5 Precision Medicine in Neurosurgery

Jeffrey Greenfield, Prajwal Rajappa, and Rachel E. Yan

This chapter includes an accompanying lecture presentation that has been prepared by the authors: Video 5.1.

KEY CONCEPTS

- Precision medicine in cancer has led to significant advances in cancer research.[1] As we look to the future, improving technologies for molecular analyses, drug delivery, intraoperative guidance, and others will continue to expand the scope of precision medicine.
- So far, applications in precision medicine have been limited in neurosurgery, but there is significant potential for use across neurosurgical specialties, including cerebrovascular neurosurgery, trauma, functional neurosurgery, epilepsy, and pediatrics.
- Precision medicine in neurosurgery is both feasible and useful in the clinical setting, as highlighted by the example of its use in pediatric neuro-oncology.

INTRODUCTION

Although there has been a renewed wave of interest in personalized medicine, it is and has always been an integral part of the practice of neurological surgery. All neurosurgical cases may be considered personalized because the surgeon must consider the individual nuances of each case and must understand each patient's unique anatomy. This may also be said of physicians in general, given the evaluation, counseling, and care for patients as individuals. However, with the improvement and development of new technologies, personalized and precision medicine have the potential to augment this and to improve treatments.

In 2016 President Obama instituted the $215 million dollar Precision Medicine Initiative, which included $130 million for the National Institutes of Health to form and study an "All of Us" voluntary national research cohort; $70 million for the National Cancer Institute to identify genomic drivers and target them in cancer treatment; $10 million for the US Food and Drug Administration (FDA) to create databases; and $5 million for the Office of the National Coordinator for Health Information Technology to support privacy and secure exchange of data.[2] Here, precision medicine refers to the more general approach of creating more granular classifications of disease to which therapies can be targeted, rather than targeting individual patient alterations.[3] Although this investment is focused on genomics and cancer, these techniques can be applied to many areas of neurosurgery. Furthermore, the resulting information and technologies can also be used to drive progress in personalized neurosurgical approaches in addition to the current standard of care. In this chapter, we will review the roots of precision medicine in oncology, examine applications across various neurosurgical specialties, then use precision medicine in pediatric neuro-oncology as a model for clinical integration.

CANCER

Ever since the discovery of DNA, there has been an allure to unlocking the secrets of the human genome. With the completion of the Human Genome Project in 2003 and the closely following 50,000-fold drop in sequencing cost, the possibility seems closer than ever, but also farther, owing to increasing recognition of its multifactorial etiology.[4] Behind this dramatic price drop was the invention of next-generation sequencing (NGS). NGS, or massively parallel sequencing, works by sequencing many short reads using polymerase chain reaction (PCR)–based amplification in parallel, followed by alignment to a reference genome.[4]

One major area of promise for whole-genome and whole-exome sequencing is its applications in cancer. Because cancer tends to be extremely heterogeneous between individuals and within the tumor itself, understanding its unique features is critical to successful therapy and improving outcomes. Furthermore, because samples are often accessible during resection or biopsy, molecular profiling is becoming more routine. In some cases, understanding underlying genetic alterations, such as the *BCR-ABL* fusion, has led to resounding success (e.g., the development of imatinib for chronic myelogenous leukemia).[1] In neuro-oncology, there have been promising results from inhibition of $BRAF^{V600E}$ (and other targeted therapies) in $BRAF^{V600E}$-mutant gliomas.[5,6] Unfortunately, targeting one lesion is rarely enough owing to tumor evolution.[7,8] For more about molecular biology and genomics, see Chapter 61.

Beyond the genetic level, there are often interacting alterations at the epigenetic (epigenome), transcriptional (transcriptome), protein (proteome), posttranslational (e.g., phosphoproteome), protein-protein (interactome), and chemical (metabolome) levels. There are also complex interactions within the tumor microenvironment, including those with infiltrating myeloid cells, lymphocytes, vasculature, and stroma,[9] as well as with systemic factors, such as the immune system[10] and the gut microbiome.[11] This interplay between tumor-intrinsic and tumor-extrinsic factors is critically important, particularly with an increasing focus on the design and application of immunotherapies for cancer.[12,13] Nevertheless, with the rapidly progressing pace of technology, we are also making progress in understanding these factors.

Clinical Application

Although NGS has led to significant advances in research, it is still emerging in its clinical applications. Comprehensive profiling remains expensive on an individual level, and analysis remains resource intensive and lacking in standardization.[14] Some centers have reported promising results from NGS approaches,[15,16] but often the equipment, personnel, and training requirements preclude this for small centers, even when limited to one technology. Furthermore, there is still a significant lack in the areas of clinical research, infrastructure, and insurance coverage, which are necessary for expansion.[17] As these issues are slowly resolved and

technologies continue to improve and decrease in cost, we expect increasing adoption to occur.

Currently, more accessible options include Sanger sequencing and microarrays. Sanger sequencing is the "first-generation" sequencing technology that preceded NGS and was used to complete the Human Genome Project. It uses chain termination to quickly provide a high-fidelity sequence of small regions, although it requires high variant allele frequency for detection and does not provide information about copy number.[18] It is best used for identifying de novo alterations in known genes. Meanwhile, microarrays can be used to detect selected panel of alterations[18] and are often commonly used for precision medicine clinically.[19] This is a reasonable approach at this time and has the benefit of translating research findings using NGS to the clinic at a lower cost.

To expand the therapeutic repertoire, several clinical trials have been designed with new strategies, such as the "umbrella" or "basket" strategies. Umbrella trials test multiple targeted therapies within tumor types; basket trials test one targeted therapy against a particular alteration across tumor types.[20] The phase 2 NCI-MATCH clinical trial is currently recruiting patients across many cancers, including glioma, to examine whether a panel of drugs will benefit patients with certain genetic abnormalities.[21] Trials with "*n*-of-1" methodology have also been proposed and performed, though there is dissention over the validity of the method.[22] New and rigorous trial designs are needed to accelerate progress for the newly stratified populations.

Drug Discovery and Selection

In line with the reasoning behind precision medicine clinical trials, recently the FDA has begun approving drugs for specific alterations, rather than tumor types, including pembrolizumab for cancers that have a high level of microsatellite instability or are mismatch repair deficient and larotrectinib for cancers with *TRK* fusion.[20] Precision medicine has also changed drug discovery by making identifying putative targets relatively inconsequential.[23] Combined with improving capabilities for synthesizing new antibodies and small-molecule inhibitors against these targets, targeting specific alterations is becoming increasingly accessible. Correlations between gene expression and polymorphisms with response to drugs may also facilitate treatment selection for individual patients when there are multiple options. The bottleneck has shifted from finding targets to validating their biologic significance. This is partially addressed by personalized drug screens, in which patient tumor models, such as organoids,[24] humanized mouse models,[25] or neural systems on a chip,[26] are exposed to a panel of drugs to determine what therapies might work best.

Nanoparticles and Drug Delivery

Even when a targeted therapy is successfully identified, a significant challenge in treating central nervous system (CNS) malignancies is the problem of drug delivery across the blood-brain barrier. To counter this, nanoparticles have been developed, including liposomes, nanoparticle albumin-bound technology, polymeric nanoparticles, magnetic nanoparticles, and molecular-targeted nanoparticles.[27] They may accumulate by means of the enhanced permeability and retention (EPR) effect, whereby large molecules accumulate in the tumor microenvironment owing to abnormal vasculature and reduced lymphatic drainage, but generally require further targeting for intracellular uptake. For example, polymeric nanoparticles have been developed to recognize platelet-derived growth factor receptor β (PDGFR-β) on glioblastoma cells and deliver dactolisib.[28]

Neurosurgeons in Targeted Therapy

The linchpin of targeted therapy for CNS tumors is sampling, and this responsibility falls on the shoulders of neurosurgeons and their teams. This is also true on a broader scale. Regardless of the neurosurgical pathologic condition, neurosurgeons are often responsible for the sampling that enables downstream analyses and discoveries. Fig. 5.1 shows a generalized precision medicine workflow. Safety remains the primary concern, but if the surgeon feels it is safe, one may consider a secondary priority in tumor resection to collect enough specimen for sequencing, preferably from multiple sites to account for tumor heterogeneity.[29,30] Similarly, in needle biopsy, it is recommended that the surgeon obtain at least two different biopsy samples using the same needle tract at different tumor depths within a bur hole.[30] After the material is collected, either a neuropathologist or a team member should be available to make sure samples are both immediately snap frozen and placed under sterile conditions with media for culture.[29] Immediate analysis is critical because many tumors are rapidly evolving. If possible, tumor evolution should also be tracked throughout time to evaluate responses to therapy and disease progression,[30,31] which often evolve in response to treatment.[32,33] Additionally, when considering metastases, even though the primary cancer may already have been profiled, there may be significant differences between the primary and metastatic tumor, including differences in drivers.[34,35] Interdisciplinary collaboration is necessary to streamline the pipeline, from collection to analysis to biobanking and research. Cross-institutional collaboration is also recommended to collect the volume of data needed to draw statistically significant conclusions and to accelerate research.

