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INTELLIGENT INTRAOPERATIVE NEUROPATHOLOGY IN BRAIN TUMOR SURGERY: STIMULATED RAMAN HISTOLOGY, RAPID NANOPORE EPIGENOMICS, AND AI-GUIDED MARGIN ASSESSMENT

Abstract

Background. Intraoperative neuropathology is moving from morphology-only frozen-section consultation toward integrated optical, molecular, and artificial-intelligence workflows capable of informing surgery before closure. Stimulated Raman histology provides label-free microscopic images from fresh tissue, whereas rapid nanopore sequencing, microfluidic polymerase-chain-reaction systems, and foundation models can estimate tumor class, molecular subtype, and infiltration within minutes.

Materials and methods. Prospective multicenter studies, translational investigations, diagnostic-accuracy cohorts, and platform-validation studies published through July 2026 were synthesized. Evidence was organized according to specimen acquisition, optical histology, machine-learning interpretation, rapid epigenomic or genetic profiling, margin assessment, turnaround time, diagnostic confidence, and clinical decision impact.

Results. Stimulated Raman histology combined with deep learning achieves near-real-time tumor classification and can detect diffuse-glioma infiltration more accurately than several conventional intraoperative adjuncts. FastGlioma produced infiltration scores within seconds in an international prospective cohort. Rapid-CNS2 generated methylation classification and copy-number information within a thirty-minute intraoperative window, while Sturgeon and MethyLYZR demonstrated classification from sparse nanopore methylation data. Hetairos extended routine hematoxylin-and-eosin analysis toward prediction of 102 methylation-associated central-nervous-system tumor subtypes. Nevertheless, low tumor purity, sampling error, rare entities, domain shift, overconfident predictions, and uncertain action thresholds remain limitations.

Conclusion. Intelligent intraoperative neuropathology should augment rather than replace neuropathology. The proposed SMART-PATH framework integrates sampling, multimodal acquisition, algorithmic confidence, rapid molecular testing, topographic mapping, pathology verification, actionable interpretation, and human oversight to support maximal safe resection and adequate biopsy.

Keywords: stimulated Raman histology; artificial intelligence; brain tumor surgery; nanopore sequencing; DNA methylation; glioma infiltration; intraoperative diagnosis; digital neuropathology; molecular classification; surgical margin.

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ИНТЕЛЛЕКТУАЛЬНАЯ ИНТРАОПЕРАЦИОННАЯ НЕЙРОПАТОЛОГИЯ В ХИРУРГИИ ОПУХОЛЕЙ ГОЛОВНОГО МОЗГА: СТИМУЛИРОВАННАЯ

РАМАНОВСКАЯ ГИСТОЛОГИЯ, БЫСТРАЯ НАНОПОРОВАЯ ЭПИГЕНОМИКА И ОЦЕНКА ГРАНИЦ С ПОМОЩЬЮ ИСКУССТВЕННОГО ИНТЕЛЛЕКТА

Аннотация

Актуальность. Интраоперационная нейропатология переходит от морфологической экспресс-диагностики замороженных срезов к интегрированным оптическим, молекулярным и искусственно-интеллектуальным системам, способным влиять на хирургическую тактику до закрытия операционной раны. Стимулированная рамановская гистология формирует микроскопические изображения свежей ткани без окрашивания, тогда как быстрое нанопоровое секвенирование, микрофлюидная полимеразная цепная реакция и фундаментальные модели позволяют оценивать класс опухоли, молекулярный подтип и степень инфильтрации в течение минут.

Материалы и методы. Синтезированы проспективные многоцентровые исследования, трансляционные работы, когорты диагностической точности и исследования валидации платформ, опубликованные до июля 2026 года.

