the syndrome, as well as patient and family preference)
- Cost. Single gene testing can cost around $1500, but cost varies based on the testing lab and the size of the gene. Insurance coverage for genetic testing varies based on the test being performed, insurance carrier, and patient history.
- Issues. Genetic testing also has the potential to raise legal, ethical, and psychosocial issues, including non-paternity.
- GINA. The Genetic Information Nondiscrimination Act (GINA) was signed into law in 2008 and prohibits discrimination in health insurance coverage and employment based on family history or genetic testing information.

Some Pitfalls

- Mutation detection rates are never 100%
- Patients may need additional testing as genetics knowledge and testing technologies improve
- Genetic variant of uncertain significance is detected
- Pseudogenes (non-functional copies of genes)
- *De novo* mutations
- Low level mosaicism

Less Commonly Recognized Tumor Predisposition Syndromes

Carney Complex (CNC). Tumors. In the neuro-oncology clinic a diagnosis of melanotic schwannoma, particularly of the psammomatous melanotic schwannoma (PMS) subtype, should prompt consideration of this syndrome.

Constitutional Mismatch Repair Deficiency (CMRD). Tumors. Gliomas and PNETs occur in over one-half of patients with CMRD. Patients have features of NF1, but especially café au lait spots and axillary freckling, often distributed in a segmental, mosaic pattern.

Lynch Syndrome. Lynch syndrome is the major cause of hereditary nonpolyposis colorectal cancer. [3,4] Glioblastoma is the brain tumor associated with Lynch syndrome., however, anaplastic astrocytoma, ganglioglioma, meningioma, and hemangioblastoma have also been reported. Lynch syndrome is one cause of Turcot syndrome.

Cowden's Syndrome (CS). Dysplastic gangliocytoma of the cerebellum, also known as Lhermitte Duclos syndrome (LD), is highly suggestive of this syndrome in adult onset cases[5].

Familial Adenomatous Polyposis Syndrome. The occurrence of medulloblastoma in a patient with familial adenomatous polyposis syndrome (FAP) represents one of the two forms of Turcot syndrome (see Lynch syndrome, above) [6].

Li-Fraumeni Syndrome. Multiple types of brain tumors are seen in patients with Li-Fraumeni syndrome, including astrocytomas, glioblastomas, medulloblastomas, neuroblastomas, and choroid plexus carcinomas. The likelihood of germline *TP53* pathogenic variants in children with choroid plexus carcinoma is very high

Melanoma-Astrocytoma Syndrome. Astrocytomas of all grades, medulloblastoma, ependymoma, meningioma, and vestibular schwannoma have been seen in these patients. Astrocytomas are the most common.

Nevoid Basal Cell Carcinoma Syndrome. Medulloblastoma in association with multiple jaw keratocysts and basal cell carcinomas should trigger consideration of nevoid basal cell carcinoma syndrome (NBCCS), or Gorlin syndrome [7]. bout 20% of cases [8].

Stereotypic Tumor Predisposition Syndromes

Neurofibromatosis type 1 (NF1). Pilocytic astrocytomas of the optic pathway [9], pilocytic or diffuse astrocytomas of the brainstem, cerebellum, or diencephalon [10], plexiform neurofibromas and malignant peripheral nerve sheath tumors are some of the nervous system tumors seen in NF1 [11]. Radiation should be used with great caution due to the high rate of second tumors.

Neurofibromatosis type 2 (NF2). Bilateral vestibular schwannomas (VS) [12], meningiomas, ependymomas, and schwannomas of other cranial or peripheral nerves are also seen.

Tuberous Sclerosis (TS). Subependymal giant cell astrocytomas (SEGA) occur as unilateral or bilateral tumors along the ependymal surface at the foramen of Monroe[13].

von Hipple Lindau Syndrome (VHL). Hemangioblastomas of the pial surface of the cerebellum and spinal cord and of the retina[14].

Familial Glioma. Approximately 5% of patients with glioma have a family member with a glioma [1], usually affecting one first or second degree relative [15]. Glioblastoma is often present in at least one family member but other gliomas are also seen. The risk of a brain tumor in additional family members is low [15].

Sturge-Weber syndrome (encephelotrigeminal angiomatosis). Choroid plexus papillomas may occur in addition to the typical port-wine stain birthmark on the face within the trigeminal nerve distribution.

Therapeutic Implications

The presence of a constitutional genetic alteration leading to a tumor predisposition syndrome would suggest that these patients should avoid physical and chemical agents that can produce additional mutations. From a diagnostic standpoint, therefore, it would be reasonable to avoid tests that employ x-rays (e.g., CT surveillance of the body for systemic cancers) when possible. Ultrasound and whole-body or organ-focused MRI would be reasonable alternatives. From a therapeutic standpoint, radiation therapy and mutagenic chemotherapy agents should be used only after consideration of the syndrome, especially for indolent or low-grade tumors (e.g., low-grade astrocytoma). Importantly, most of the emerging targeted and immune modulated therapies are not mutagenic and thus are good considerations in these patients. Once a malignant or high-grade tumor is diagnosed, the literature supports the use of standard cancer treatment regimens [16].

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