Work is also being done on intraoperative genotyping to assist in neurosurgical decision making on whether to continue pursuing aggressive resection or not. Shankar and coworkers have reported the use of their OperaGen assay to evaluate *TERT* promoter and *IDH1* status within 60 minutes.[36] Although still limited at this time, this method has potential to complement histologic analysis and to provide further detail, particularly with increasing knowledge about molecular classifications.

Intraoperative Guidance and Imaging

Although every surgical case is, by definition, tackled in a personalized way, they may be augmented by techniques to improve surgical planning and provide intraoperative guidance. Achievement of gross total resection of tumors is often critical to overall survival,[37] making it a priority in research. However, this is greatly complicated by diffuse margins and variations in individual anatomy and functionality. Current modalities to improve resections include intraoperative neuronavigation,[38] which uses preoperative CT or MRI for guidance, and intraoperative MRI,[39-41] which monitors in real time (see Chapters 154, 156, and 157). Intraoperative ultrasonography,[42] intraoperative Raman spectroscopy,[43] and hyperspectral imaging[44] have also been proposed as noninvasive imaging modalities, although further exploration is needed.[42]

Nanoparticles that are used for drug delivery also have applications in imaging. Another modality that holds promise is near-infrared fluorescence paired with optical fluorescence contrast agents. These contrast agents may be acquired via EPR or specifically targeted to unique features on tumors or stimuli in their microenvironment.[45] An example of this is a zwitterionic near-infrared fluorophore that can be conjugated with targeting ligands such as EGFR.[46,47] Other targeted fluorophores include small-molecule florophores,[48] tumor-specific antibody- or peptide-conjugated fluorophores, and activatable fluorophores.[49-51]

Fluorescent tumor markers may also be used to improve margins for high-grade gliomas in adults, as well as in combination with other imaging techniques, such as intraoperative neuronavigation

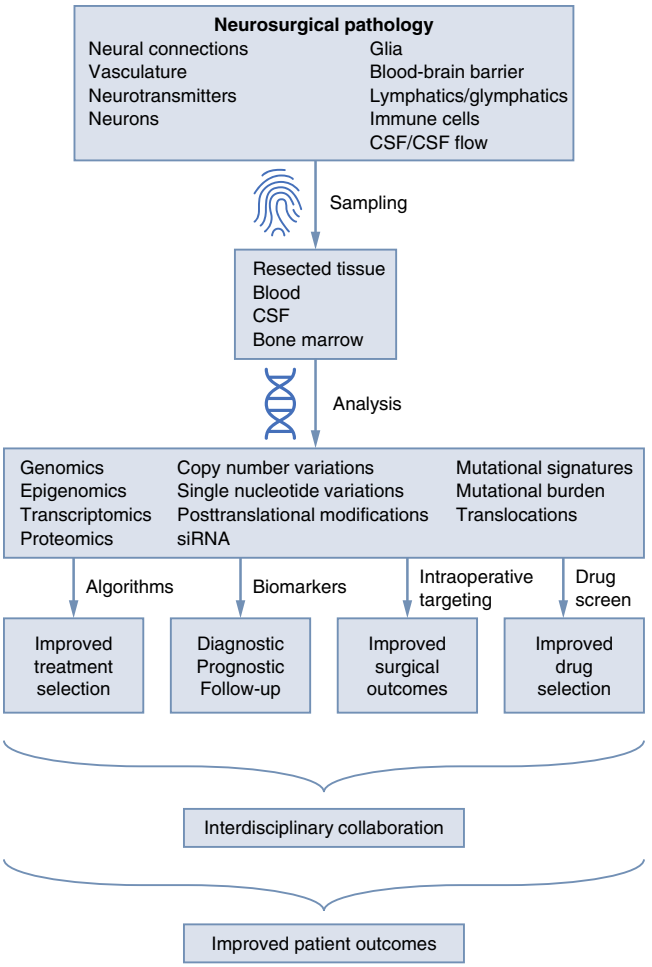

Figure 5.1. A generalized workflow for precision medicine in neurosurgery. When safe and convenient, sampling should be as comprehensive as is appropriate to understand the interacting factors of each pathologic condition. Shown are just some of the different analytic methods available, which may lead to benefits such as algorithms for improved treatment selection; biomarkers for diagnostic, prognostic, and follow-up purposes; intraoperative markers for improved surgical outcomes, and drug screens for better drug selection. Through interdisciplinary collaboration, precision medicine approaches can lead to overall improved patient outcomes. *CSF,* Cerebrospinal fluid.

and iMRI.[38,52] These agents include sodium fluorescein and 5-aminolevulinic acid (5-ALA) with protoporphyrin IX (PpIX) for high-grade glioma in adults.[53,54] Though there are concerns about specificity and sensitivity,[49] there is promising evidence about the utility of 5-ALA in maximizing safe resections.[55]

Overall, these precision agents allow for high-resolution imagining and guidance. With these, our capabilities for already personalized procedures only continue to improve. Work is also being done to combine these imaging modalities with three-dimensional modeling techniques for use as surgical augmentation (augmented reality [AR]),[56-58] or preoperative virtual reality (VR) models.[59-61] For more about AR, see Chapter 30.

Adaptive Hybrid Surgery

Adaptive hybrid surgery (AHS) is a term describing a planned subtotal resection. Beyond this, it is a tailored approach to the patient and tumor, balancing the risks and benefits of various modalities, including microsurgical resection and radiation.[62] This is commonly used for resection of vestibular schwannomas (VSs), which are benign, slow-growing neoplasms of the cerebellopontine angle at the vestibular portion of cranial nerve VIII. VSs provide a challenge owing to their location, which may result in risks of hearing and/or facial nerve disruption during resection. For VSs under 3 cm in diameter, stereotactic radiosurgery is the standard of care. For VSs that are too large to be an ideal radiosurgical target, gross total resection has traditionally been performed. However, emerging research suggests that AHS provides advantages in terms of facial nerve function and hearing preservation.[63] This is tailored to the patient and tumor target by balancing maximization of resection and preservation of a good radiosurgical target.[64] In the future, it is likely that this framework may be used for other tumors in which it is difficult to achieve gross total resection without disrupting critical structures.

SUBSPECIALTY IMPLICATIONS

While oncology has paved the path in precision medicine, other neurosurgical specialties also utilize these approaches. With the understanding that all people are mosaics,[65] some of the major controversies in neurosurgery may be resolved by understanding the unique profiles of individuals, or the answers may be more finely granulated by sorting answers into silos for specific profiles. Here, we provide a brief review of some of the major implications for each subspecialty and encourage more research in precision medicine across the field. For a general overview for what a precision medicine workflow could look like, see Fig. 5.1.