Результаты. Сочетание стимулированной рамановской гистологии и глубокого обучения обеспечивает близкую к реальному времени классификацию опухолей и выявляет инфильтрацию диффузной глиомы. FastGlioma формирует показатель инфильтрации за секунды. Rapid-CNS2 предоставляет метилированную классификацию и информацию о числе копий в пределах тридцатиминутного интраоперационного окна. Sturgeon и MethyLYZR классифицируют опухоли по разреженным данным нанопорового метилирования, а Hetairos прогнозирует 102 метилирование-ассоциированных подтипа опухолей центральной нервной системы по рутинным H&E-препаратам. Ограничениями остаются низкая опухолевая чистота, ошибка отбора ткани, редкие нозологии, межцентровой сдвиг данных, чрезмерная уверенность алгоритма и отсутствие проверенных порогов хирургического действия. Особое значение имеет сохранение пространственной привязки каждого образца к навигационной координате, поскольку диагностический ответ должен соответствовать конкретной зоне резекции или биопсии пациента.

Заключение. Интеллектуальная интраоперационная нейропатология должна дополнять, а не заменять специалиста. Модель SMART-PATH объединяет отбор образцов, мультимодальное получение данных, алгоритмическую уверенность, быстрое молекулярное тестирование, топографическое картирование, верификацию патоморфологом, клинически применимую интерпретацию и человеческий контроль для поддержки максимальной безопасной резекции и адекватной биопсии.

Ключевые слова: стимулированная рамановская гистология; искусственный интеллект; хирургия опухолей мозга; нанопоровое секвенирование; метилирование ДНК; инфильтрация глиомы; интраоперационная диагностика; цифровая нейропатология; молекулярная классификация; хирургическая граница.

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SamDTU huzuridagi neyroxirurgiya va neyroreabilitatsiya ixtisoslashtirilgan ilmiy-amaliy markazi

MIYA O‘SMALARI JARROHLIGIDA INTELLEKTUAL INTRAOPERATSION NEYROPATOLOGIYA: STIMULLANGAN RAMAN GISTOLOGIYASI, TEZKOR NANOPORA EPIGENOMIKASI VA SUN’IY INTELLEKT ASOSIDAGI CHEGARA BAHOLASH

Annotatsiya

Dolzarblik. Intraoperatsion neyropatologiya muzlatilgan kesmalarni faqat morfologik baholashdan operatsion yara yopilishidan oldin jarrohlik taktikasiga ta’sir ko‘rsata oladigan integratsiyalashgan optik, molekulyar va sun’iy intellekt tizimlariga o‘tmoqda. Stimullangan Raman gistologiyasi yangi olingan to‘qimadan bo‘yashsiz mikroskopik tasvirlar hosil qiladi, tezkor nanopora sekvenslash, mikroflyuid polimeraza zanjir reaksiyasi va fundamental modellar esa o‘sma sinfi, molekulyar turi va infiltratsiya darajasini bir necha daqiqada baholash imkonini beradi.

Material va usullar. 2026-yil iyuligacha chop etilgan prospektiv ko‘p markazli tadqiqotlar, translatsion ishlar, diagnostik aniqlik kohortalari va platforma validatsiyalari sintez qilindi.

Natijalar. Stimullangan Raman gistologiyasi va chuqur o‘rganish o‘smani real vaqtga yaqin tasniflaydi hamda diffuz glioma infiltratsiyasini aniqlaydi. Fast Glioma infiltratsiya ko‘rsatkichini soniyalar ichida beradi. Rapid-CNS2 o‘ttiz daqiqalik intraoperatsion oynada metillanish klassifikatsiyasi va nusxa soni ma’lumotini taqdim etadi. Sturgeon hamda MethyLYZR siyrak nanopora metillanish ma’lumotlaridan foydalanadi, Hetairos esa oddiy H&E preparatlaridan markaziy nerv tizimi o‘smalarining 102 metillanishga bog‘liq turini bashorat qiladi. Past o‘sma tozaligi, noto‘g‘ri namuna olish, kam uchraydigan kasalliklar, markazlararo ma’lumot siljishi, algoritmning ortiqcha ishonchi va tasdiqlangan jarrohlik chegaralarining yo‘qligi asosiy cheklovlardir. Har bir namunaning navigatsion koordinata bilan bog‘lanishi diagnostik natijani aniq rezeksiya yoki biopsiya zonasiga tatbiq qilish uchun muhimdir.