Cerebrovascular Neurosurgery

Highlighted by the example of stroke, the heterogeneity of the population may lead to vastly different outcomes for similar pathologic conditions. In stroke, current guidelines rule out intravenous thrombolysis for patients with acute stroke onset longer than 4.5 hours,[66-68] although a case study has found symptom resolution 80 days after symptom onset.[69,70] Subsequent studies have supported moving away from these strict cutoffs in recognition of these spectrums. For example, CT perfusion has been used to select patients who are likely to benefit from reperfusion after this window has closed.[71,72] This has led to an update in the 2018 American Heart Association (AHA) guidelines, recommending reperfusion up to 24 hours after onset, based on imaging findings.[73] Genetically, 35 loci have been linked to stroke risk, with certain variations linked to specific subtypes,[74] but no studies to our knowledge have evaluated differences in treatment response. By understanding the mechanism behind these differences, we may be able to better predict who should receive intravenous thrombolysis, mechanical intervention, or no treatment.

Similarly, although the genetics of intracranial aneurysms has been well studied in genome-wide association studies, in case-control studies for gene association and with whole-exome sequencing,[75] little is known about the differences between populations (see Chapter 424). Genetic syndromes known to be associated with elevated aneurysm incidence include autosomal dominant polycystic kidney disease, type IV Ehlers-Danlos syndrome, and pseudoxanthoma elasticum.[76] Based on the diagnosis of autosomal dominant polycystic kidney disease, screening is recommended.[76] With better understanding of the more granulated profiles, recommendations for additional monitoring and intervention, or the lack thereof, may be asserted.

Another precision approach for aneurysm monitoring that has been proposed is ferumoxytol uptake. Uptake of ferumoxytol in aneurysm walls, as imaged with MRI, has been associated with aneurysm instability and has been proposed as a marker for early intervention.[77,78] Ferumoxytol is an iron oxide nanoparticle

that is cleared by reticuloendothelial macrophages; therefore ferumoxytol in the aneurysm walls may indicate macrophage infiltration.[79] This highlights how biology can be used to develop new tools for precision care.

Considering cerebral vascular malformations, it has long been asked why some lesions rupture and hemorrhage while others remain asymptomatic. Some progress toward answering this question has been made by investigating heritable models, such as *CCM* mutations[80] and polymorphisms.[81] Understanding these alterations and their effects on the CCM trimer structure, interactions, and signaling has led to significant advances in our understanding of the pathogenesis.[82] Although not yet translated, understanding the effects of the specific genetic lesions may eventually help to inform decisions such as whether observation or intervention is better for a given patient in unruptured cases. For more information, see Chapter 460.

Precision medicine may also be used to improve surgical techniques in cerebrovascular procedures. For example, indocyanine green (ICG) fluorescence has been used to improve visualization in resection of arteriovenous malformations, extracranial-intracranial bypass, and aneurysm surgery.[49]

Trauma

Traumatic brain injury (TBI) and spinal cord injury (SCI) may affect anyone, resulting in extremely heterogeneous patient populations. This is also true of their variations in severity and presentation, particularly with TBI. In order to learn more about their mechanisms, several gene polymorphisms have been investigated that may correlate with outcomes. These have largely arisen from genome-wide association studies identifying common polymorphisms associated with risk for and worse outcomes after TBI or SCI. Identified polymorphisms have spanned many genes, although a systematic review found only *APOE* promoter −219G/T polymorphism and the BDNF Met/Met genotype to be consistently associated with risk.[83] Despite these associations, few mechanisms for their associations have been established. For more on the genetics of TBI, please see Chapter 377.

Additionally, because of the difficulty of diagnosis and lack of prognostic information, biomarkers have been of significant interest in TBI and SCI. Identifying reliable biomarkers may help improve treatment selection, presurgical planning, and understanding of prognosis. Markers that have been proposed are associated with neuronal, axonal, and astroglial injury, and inflammation.[84,85] In addition to genomic methods, miRNA profiling has identified significant associations with various regulatory miRNAs,[86,87] which have also been proposed as therapeautics,[88] and proteomic profiling has identified biomarkers directly from protein level data.[89-91] For more about biomarkers for TBI, see Chapter 379.

Spine

Degenerative disk disease is extremely common. Based on twin studies, including a large Finnish twin study,[92] an Australian MRI twin study,[93] and several case reports,[94] it seems that it also has a strong heritable component. A population-based study measuring genetic distance between patients found that first-degree relatives have more than five times the risk of developing cervical spondylotic myelopathy.[95] When looking for associated alterations, degenerative disk disease has been associated with a number of collagen-related genes and other alleles in various ethnic populations, although the association often fails to be shown in meta-analysis.[96-98] This may indicate linkage within these populations, although further studies are needed. There have also been strong genetic associations found in ossification of the posterior longitudinal ligament (OPLL). A genome-wide association study identified and confirmed six loci to be associated with OPLL in a Japanese population,[99] and recent whole-genome sequencing studies have identified common mutations among Chinese OPLL patients[100,101]— although again, further studies are needed across populations.

As a proof of concept, Ward and colleagues performed a genome-wide association study, identified 53 associated single nucleotide polymorphisms (SNPs) with scoliotic curvature in Caucasian females, and calculated the risk of curvature progression, which was marketed as "ScoliScore."[102,103] Although this failed to be replicated in more diverse populations, a larger study including more diverse populations could follow a similar workflow to define a more applicable algorithm in this and other disorders.

Functional Neurosurgery

Functional neurosurgery has grown alongside personalized neurosurgery owing to the necessity of understanding the precise location to lesion or stimulate, where millimeters are often critical.[104,105] Beyond targeting discrete gray matter nuclei, there has also been increasing development toward targeting white matter tracts and functional networks, which are often more variable between individuals.[106] This requires use of additional imaging methods such as diffusion-weighted imaging (DWI) and resting state functional MRI (rsfMRI) (see Chapters 107 and 108).[107] With these and other advances in imaging, connectome targeting is becoming available. Under this framework, normalization of individual patient brains into an average brain allows specific electrode localization and estimation of the volume of tissue activated, which can then be used to precisely target probable locations of efficacy or certain clinical benefits and avoid adverse events.[105,108] Large-scale initiatives such as the Human Connectome Project will increase accuracy and may make it possible to further customize this for individual patients.[107]

Functional neurosurgery has also looked toward biologically based treatments for neurological disorders. Adeno-associated virus (AAV)–glutamic acid decarboxylase (GAD) gene therapy to the subthalamic nucleus has now successfully been used in a double-blind randomized phase 2 trial for Parkinson disease.[109] This has led to development of similar approaches to deliver aromatic acid decarboxylase (AADC) to the striatum,[110] all three dopamine biosynthetic genes to the striatum,[111] and genes for growth factors to prevent neurodegeneration.[112] There is now also a search for biomarkers to predict efficacy,[111] which may also help to identify the best treatment for each patient. Furthermore, development is underway to target specific forms of Parkinson disease, including treatment with wild-type glucocerebrosidase (GBA) for GBA-mutated forms and silencing of α-synuclein for syncleinopathy.[111,113] These approaches will also likely have broad implications for other neurological diseases.

Epilepsy

Epilepsy is a promising target for precision medicine owing to its heterogeneous etiology and presentations, including lesional, nonlesional, and genetic forms (see Chapter 80). The genetic causes range from mutations in ion channel coding genes to those in the synaptic vesicle cycle, metabolism, and neurotransmitter receptors.[114] Because of this, genetic testing is more common and useful,[115] although it is not universal because most causes are still not understood at a genetic level.[114] In order to address this, many large-scale cohort studies are being undertaken. One example is the EPISTOP study, which is prospectively evaluating biomarkers of epileptogenesis in one of the genetic models of epilepsy (tuberous sclerosis complex) across Europe and in the United States. Within the study, one branch evaluated early targeted treatment against the genetic lesion,[116] providing valuable insight to this unique population.

Although there are many medical treatments available for epilepsy, often they do not work or they lose efficacy. Epilepsy surgery aims to resect or disconnect the epileptogenic zone (EZ) that causes seizures.[117] Because this may vary greatly from patient to patient, many modalities have been developed to identify this precise location for each patient. These include high-resolution MRI and scalp video-electroencephalography (EEG) monitoring, as well as additional modalities such as functional MRI (fMRI), an EEG-fMRI combination, fluorodeoxyglucose–positron emission tomography (FDG-PET), ictal single-photon emission computed tomography (SPECT), magnetoencephalography (MEG), and magnetic resonance spectroscopy (MRS), alongside psychological evaluation (see Chapters 84–87). At the same time, it is important to avoid damaging functional areas of the brain during surgery, and these also vary from person to person. If the lesion is too close to a functional area, surgery is not advisable. This can be determined with Wada testing, which entails injection of anesthetic as a reversible method of ablation and evaluation of various language, memory, and motor tests, though it may be increasingly replaced by fMRI.[118] Cortical stimulation mapping may also be done preoperatively and intraoperatively using electrocorticography. If further localization is needed, intracranial electroencephalography may be performed (see Chapters 88 and 89). These strategies also provide valuable information that can be used outside of the operating room—for example, a patient-specific algorithm has been proposed to predict seizure onset.[119] Significant progress has been made in personalized approaches to epilepsy, and it will be interesting to see them further develop, as well as cross-disciplinary applications.

Pediatrics

When pediatric and adult epileptologists in North America were surveyed on whether they would order genetic testing for an 18-year-old suspected to have epilepsy, it is interesting to note that pediatric neurologists were much more likely to order genetic testing.[120] Although this is a very limited finding, it hints at some of the particular relevance of precision medicine to pediatrics. Because genetic disorders classically tend to present in childhood, genetic testing has long been a part of pediatric practice. Furthermore, because these diseases are often rare, including the individual tumor types within the spectrum of pediatric brain tumors (see Chapter 231), precision medicine is almost an inherent approach. Despite this, research has been limited in other pediatric pathologic conditions in the neurosurgical space.

For example, craniosynostoses have been traditionally divided into syndromic and nonsyndromic craniosynostosis, although nonsyndromic cases may also have genetic mechanisms (see Chapter 218). One set of craniosynostoses is characterized by activation of *FGFR2*, including Crouzon, Apert, Pfeiffer, Antley-Bixler, Beare-Stevenson cutis gyrata, Jackson-Weiss, bent bone dysplasia, and Saethre-Chotzen–like syndromes.[121] Although understanding of the mechanism is increasing, more research is needed to understand why its presentations are so heterogeneous and whether these alterations may be targeted with drugs. This understanding could also help in planning the timing and strategy of surgery.

Another significant question in pediatric neurosurgical practice is when to operate on Chiari I malformations. The etiology of Chiari malformations is not well understood, although an underlying genetic etiology is highly suspected.[122,123] Several cases have been studied using whole-exome sequencing[124,125] and comparative genome hybridization (for copy number alterations),[126] but patient numbers tend to be limited. There have also been numerous case reports of associations between Chiari I malformation and various syndromes, including tuberous sclerosis complex,[127] neurofibromatosis type 1,[128,129] *PTEN* hamartoma syndrome,[130] Ehlers-Danlos syndrome,[131] Floating-Harbor syndrome,[132] and others. A case-control association study of SNPs across 58 candidate genes in 415 Chiari I malformation patients revealed a risk haplotype in *ALDH1A2* and *CDX1*,[133] although further studies are needed to validate this in independent cohorts. Larger, more comprehensive studies using precision medicine methodology will likely help to verify and collate these pieces of data.

OUTLOOK: CLINICAL INTEGRATION INTO NEUROSURGICAL PRACTICE

The crossover between precision medicine and neurosurgery has already occurred and continuously strengthens within each discipline. One example of the clinical integration of precision medicine has been in the treatment of brain tumors. An increasing recognition of their diverse molecular etiologies has been highlighted by several new molecularly based subclassifications for CNS tumors in the World Health Organization Classification of CNS Tumors, 2016.[135] We further focus in on pediatric brain tumors, which are exceedingly rare and potentially even more diverse than adult brain tumors.

Across cancer types, there have been a multitude of trials over the past years on integrating precision medicine approaches into the clinic, commencing with adult cancers in the Michigan Oncology Sequencing Center (MI-ONCOSEQ) project starting in 2011,[16] followed by a similar trial for pediatric cancers, PEDS-MIONCOSEQ, in 2012.[15] In the pediatric trial, of the 91 of 102 enrolled patients with agreement to receive incidental findings, 42 potentially actionable findings were identified. This resulted in action through treatment changes for 14 patients, genetic counseling for 9 patients, and both for one patient. Reasons that potentially actionable findings were not acted on included remission, the treating physician's judgment, limited access to drugs, family preference, and timing.[15]

In pediatric CNS tumors specifically, clinically relevant findings were identified in 81% of 31 tumors (enriched for high-grade gliomas),[136] 56% of 203 brain tumors,[137] 80% of 68 CNS tumors prospectively,[138] and 63% of 50 high-risk brain tumors[139] in four studies of clinical integration. These studies used targeted exome sequencing and RNA-Seq RNA sequencing to profile these tumors. Limitations to clinical integration include lack of targeted therapies that are FDA approved for pediatric brain tumors and unknown clinical significance for most of the variants identified.[136-139] These will require further studies and biologic validation before they are actionable. Despite these limitations, the demonstrated feasibility and potential utility of precision medicine in pediatric brain tumors has spurred a recent consensus recommendation for further pursuit.[140]

We have a collaborative program at Weill Cornell Brain and Spine and the Englander Institute for Precision Medicine integrating precision medicine into the standard of care for our pediatric patients with CNS tumors. Our patient's tumors and blood samples receive whole-exome sequencing of their DNA, as well as RNA sequencing and/or methylation array profiling in some cases. We have expanded beyond the methodology of previous studies by incorporating targeted drug screen assays and patient-derived xenografts for selected cases. These in vivo approaches helped to validate our biologic hypotheses (unpublished data). Alterations of significant clinical relevance are presented at multidisciplinary tumor boards alongside clinical, radiologic, and histologic findings, demonstrating the importance of a collaborative approach. In the future, we expect developing technologies to further improve precision treatments.

CONCLUSION

While one might say that each neurosurgical case already is inherently personalized, precision medicine has a wealth of

opportunity to offer to neurosurgery. Most work in precision medicine has been done in cancer, but it may also be applied to other neurosurgical conditions. The use of newer precision medicine techniques, such as multi-omic profiling, may increase our understanding of chronic neurological conditions and diseases significantly. With this understanding, we will be able to improve medical and surgical decision making, discover new drugs and targets, and improve surgical techniques. Precision medicine is just beginning to take root in neurosurgery, but it has the potential to improve outcomes across the neurosurgical spectrum.

SUGGESTED READINGS

Arboleda VA, Xian RR. An overview of DNA analytical methods. *Methods Mol Biol (Clifton, NJ)*; 2019;1897:385–402.

Dong J, Lu M, He X, et al. Identifying the role of microRNAs in spinal cord injury. *Neurol Sci*. 2014;35(11):1663–1671.

Dugger SA, Platt A, Goldstein DB. Drug development in the era of precision medicine. *Nat Rev Drug Discov*. 2017;17:183.

Goodwin S, McPherson JD, McCombie WR. Coming of age: ten years of next-generation sequencing technologies. *Nat Rev Genet*. 2016;17(6):333–351.

Hasan D,M, Mahaney K,B, Magnotta V,A, et al. Macrophage imaging within human cerebral aneurysms wall using ferumoxytol-enhanced MRI: a pilot study. *Arterioscler Thromb Vasc Biol*. 2012;32(4):1032–1038.

Helbig KL, Farwell Hagman KD, Shinde DN, et al. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. *Genet Med*. 2016;18:898.

Hierro C, Matos I, Martin-Liberal J, Ochoa de Olza M, Garralda E. Agnostic-histology approval of new drugs in oncology: are we already there? *Clin Cancer Res*. 2019;25(11):3210–3219.

Martinkovic L, Hecimovic H, Sulc V, Marecek R, Marusic P. Modern techniques of epileptic focus localization. *Int Rev Neurobiol*. 2014;114:245–278.

Miklja Z, Pasternak A, Stallard S, et al. Molecular profiling and targeted therapy in pediatric gliomas: review and consensus recommendations. *Neuro-Oncology*. 2019.