Xulosa. Intellektual intraoperatsion neyropatologiya mutaxassisni almashtirmasdan uni kuchaytirishi kerak. SMART-PATH modeli namuna olish, multimodal ma’lumot yig‘ish, algoritmik ishonch, tezkor molekulyar test, topografik xaritalash, patologik tekshiruv, amaliy talqin va inson nazoratini birlashtiradi. Bu yondashuv maksimal xavfsiz rezeksiya, yetarli biopsiya va operatsion qarorlarning izchil hujjatlashtirilishini qo‘llab-quvvatlaydi kundalik amaliyotda.

Kalit so‘zlar: stimullangan Raman gistologiyasi; sun’iy intellekt; miya o‘smalari jarrohligi; nanopora sekvenslash; DNK metillanishi; glioma infiltratsiyasi; intraoperatsion diagnostika; raqamli neyropatologiya; molekulyar klassifikatsiya; jarrohlik chegarasi.

Introduction. The diagnosis of central nervous system tumors has changed from a predominantly morphology-based discipline into an integrated process combining histological architecture, immunophenotype, genomic alterations, DNA methylation, copy-number variation, and clinical–radiological context. This transformation has increased diagnostic precision but has also widened the temporal gap between surgery and definitive classification. A conventional intraoperative consultation may identify whether tissue is neoplastic, inflammatory, necrotic, glial, metastatic, lymphoid, or meningeal, yet the final entity and molecular grade may remain uncertain for days or weeks [1, 2, 3]. This diagnostic delay is clinically important because the biological identity of a tumor can influence the operation itself. A diffuse glioma may justify maximal safe cytoreduction with

functional mapping, whereas a primary central nervous system lymphoma usually requires an adequate diagnostic biopsy rather than extensive resection. A circumscribed low-grade tumor, infiltrating glioma, metastasis, treatment-related change, or inflammatory lesion may demand different sampling strategies, operative boundaries, and postoperative planning [3, 6, 10]. Frozen-section and smear cytology remain valuable because they provide direct morphological information during surgery. Their limitations include freezing artifact, tissue distortion, small sample size, heterogeneous tumors, limited access to specialist neuropathology, and insufficient ability to reproduce the integrated molecular classification of modern CNS tumors. Interpretation may be particularly difficult in infiltrative margins, recurrent treated lesions, stereotactic biopsies, pediatric tumors, and specimens containing extensive necrosis [5, 11, 16]. The problem is not simply diagnostic speed. The neurosurgeon must know whether the result is sufficiently reliable to justify an irreversible action. Continuing resection near eloquent cortex, stopping after a biopsy, extending sampling to another radiological region, or changing the operative corridor requires different levels of evidentiary confidence. An algorithm producing a rapid label without calibrated uncertainty may be less useful than a slower system that appropriately abstains when the specimen is inadequate or unfamiliar. Stimulated Raman histology has emerged as a label-free method for imaging fresh, unprocessed tissue. Stimulated Raman scattering detects molecular vibrations related mainly to lipid, protein, and nucleic-acid composition. By acquiring complementary Raman channels and computationally transforming them into a histology-like color representation, SRH creates digital images resembling conventional hematoxylin-and-eosin sections without freezing, fixation, sectioning, or staining [4, 7, 14]. Initial clinical work demonstrated that SRH could provide high-resolution optical histology within minutes and reproduce major diagnostic features of CNS tumors. A multicenter prospective study subsequently combined SRH with deep neural networks and achieved near-real-time automated classification with performance comparable to pathologist interpretation of conventional intraoperative preparations [8, 9, 25]. The transition from convolutional neural networks to foundation models represents a further development. Conventional supervised models are trained to recognize a predefined set of diagnoses. Foundation models are pretrained through self-supervised learning on millions of images and can then be adapted to multiple tasks, including tumor classification, infiltration detection, molecular prediction, image segmentation, and identification of previously unseen tissue patterns.

FastGlioma is a visual foundation model developed from approximately four million SRH images. In a prospective multicenter international cohort of 220 patients with diffuse glioma, it quantified tumor infiltration with an average area under the receiver-operating-characteristic curve of 92.1%. It generated predictions in less than ten seconds and outperformed conventional image-guided and fluorescence-guided adjuncts in a prospective head-to-head cohort of 129 patients [10, 13, 23]. Parallel advances in nanopore sequencing allow molecular information to become available during the same operation. Nanopore platforms detect changes in electrical current as individual DNA molecules pass through a nanoscale pore. The technology can provide sequence variation, DNA methylation, and copy-number information without waiting for conventional short-read sequencing or methylation-array processing. Ultra-rapid classifiers such as Sturgeon, MethyLYZR, and Rapid-CNS² are designed to interpret sparse genomic or epigenomic information as reads accumulate. These platforms do not require a complete genome. They estimate the most likely CNS tumor family or methylation class from

a small fraction of CpG sites and update the prediction continuously as additional reads become available [2, 3, 18]. The emergence of histology-derived molecular prediction adds another layer. Hetairos, reported in 2026, analyzes routine digital H&E slides and predicts 102 methylation-associated CNS tumor subtypes. It does not directly measure methylation; it identifies morphological patterns statistically associated with molecular classes. Such systems may accelerate or prioritize confirmatory testing, particularly where comprehensive molecular platforms are unavailable, but they should not be confused with direct molecular assays [6, 13, 28].

The future intraoperative diagnostic environment will therefore be multimodal. Fresh tissue may be analyzed by SRH for immediate morphology and infiltration, nanopore sequencing for methylation and copy-number classification, rapid PCR for actionable mutations, mass spectrometry for oncometabolites, and conventional neuropathology for morphological verification. The challenge is to integrate these signals into a coherent and safe surgical workflow.

Materials and Methods. This manuscript was designed as a structured integrative review with an original workflow-oriented synthesis. Prospective multicenter clinical studies, diagnostic-accuracy cohorts, translational investigations, platform-validation studies, public-dataset reports, and clinically relevant methodological studies published through July 2026 were evaluated. The principal technologies included stimulated Raman histology, stimulated Raman scattering microscopy, artificial-intelligence image classification, vision foundation models, rapid nanopore sequencing, sparse methylation classification, rapid polymerase-chain-reaction systems, droplet digital PCR, mass spectrometry, rapid evaporative ionization mass spectrometry, conventional digital H&E pathology, and intraoperative molecular-margin assessment. Evidence was organized according to specimen acquisition, tissue preparation, analytical time, diagnostic target, tumor purity, spatial localization, output confidence, external validation, diagnostic abstention, influence on surgical decision-making, and compatibility with routine neuropathology. The principal clinical outcomes were diagnostic accuracy, sensitivity, specificity, area under the receiver-operating-characteristic curve, turnaround time, proportion of high-confidence predictions, classification abstention, margin-detection performance, concordance with final integrated diagnosis, and potential influence on operative strategy. No new patient cohort was generated and no independent meta-analysis was performed. Numerical results were interpreted in relation to specimen quality, reference standard, tumor spectrum, model architecture, validation design, institutional setting, and prevalence of rare entities. The tables represent an original synthesis rather than fabricated clinical data.

Results. Frozen section and smear preparation remain the clinical reference for intraoperative tissue consultation. Smear cytology is rapid and preserves cellular detail but provides limited architectural context. Frozen sections retain architecture but can introduce ice-crystal artifact, crush distortion, fragmentation, and uneven staining. The reliability of conventional consultation depends on tissue selection. Necrotic tissue may establish high-grade behavior but fail to identify viable tumor. Reactive gliosis at an infiltrative margin may mimic or conceal low-density tumor. Lymphoma may be distorted by corticosteroid exposure. Metastases can resemble high-grade glioma when only poorly differentiated tissue is sampled. The final integrated diagnosis may require IDH1/2, histone H3, BRAF, TERT promoter, ATRX, TP53, EGFR, CDKN2A/B, 1p/19q, and methylation testing. Therefore, an intraoperative morphological impression should be communicated as a provisional answer with

explicit limitations rather than an abbreviated final diagnosis [11, 12, 20]. Intelligent technologies should not eliminate these principles. They still depend on representative tissue, adequate cellularity, correct labeling, appropriate controls, and correlation with radiology and clinical history.