Mochizuki AY, Frost IM, Mastrodimos MB, et al. Precision medicine in pediatric neurooncology: a review. *ACS Chem Neurosci*. 2018;9(1):11–28.

Musolf AM, Ho WSC, Long KA, et al. Small posterior fossa in Chiari I malformation affected families is significantly linked to 1q43-44 and 12q23-24.11 using whole exome sequencing. *Eur J Hum Genet*. 2019;27(10):1599–1610.

Nemeth E, Krzystanek M, Reiniger L, et al. The genomic imprint of cancer therapies helps timing the formation of metastases. *Int J Cancer*. 2019;145(3):694–704.

Panenka WJ, Gardner AJ, Dretsch MN, Crynen GC, Crawford FC, Iverson GL. Systematic review of genetic risk factors for sustaining a mild traumatic brain injury. *J Neurotrauma*. 2017;34(13):2093–2099.

Patel AA, Spiker WR, Daubs M, Brodke DS, Cannon-Albright LA. Evidence of an inherited predisposition for cervical spondylotic myelopathy. *Spine (Phila Pa 1976)*. 2012;37(1):26–29.

Phillips KA, Trosman JR, Deverka PA, et al. Insurance coverage for genomic tests. *Science (New York, NY)*. 2018;360(6386):278–279.

Ramkissoon SH, Bandopadhayay P, Hwang J, et al. Clinical targeted exome-based sequencing in combination with genome-wide copy number profiling: precision medicine analysis of 203 pediatric brain tumors. *Neuro-Oncology*. 2017;19(7):986–996.

Rinaldi C, Bramanti P, Scimone C, et al. Relevance of CCM gene polymorphisms for clinical management of sporadic cerebral cavernous malformations. *J Neurol Sci*. 2017;380:31–37.

Rodney T, Osier N, Gill J. Pro- and anti-inflammatory biomarkers and traumatic brain injury outcomes: a review. *Cytokine*. 2018;110:248–256.

Rutkowski S, Modena P, Williamson D, et al. Biological material collection to advance translational research and treatment of children with CNS tumours: position paper from the SIOPE brain tumour group. *Lancet Oncol*. 2018;19(8):e419–e428.

Sarkis GA, Mangaonkar MD, Moghieb A, et al. The application of proteomics to traumatic brain and spinal cord injuries. *Curr Neurol Neurosci Rep*. 2017;17(3):23.

Shankar GM, Francis JM, Rinne ML, et al. Rapid intraoperative molecular characterization of glioma. *JAMA Oncol*. 2015;1(5):662–667.

Suero Molina E, Schipmann S, Stummer W. Maximizing safe resections: the roles of 5-aminolevulinic acid and intraoperative MR imaging in glioma surgery-review of the literature. *Neurosurg Rev*. 2019;42(2):197–208.

Tomaszewski W, Sanchez-Perez L, Gajewski TF, Sampson JH. Brain tumor microenvironment and host state: implications for immunotherapy. *Clin Cancer Res*. 2019;25(14):4202–4210.

Xu Z, Rui YN, Hagan JP, Kim DH. Intracranial aneurysms: pathology, genetics, and molecular mechanisms. *Neuromolecular Med*. 2019;21(4):325–343.

Yang SH, Lou M, Luo B, Jiang WJ, Liu R. Precision medicine for ischemic stroke, let Us move beyond time is brain. *Transl Stroke Res*. 2018;9(2):93–95.

Zhang J, Yao TW, Hashizume R, et al. Combined BRAF(V600E) and MEK blockade for BRAF(V600E)-mutant gliomas. *J Neurooncol*. 2017;131(3):495–505.