Stimulated Raman Histology. SRH creates virtual histological images from the intrinsic biochemical composition of fresh tissue. Lipid-rich structures, protein-dense nuclei, collagen, myelin, necrosis, and cellular architecture generate distinctive spectral and spatial patterns. The specimen is gently compressed between slides or imaging substrates and scanned without fixation or staining. The technique can visualize hypercellularity, nuclear atypia, microvascular proliferation, necrosis, axonal structures, myelinated white matter, Rosenthal fibers, psammoma bodies, and other diagnostically useful features. Because preparation is minimal, the same tissue can subsequently undergo conventional histology or molecular testing. The original clinical development demonstrated greater than 92% diagnostic accuracy and strong concordance with conventional histology in an intraoperative simulation. The subsequent multicenter deep-learning study showed that automated interpretation could be completed within approximately 150 seconds and achieve diagnostic performance comparable to pathologists [15, 17, 27]. SRH offers particular value when frozen-section infrastructure or specialist neuropathology is unavailable. Digital images can be reviewed remotely, shared between centers, and analyzed automatically. However, equipment cost, optical calibration, tissue handling, image artifacts, and training requirements remain barriers. Blood contamination can obscure the tissue surface. Thick, folded, fragmented, calcified, fibrous, or cauterized specimens may generate low-quality images. Small biopsies must be divided carefully so that optical analysis does not consume or damage material required for permanent diagnosis.

Artificial Intelligence Classification of SRH. Early SRH classifiers used supervised convolutional neural networks trained on common tumor categories. Their output depended on the diagnostic spectrum represented in the training set. A model trained mainly on glioma, meningioma, metastasis, and schwannoma may be forced to assign a rare inflammatory or embryonal lesion to the nearest familiar category. OpenSRH addressed part of this problem by releasing a public dataset containing more than 300 patients and over 1,300 whole-slide optical images, including diagnostic annotations, tumor segmentation, and raw imaging data. Public resources permit external benchmarking, model comparison, and methodological reproducibility [7, 14, 19]. Foundation models reduce dependence on narrowly labeled datasets by learning general representations from large numbers of unlabeled images. They can capture tissue morphology, biochemical texture, and spatial organization before being fine-tuned for a clinical task. FastGlioma was pretrained through self-supervision on approximately four million SRH images. It generates a normalized infiltration score rather than only a categorical label. This is clinically important because diffuse glioma margins are continuous rather than binary. A tissue sample can contain a low fraction of infiltrating tumor cells without forming a discrete tumor mass. In the prospective international cohort, FastGlioma maintained high performance across different centers, molecular subtypes, and patient characteristics. It also showed zero-shot generalization to additional adult and pediatric tumor diagnoses, although zero-shot performance does not replace dedicated prospective validation for each new entity [16, 23, 30].

Table 1. Comparison of Intraoperative Optical and Histological Technologies

Technology	Tissue preparation	Approximate analytical time	Principal output	Main advantage	Main limitation
Frozen section	Freezing, cutting, staining	15–30 minutes	Morphological diagnosis	Established clinical workflow	Freezing artifact and specialist dependence
Smear cytology	Mechanical smear and staining	5–15 minutes	Cellular morphology	Rapid and tissue-efficient	Limited architecture
Stimulated Raman histology	Fresh unprocessed tissue	Minutes	Virtual histology	Label-free digital imaging	Dedicated optical system
AI-classified SRH	Fresh tissue plus automated analysis	Seconds to minutes	Tumor class or infiltration score	Rapid and scalable interpretation	Dataset and domain dependence
Third-harmonic microscopy	Fresh tissue	Minutes	Label-free morphology	Minimal preparation	Smaller evidence base
Optical coherence methods	Fresh tissue or in situ surface	Seconds to minutes	Tissue microstructure	Potential real-time interrogation	Limited molecular specificity
Digital H&E foundation model	Standard paraffin H&E slide	Minutes after slide scanning	Predicted molecularly associated class	Uses routine pathology infrastructure	Not fully intraoperative in most centers

Glioma-Infiltration and Margin Assessment. The infiltrative margin is the principal unresolved problem in diffuse-glioma surgery. Neuronavigation becomes progressively inaccurate because of brain shift. Fluorescence identifies selected biological compartments but may be absent in low-grade or nonenhancing tumor. Intraoperative MRI and ultrasound update anatomy but do not directly provide cellular or molecular confirmation. SRH studies have demonstrated that tissue obtained from radiologically uncertain margins can contain recognizable microscopic tumor infiltration. FastGlioma extends this concept by quantifying infiltration rather than requiring a binary tumor-versus-normal decision [21, 24, 31]. A margin result becomes useful only when it is linked to location. Each specimen should be assigned a navigation coordinate or anatomical description before removal. The result must distinguish whether the sample originated from the enhancing core, nonenhancing FLAIR region, cavity wall, white-matter tract boundary, ventricular surface, or eloquent cortical margin. The same infiltration score may lead to different actions. Additional resection may be appropriate at a noneloquent superficial margin but unsafe near the corticospinal tract, language cortex, optic radiation, basal ganglia, or perforating vessels. The diagnostic platform informs the presence of tumor; it does not determine the acceptable neurological risk. Sampling density also matters. A

negative result from one point cannot establish a tumor-free cavity because glioma infiltration is spatially heterogeneous. Sequential multi-site sampling improves coverage but increases analytical workload and risks consuming tissue or extending operative time.

Rapid Nanopore Epigenomic Classification. DNA methylation profiling has become a powerful method for CNS tumor classification because epigenomic patterns integrate cell lineage, developmental state, and tumor biology. Standard array-based classification is highly informative but generally incompatible with an intraoperative timeframe. Nanopore sequencing produces data continuously. Rapid workflows extract DNA, prepare a sequencing library, begin sequencing, and classify the specimen while reads accumulate. The principal challenge is extreme sparsity: only a small fraction of the methylation sites used by conventional arrays are covered during the first minutes. Sturgeon uses transfer learning and simulated sparse nanopore data to classify CNS tumors. In retrospective testing, it reached an accurate diagnosis within 40 minutes of sequencing in 45 of 50 specimens and appropriately abstained in five. During 25 real-time operations, it produced 18 correct diagnoses, while seven cases did not meet the confidence threshold. The total intraoperative turnaround was less than 90 minutes [23, 30, 32]. Abstention is an important safety property. A system that declines to classify low-purity or unfamiliar tissue is preferable to one that generates a confident but incorrect answer. The Sturgeon study demonstrated reduced performance in specimens with low tumor fraction, rare classes, germline predisposition syndromes, or poorly classifiable methylation profiles. MethyLYZR uses a probabilistic framework that can update predictions live with minimal computational overhead. It evaluated more than 200 brain-tumor samples, including ten sequenced near the operating room, and generated highly accurate classification within approximately 15 minutes of sequencing [1, 10, 13, 32]. Rapid-CNS² uses adaptive nanopore sequencing and integrates methylation, copy-number, and sequence information. The multicenter validation included 301 archival and prospective specimens, with 18 samples sequenced intraoperatively. The system provided real-time methylation classification and copy-number information within 30 minutes, followed by broader molecular profiling within 24 hours [3, 10, 18, 27]. The associated MNP-Flex classifier encompassed 184 methylation classes and was validated across more than 78,000 frozen and paraffin-embedded samples from several technologies. Reported accuracy reached 99.6% at the methylation-family level and 99.2% at the class level when clinically applicable thresholds were used. These figures reflect the classifier validation dataset and should not be interpreted as guaranteed performance for every low-purity intraoperative specimen.

Table 2. Rapid Molecular Platforms Relevant to Brain-Tumor Surgery

Platform	Analytical principle	Approximate intraoperative output	Information provided	Principal vulnerability
Sturgeon	Sparse nanopore methylation with transfer learning	Under 90 minutes total workflow	CNS tumor class	Low purity and absent reference classes
MethyLYZR	Live Bayesian classification of	About 15 minutes of sequencing	Methylation-associated class	DNA extraction and sequencing throughput

	nanopore methylation			
Rapid-CNS²	Adaptive nanopore sequencing	About 30 minutes	Methylation family and copy number	Specialized sequencing workflow
Microfluidic PCR	Rapid mutation-specific amplification	Approximately 20–30 minutes	IDH1 and selected TERT alterations	Restricted predefined targets
Rapid ddPCR	Droplet-based quantitative mutation detection	Minutes to under one hour	Tumor fraction and residual burden	Requires known mutation
Mass spectrometry	Detection of oncometabolites or lipid spectra	Seconds to minutes	IDH-associated 2HG or tissue class	Instrumentation and spectral validation
Conventional targeted NGS	Amplicon or hybrid sequencing	Hours to days	Broader mutations and copy-number changes	Usually too slow for surgical decisions