See a full reference list on ExpertConsult.com

REFERENCES

1. Sacha T. Imatinib in chronic myeloid leukemia: an overview. *Mediterr J Hematol Infect Dis*. 2014;6(1). e2014007-e2014007.
2. FACT SHEET: President Obama's Precision Medicine Initiative. https://obamawhitehouse.archives.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative. Published 2015. Updated January 30, 2015. Accessed June 16, 2019.
3. Katsnelson A. Momentum grows to make 'personalized' medicine more 'precise'. *Nat Med*. 2013;19:249.
4. Goodwin S, McPherson JD, McCombie WR. Coming of age: ten years of next-generation sequencing technologies. *Nat Rev Genet*. 2016;17(6):333–351.
5. Zhang J, Yao TW, Hashizume R, et al. Combined BRAF(V600E) and MEK blockade for BRAF(V600E)-mutant gliomas. *J Neurooncol*. 2017;131(3):495–505.
6. Toll SA, Tran HN, Cotter J, et al. Sustained response of three pediatric BRAF(V600E) mutated high-grade gliomas to combined BRAF and MEK inhibitor therapy. *Oncotarget*. 2019;10(4):551–557.
7. Gatenby RA. A change of strategy in the war on cancer. *Nature*. 2009;459:508.
8. Ding L, Ley TJ, Larson DE, et al. Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. *Nature*. 2012;481:506.
9. Tomaszewski W, Sanchez-Perez L, Gajewski TF, Sampson JH. Brain tumor microenvironment and host state: implications for immunotherapy. *Clin Cancer Res*. 2019;25(14):4202–4210.
10. Chongsathidkiet P, Jackson C, Koyama S, et al. Sequestration of T cells in bone marrow in the setting of glioblastoma and other intracranial tumors. *Nat Med*. 2018;24(9):1459–1468.
11. Forssberg H. Microbiome programming of brain development: implications for neurodevelopmental disorders. *Dev Med Child Neurol*. 2019;61(7):744–749.
12. Sayour EJ, Mitchell DA. Immunotherapy for pediatric brain tumors. *Brain Sci*. 2017;7(10).
13. Sampson JH, Maus MV, June CH. Immunotherapy for brain tumors. *J Clin Oncol*. 2017;35(21):2450–2456.
14. Stenzinger A, Allen JD, Maas J, et al. Tumor mutational burden standardization initiatives: recommendations for consistent tumor mutational burden assessment in clinical samples to guide immunotherapy treatment decisions. *Genes Chromosomes Cancer*. 2019;58(8):578–588.
15. Mody RJ, Wu YM, Lonigro RJ, et al. Integrative clinical sequencing in the management of refractory or relapsed cancer in youth. *JAMA*. 2015;314(9):913–925.
16. Roychowdhury S, Iyer MK, Robinson DR, et al. Personalized oncology through integrative high-throughput sequencing: a pilot study. *Sci Transl Med*. 2011;3(111): 111ra121-111ra121.
17. Phillips KA, Trosman JR, Deverka PA, et al. Insurance coverage for genomic tests. *Science (New York, NY)*. 2018;360(6386):278–279.
18. Arboleda VA, Xian RR. An overview of DNA analytical methods. *Methods Mol Biol (Clifton, NJ)*.2019;1897:385–402.
19. Li X, Quigg RJ, Zhou J, Gu W, Nagesh Rao P, Reed EF. Clinical utility of microarrays: current status, existing challenges and future outlook. *Curr Genomics*. 2008;9(7):466–474.
20. Hierro C, Matos I, Martin-Liberal J, Ochoa de Olza M, Garralda E. Agnostic-histology approval of new drugs in oncology: are we already there? *Clin Cancer Res*. 2019;25(11):3210–3219.
21. Flaherty KT, Gray R, Chen A, et al. The Molecular Analysis for Therapy Choice (NCI-MATCH) Trial: Lessons for Genomic Trial Design. *J Natl Cancer Inst*. 2020 Jan 10;djz245. doi: 10.1093/jnci/djz245. Online ahead of print.
22. Mirza RD, Guyatt GH. A randomized clinical trial of n-of-1 trials—tribulations of a trial. *JAMA Intern Med*. 2018;178(10):1378–1379.
23. Dugger SA, Platt A, Goldstein DB. Drug development in the era of precision medicine. *Nat Rev Drug Discov*. 2017;17:183.
24. Wang Z, Wang SN, Xu TY, Miao ZW, Su DF, Miao CY. Organoid technology for brain and therapeutics research. *CNS Neurosci Ther*. 2017;23(10):771–778.
25. Chen Q, Wang J, Liu WN, Zhao Y. Cancer Immunotherapies and humanized mouse drug testing platforms. *Transl oncol*. 2019;12(7):987–995.
26. Haring AP, Sontheimer H, Johnson BN. Microphysiological human brain and neural systems-on-a-chip: potential alternatives to small animal models and emerging platforms for drug discovery and personalized medicine. *Stem Cell Rev*. 2017;13(3):381–406.
27. Mochizuki AY, Frost IM, Mastrodimos MB, et al. Precision medicine in pediatric neurooncology: a review. *ACS Chem Neurosci*. 2018;9(1):11–28.
28. Monaco I, Camorani S, Colecchia D, et al. Aptamer functionalization of nanosystems for glioblastoma targeting through the blood-brain barrier. *J Med Chem*. 2017;60(10):4510–4516.
29. Rutkowski S, Modena P, Williamson D, et al. Biological material collection to advance translational research and treatment of children with CNS tumours: position paper from the SIOPE brain tumour group. *Lancet Oncol*. 2018;19(8):e419–e428.
30. Greenfield JP, Castaneda Heredia A, George E, Kieran MW, Morales La Madrid A. Gliomatosis cerebri: a consensus summary report from the First International Gliomatosis Cerebri Group Meeting, March 26-27, 2015, Paris, France. *Pediatr Blood Cancer*. 2016;63(12):2072–2077.
31. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126(4):663–676.
32. Nemeth E, Krzystanek M, Reiniger L, et al. The genomic imprint of cancer therapies helps timing the formation of metastases. *Int J Cancer*. 2019;145(3):694–704.
33. Staňková K, Brown JS, Dalton WS, Gatenby RA. Optimizing cancer treatment using game theory: a review. *JAMA Oncol*. 2019;5(1):96–103.
34. Brastianos PK, Carter SL, Santagata S, et al. Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. *Cancer Discov*. 2015;5(11):1164–1177.
35. Venur VA, Cohen JV, Brastianos PK. Targeting molecular pathways in intracranial metastatic disease. *Front Oncol*. 2019;9(99).
36. Shankar GM, Francis JM, Rinne ML, et al. Rapid intraoperative molecular characterization of glioma. *JAMA Oncol*. 2015;1(5): 662–667.
37. Tang J, Liu J, Zhou C, et al. Mmp-9 deficiency enhances collagenase-induced intracerebral hemorrhage and brain injury in mutant mice. *J Cereb Blood Flow Metab*. 2004;24(10):1133–1145.
38. Suero Molina E, Schipmann S, Stummer W. Maximizing safe resections: the roles of 5-aminolevulinic acid and intraoperative MR imaging in glioma surgery-review of the literature. *Neurosurg Rev*. 2019;42(2):197–208.
39. Olubiyi OI, Ozdemir A, Incekara F, et al. Intraoperative magnetic resonance imaging in intracranial glioma resection: a single-center, retrospective blinded volumetric study. *World Neurosurg*. 2015;84(2):528–536.
40. Marongiu A, D'Andrea G, Raco A. 1.5-T Field intraoperative magnetic resonance imaging improves extent of resection and survival in glioblastoma removal. *World Neurosurg*. 2017;98:578–586.
41. Swinney C, Li A, Bhatti I, Veeravagu A. Optimization of tumor resection with intra-operative magnetic resonance imaging. *J Clin Neurosci*. 2016;34:11–14.
42. Hu S, Kang H, Baek Y, El Fakhri G, Kuang A, Choi HS. Real-time imaging of brain tumor for image-guided surgery. *Adv Healthc Mater*. 2018;7(16):e1800066.
43. Brusatori M, Auner G, Noh T, Scarpace L, Broadbent B, Kalkanis SN. Intraoperative raman spectroscopy. *Neurosurg Clin N Am*. 2017;28(4):633–652.
44. Fabelo H, Halicek M, Ortega S, et al. Deep learning-based framework for in vivo identification of glioblastoma tumor using hyperspectral images of human brain. *Sensors (Basel)*. 2019;19(4).
45. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. *J Control Release*. 2000;65(1-2):271–284.
46. Choi HS, Gibbs SL, Lee JH, et al. Targeted zwitterionic near-infrared fluorophores for improved optical imaging. *Nat Biotechnol*. 2013;31(2):148–153.
47. Kim H, Cho MH, Choi HS, Lee BI, Choi Y. Zwitterionic near-infrared fluorophore-conjugated epidermal growth factor for fast, real-time, and target-cell-specific cancer imaging. *Theranostics*. 2019;9(4):1085–1095.
48. Owens EA, Lee S, Choi J, Henary M, Choi HS. NIR fluorescent small molecules for intraoperative imaging. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2015;7(6):828–838.
49. Hu S, Kang H, Baek Y, El Fakhri G, Kuang A, Choi HS. Real-time imaging of brain tumor for image-guided surgery. *Adv Healthc Mater*. 2018;7(16):1800066.

50. Belykh E, Martirosyan NL, Yagmurlu K, et al. Intraoperative fluorescence imaging for personalized brain tumor resection: current state and future directions. *Front Surg*. 2016;3(55).
51. Olson ES, Jiang T, Aguilera TA, et al. Activatable cell penetrating peptides linked to nanoparticles as dual probes for in vivo fluorescence and MR imaging of proteases. *Proc Natl Acad Sci*. 2010;107(9):4311–4316.
52. Tsugu A, Ishizaka H, Mizokami Y, et al. Impact of the combination of 5-aminolevulinic acid–induced fluorescence with intraoperative magnetic resonance imaging–guided surgery for glioma. *World Neurosurg*. 2011;76(1):120–127.
53. Li Y, Rey-Dios R, Roberts DW, Valdés PA, Cohen-Gadol AA. Intraoperative fluorescence-guided resection of high-grade gliomas: a comparison of the present techniques and evolution of future strategies. *World Neurosurg*. 2014;82(1):175–185.
54. Su X, Huang Q-F, Chen H-L, Chen J. Fluorescence-guided resection of high-grade gliomas: a systematic review and meta-analysis. *Photodiagn Photodyn Ther*. 2014;11(4):451–458.
55. Hadjipanayis CG, Widhalm G, Stummer W. What is the surgical benefit of utilizing 5-aminolevulinic acid for fluorescence-guided surgery of malignant gliomas? *Neurosurgery*. 2015;77(5):663–673.
56. Taichi K, Hirofumi N, Masaaki S, et al. A new strategic neurosurgical planning tool for brainstem cavernous malformations using interactive computer graphics with multimodal fusion images. *J Neurosurg JNS*. 2012;117(1):78–88.
57. Yoon JW, Chen RE, Kim EJ, et al. Augmented reality for the surgeon: systematic review. *Int J Med Robot*. 2018;14(4):e1914.
58. Incekara F, Smits M, Dirven C, Vincent A. Clinical feasibility of a wearable mixed-reality device in neurosurgery. *World Neurosurg*. 2018;118:e422–e427.
59. Sun G-c, Wang F, Chen X-l, et al. Impact of virtual and augmented reality based on intraoperative magnetic resonance imaging and functional neuronavigation in glioma surgery involving eloquent areas. *World Neurosurg*. 2016;96:375–382.
60. Lee C, Wong GKC. Virtual reality and augmented reality in the management of intracranial tumors: a review. *J Clin Neurosci*. 2019;62:14–20.
61. Mikhail M, Mithani K, Ibrahim GM. Presurgical and intraoperative augmented reality in neuro-oncologic surgery: clinical experiences and limitations. *World Neurosurg*. 2019;128:268–276.
62. Cohen-Inbar O, Sviri GE. Adaptive hybrid surgery: paradigm shift for patient-centered neurosurgery. *Rambam Maimonides Med J*. 2018;9(3).
63. Pan HC, Sheehan J, Sheu ML, Chiu WT, Yang DY. Intracapsular decompression or radical resection followed by Gamma Knife surgery for patients harboring a large vestibular schwannoma. *J Neurosurg*. 2012;117(suppl):69–77.
64. Sheppard JP, Lagman C, Prashant GN, et al. Planned Subtotal resection of vestibular schwannoma differs from the ideal radiosurgical target defined by adaptive hybrid surgery. *World Neurosurg*. 2018;114:e441–e446.
65. Yizhak K, Aguet F, Kim J, et al. RNA sequence analysis reveals macroscopic somatic clonal expansion across normal tissues. *Science*. 2019;364(6444).
66. Del Zoppo GJ, Saver JL, Jauch EC, Adams Jr HP. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke*. 2009;40(8):2945–2948.
67. Mikulik R, Wahlgren N. Treatment of acute stroke: an update. *J Intern Med*. 2015;278(2):145–165.
68. Siegel J, Pizzi MA, Brent Peel J, et al. Update on neurocritical care of stroke. *Curr Cardiol Rep*. 2017;19(8):67.
69. Yang SH, Lou M, Luo B, Jiang WJ, Liu R. Precision medicine for ischemic stroke, let us move beyond time is brain. *Transl Stroke Res*. 2018;9(2):93–95.
70. Yu W, Kostanian V, Fisher M. Endovascular recanalization of basilar artery occlusion 80 days after symptom onset. *Stroke*. 2007;38(4):1387–1389.
71. Lansberg MG, Christensen S, Kemp S, et al. Computed tomographic perfusion to predict response to recanalization in ischemic stroke. *Ann Neurol*. 2017;81(6):849–856.
72. Byrne D, Walsh JP, MacMahon PJ. An acute stroke CT imaging algorithm incorporating automated perfusion analysis. *Emerg Radiol*. 2019;26(3):319–329.
73. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49(3):e46–e110.
74. Dichgans M, Pulit SL, Rosand J. Stroke genetics: discovery, biology, and clinical applications. *Lancet Neurol*. 2019;18(6):587–599.
75. Xu Z, Rui YN, Hagan JP, Kim DH. Intracranial aneurysms: pathology, genetics, and molecular mechanisms. *Neuromolecular Med*. 2019;21(4):325–343.
76. Vega C, Kwoon JV, Lavine SD. Intracranial aneurysms: current evidence and clinical practice. *Am Fam Physician*. 2002;66(4):601–608.
77. Hasan D, Chalouhi N, Jabbour P, et al. Early change in ferumoxytol-enhanced magnetic resonance imaging signal suggests unstable human cerebral aneurysm. *Stroke*. 2012;43(12):3258–3265.
78. Hasan D,M, Mahaney K,B, Magnotta V,A, et al. Macrophage imaging within human cerebral aneurysms wall using ferumoxytol-enhanced MRI: a pilot study. *Arterioscler Thromb Vasc Biol*. 2012;32(4):1032–1038.
79. Turan N, Heider RA, Roy AK, et al. Current perspectives in imaging modalities for the assessment of unruptured intracranial aneurysms: a comparative analysis and review. *World Neurosurg*. 2018;113:280–292.
80. Scimone C, Bramanti P, Alafaci C, et al. Update on novel CCM gene mutations in patients with cerebral cavernous malformations. *J Mol Neurosci*. 2017;61(2):189–198.
81. Rinaldi C, Bramanti P, Scimone C, et al. Relevance of CCM gene polymorphisms for clinical management of sporadic cerebral cavernous malformations. *J Neurol Sci*. 2017;380:31–37.
82. Baranoski JF, Kalani MY, Przybylowski CJ, Zabramski JM. Cerebral cavernous malformations: review of the genetic and protein-protein interactions resulting in disease pathogenesis. *Front Surg*. 2016;3:60.
83. Panenka WJ, Gardner AJ, Dretsch MN, Crynen GC, Crawford FC, Iverson GL. systematic review of genetic risk factors for sustaining a mild traumatic brain injury. *J Neurotrauma*. 2017;34(13):2093–2099.
84. Lorente L. Biomarkers associated with the outcome of traumatic brain injury patients. *Brain Sci*. 2017;7(11).
85. Rodney T, Osier N, Gill J. Pro- and anti-inflammatory biomarkers and traumatic brain injury outcomes: a review. *Cytokine*. 2018;110:248–256.
86. Dong J, Lu M, He X, et al. Identifying the role of microRNAs in spinal cord injury. *Neurol Sci*. 2014;35(11):1663–1671.
87. Slota JA, Booth SA. MicroRNAs in neuroinflammation: implications in disease pathogenesis, biomarker discovery and therapeutic applications. *Noncoding RNA*. 2019;5(2).
88. Sun P, Liu DZ, Jickling GC, Sharp FR, Yin KJ. MicroRNA-based therapeutics in central nervous system injuries. *J Cereb Blood Flow Metab*. 2018;38(7):1125–1148.
89. Connor Jr DE, Chaitanya GV, Chittiboina P, et al. Variations in the cerebrospinal fluid proteome following traumatic brain injury and subarachnoid hemorrhage. *Pathophysiol*. 2017;24(3):169–183.
90. Sowers JL, Wu P, Zhang K, DeWitt DS, Prough DS. Proteomic changes in traumatic brain injury: experimental approaches. *Curr Opin Neurol*. 2018;31(6):709–717.
91. Sarkis GA, Mangaonkar MD, Moghieb A, et al. The application of proteomics to traumatic brain and spinal cord injuries. *Curr Neurol Neurosci Rep*. 2017;17(3):23.
92. Battie MC, Videman T, Gibbons LE, Fisher LD, Manninen H, Gill K. 1995 Volvo award in clinical sciences. determinants of lumbar disc degeneration. a study relating lifetime exposures and magnetic resonance imaging findings in identical twins. *Spine (Phila Pa 1976)*. 1995;20(24):2601–2612.
93. Sambrook PN, MacGregor AJ, Spector TD. Genetic influences on cervical and lumbar disc degeneration: a magnetic resonance imaging study in twins. *Arthritis Rheum*. 1999;42(2):366–372.
94. Nitin M, Ernest JS. Identical twins with cervical myelopathy: a case for hereditary cervical spondylosis? *J Neurosurg: Spine SPI*. 2007;6(4):344–349.
95. Patel AA, Spiker WR, Daubs M, Brodke DS, Cannon-Albright LA. Evidence of an inherited predisposition for cervical spondylotic myelopathy. *Spine (Phila Pa 1976)*. 2012;37(1):26–29.
96. Jiang Y, Han S, Cheng W, Wang Z, Wu A. NFAT1-regulated IL6 signalling contributes to aggressive phenotypes of glioma. *Cell Commun Signal*. 2017;15(1):54.
97. Pekala PA, Henry BM, Taterra D, et al. FokI as a genetic factor of intervertebral disc degeneration: a PRISMA-compliant systematic review of overlapping meta-analyses. *J Clin Neurosci*. 2019;60:36–43.

98. Huang D, Deng X, Ma K, et al. Association of COL9A3 trp3 polymorphism with intervertebral disk degeneration: a meta-analysis. *BMC Musculoskelet Disord*. 2018;19(1):381.
99. Nakajima M, Takahashi A, Tsuji T, et al. A genome-wide association study identifies susceptibility loci for ossification of the posterior longitudinal ligament of the spine. *Nat Genet*. 2014;46:1012.
100. Wang P, Liu X, Zhu B, et al. Identification of susceptibility loci for thoracic ossification of the posterior longitudinal ligament by whole-genome sequencing. *Mol Med Rep*. 2018;17(2):2557–2564.
101. Liang C, Wang P, Liu X, et al. Whole-genome sequencing reveals novel genes in ossification of the posterior longitudinal ligament of the thoracic spine in the Chinese population. *J Orthop Surg Res*. 2018;13(1):324.
102. Carlson B. ScoliScore AIS prognostic test personalizes treatment for children with spinal curve. *Biotechnol Healthc*. 2011;8(2):30–31.
103. Ward K, Ogilvie JW, Singleton MV, Chettier R, Engler G, Nelson LM. Validation of DNA-based prognostic testing to predict spinal curve progression in adolescent idiopathic scoliosis. *Spine (Phila Pa 1976)*. 2010;35(25):E1455–E1464.
104. Ewert S, Plettig P, Li N, et al. Toward defining deep brain stimulation targets in MNI space: a subcortical atlas based on multimodal MRI, histology and structural connectivity. *NeuroImage*. 2018;170:271–282.
105. Horn A, Li N, Dembek TA, et al. Lead-DBS v2: Towards a comprehensive pipeline for deep brain stimulation imaging. *NeuroImage*. 2019;184:293–316.
106. Akram H, Sotiropoulos SN, Jbabdi S, et al. Subthalamic deep brain stimulation sweet spots and hyperdirect cortical connectivity in Parkinson's disease. *NeuroImage*. 2017;158:332–345.
107. Aum DJ, Tierney TS. Deep brain stimulation: foundations and future trends. *Front Biosci (Landmark Ed)*. 2018;23:162–182.
108. Butson CR, Cooper SE, Henderson JM, Wolgamuth B, McIntyre CC. Probabilistic analysis of activation volumes generated during deep brain stimulation. *NeuroImage*. 2011;54(3):2096–2104.
109. LeWitt PA, Rezai AR, Leehey MA, et al. AAV2-GAD gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomised trial. *The Lancet Neurology*. 2011;10(4):309–319.
110. Mittermeyer G, Christine CW, Rosenbluth KH, et al. Long-term evaluation of a phase 1 study of AADC gene therapy for Parkinson's disease. *Human Gene Therapy*. 2012;23(4):377–381.
111. Kaplitt MG. Gene-targeting approaches for movement disorders: recent advances. *Curr Opin Neurol*. 2019;32(4):566–570.
112. Marks Jr WJ, Baumann TL, Bartus RT. Long-term safety of patients with Parkinson's disease receiving raav2-neurturin (CERE-120) gene transfer. *Human Gene Therapy*. 2016;27(7):522–527.
113. Xhima K, Nabbouh F, Hynynen K, Aubert I, Tandon A. Noninvasive delivery of an alpha-synuclein gene silencing vector with magnetic resonance-guided focused ultrasound. *Mov Disord*. 2018;33(10):1567–1579.
114. Weber YG, Biskup S, Helbig KL, Von Spiczak S, Lerche H. The role of genetic testing in epilepsy diagnosis and management. *Expert Rev Mol Diagn*. 2017;17(8):739–750.
115. Helbig KL, Farwell Hagman KD, Shinde DN, et al. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. *Genet Med*. 2016;18:898.
116. Krueger DA, Capal JK, Curatolo P, et al. Short-term safety of mTOR inhibitors in infants and very young children with tuberous sclerosis complex (TSC): Multicentre clinical experience. *Eur J Paediatr Neurol*. 2018;22(6):1066–1073.
117. Martinkovic L, Hecimovic H, Sulc V, Marecek R, Marusic P. Modern techniques of epileptic focus localization. *Int Rev Neurobiol*. 2014;114:245–278.
118. Bauer PR, Reitsma JB, Houweling BM, Ferrier CH, Ramsey NF. Can fMRI safely replace the Wada test for preoperative assessment of language lateralisation? A meta-analysis and systematic review. *J Neurol Neurosurg Psychiatry*. 2014;85(5):581–588.
119. Direito B, Teixeira CA, Sales F, Castelo-Branco M, Dourado A. A realistic seizure prediction study based on multiclass SVM. *Int J Neural Syst*. 2017;27(3):1750006.
120. Ferraro L, Pollard JR, Helbig I. Attitudes toward epilepsy genetics testing among adult and pediatric epileptologists-results of a Q-PULSE survey. *Epilepsy Curr*. 2016;16(1):46–47.
121. Azoury SC, Reddy S, Shukla V, Deng CX. Fibroblast growth factor receptor 2 (FGFR2) mutation related syndromic craniosynostosis. *Int J Biol Sci*. 2017;13(12):1479–1488.
122. Benjamin DS, Brian PW, Brian VN, Kristopher TK, Yan Michael L, Jean-Valery CEC. Familial Chiari malformation: case series. *Neurosurg Focus FOC*. 2011;31(3):E1.
123. Abbott D, Brockmeyer D, Neklason DW, Teerlink C, Cannon-Albright LA. Population-based description of familial clustering of Chiari malformation type I. *J Neurosurg*. 2018;128(2):460–465.
124. Merello E, Tattini L, Magi A, et al. Exome sequencing of two Italian pedigrees with non-isolated Chiari malformation type I reveals candidate genes for cranio-facial development. *Eur J Hum Genet*. 2017;25(8):952–959.
125. Musolf AM, Ho WSC, Long KA, et al. Small posterior fossa in Chiari I malformation affected families is significantly linked to 1q43-44 and 12q23-24.11 using whole exome sequencing. *Eur J Hum Genet*. 2019;27(10):1599–1610.
126. Keser N, Kuskucu A, Is M, Celikoglu E. Familial Chiari Type 1: A molecular karyotyping study in a Turkish family and review of the literature. *World Neurosurg*. 2019;121:e852–e857.
127. Grilli G, Moffa AP, Perfetto F, et al. Neuroimaging features of tuberous sclerosis complex and Chiari Type I malformation: a rare association. *J Pediatr Neurosci*. 2018;13(2):224–228.
128. Pozetti M, Belsuzarri TA, Belsuzarri NC, Seixas NB, Araujo JF. Neurofibromatosis type 1 and Chiari type 1 malformation: a case report and literature review of a rare association. *Surg Neurol Int*. 2016;7(suppl 16):S469–S472.
129. Tubbs RS, Beckman J, Naftel RP, et al. Institutional experience with 500 cases of surgically treated pediatric Chiari malformation Type I. *J Neurosurg Pediatr*. 2011;7(3):248–256.
130. Saletti V, Esposito S, Maccaro A, Giglio S, Valentini LG, Chiapparini L. Chiari I malformation in a child with PTEN hamartoma tumor syndrome: association or coincidence? *Eur J Med Genet*. 2017;60(5):261–264.
131. Nagy L, Mobley J, Ray C. Familial aggregation of Chiari malformation: presentation, pedigree, and review of the literature. *Turk Neurosurg*. 2016;26(2):315–320.
132. Kurzbuch AR, Magdum S. Chiari I malformation as part of the Floating-Harbor syndrome? *Eur J Med Genet*. 2016;59(12):615–617.
133. Urbizu A, Toma C, Poca MA, et al. Chiari malformation type I: a case-control association study of 58 developmental genes. *PLoS One*. 2013;8(2):e57241.
134. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA: A Cancer J Clin*. 2019;69(1):7–34.
135. Louis DN, Perry A, Reifenberger G, et al. The 2016 world health organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131(6):803–820.
136. Kline CN, Joseph NM, Grenert JP, et al. Targeted next-generation sequencing of pediatric neuro-oncology patients improves diagnosis, identifies pathogenic germline mutations, and directs targeted therapy. *Neuro-Oncology*. 2016;19(5):699–709.
137. Ramkissoon SH, Bandopadhayay P, Hwang J, et al. Clinical targeted exome-based sequencing in combination with genome-wide copy number profiling: precision medicine analysis of 203 pediatric brain tumors. *Neuro-Oncology*. 2017;19(7):986–996.
138. Cole BL, Lockwood CM, Stasi S, et al. Year 1 in the molecular Era of pediatric brain tumor diagnosis: application of universal clinical targeted sequencing in an unselected cohort of children. *JCO Precision Oncology*. 2018;(2):1–13.
139. Koschmann C, Wu Y-M, Kumar-Sinha C, et al. Clinically integrated sequencing alters therapy in children and young adults with high-risk glial brain tumors. *JCO Precision Oncology*. 2018;(2):1–34.
140. Miklja Z, Pasternak A, Stallard S, et al. Molecular profiling and targeted therapy in pediatric gliomas: review and consensus recommendations. *Neuro-Oncology*. 2019;21(8):968–980.