Rapid Mutation-Specific Testing. Mutation-specific testing may be preferable when one or two markers are sufficient to answer the intraoperative question. Microfluidic real-time PCR systems can perform rapid thermal cycling and detect IDH1 R132H and common TERT promoter mutations from small tissue samples. The GeneSoC-based system completed rapid PCR cycling and detected selected IDH1 and TERT promoter mutations within approximately 25 minutes. The reported analytical detection limit was at least a 5% variant-allele fraction, suggesting potential use for both tumor classification and margin assessment [4, 14, 19, 25]. An automatic integrated gene-detection system has also been applied to intraoperative glioma subtyping and surgical guidance. Such targeted systems are faster and simpler than whole-genome approaches but cannot identify unexpected alterations or classify tumors whose defining biology lies outside the selected panel. Ultra-fast droplet digital PCR can quantify mutant alleles and estimate tumor-cell burden at the resection margin. Quantification may be more informative than a binary result because low-level mutant DNA can persist in infiltrated tissue. The clinical threshold at which molecular positivity should change resection remains undefined [5, 16, 20, 30]. Rapid mass spectrometry provides an alternative molecular pathway. IDH-mutant gliomas accumulate the oncometabolite D-2-hydroxyglutarate. Mass-spectrometric workflows can detect 2HG and related metabolic ratios in fresh tissue, allowing rapid inference of IDH status and potential identification of infiltrated margins [2, 6, 10, 13].

Histology-Based Prediction of Molecular Class. Routine H&E slides contain morphological information associated with molecular alterations. Nuclear shape, vascular pattern, stromal composition, necrosis, cellular density, growth architecture, and immune-cell distribution can correlate with methylation class and genomic subtype. Hetairos was trained and evaluated using 9,606 tumors and more than 11,000 slides from 11 centers on four continents. It predicts 102 diagnostically relevant methylation-associated CNS tumor subtypes from digital H&E whole-slide images. High-confidence

predictions were generated for approximately 50–70% of slides, with accuracy around 0.87 in that subset [11–14]. In a direct morphology-only comparison, Hetairos outperformed five board-certified neuropathologists for the model's top prediction. Prospective evaluation reduced the computational diagnostic turnaround from the approximately 12-day molecular workflow to about 12 minutes after slide digitization [11, 15, 17, 20]. The result should be interpreted as decision support rather than molecular replacement. The model estimates a molecularly associated class from morphology, patient age, and anatomical location. It cannot directly prove the presence of a mutation, fusion, deletion, or methylation pattern. The model's ability to abstain or communicate uncertainty is therefore essential. High-confidence predictions may prioritize confirmatory immunohistochemistry or sequencing, whereas low-confidence predictions should broaden rather than narrow the differential diagnosis.

Lymphoma, Glioblastoma, and High-Stakes Differentiation. Distinguishing primary CNS lymphoma from glioblastoma has immediate surgical importance. Extensive resection is frequently pursued for glioblastoma but is not generally the primary objective for lymphoma, where a representative biopsy is usually sufficient. An AI classifier based on SRH and a transformer-derived architecture was trained using images from patients with CNS lymphoma and glioblastoma. The study reported an overall accuracy of 92.5%, sensitivity of 84.2%, and specificity of 100% for differentiating the two categories [1, 2, 10, 13]. The result is promising but should be interpreted in relation to sample size and spectrum. Steroid-treated lymphoma, necrotic glioblastoma, inflammatory lesions, and unusual hematolymphoid tumors may be more difficult than classic examples. High-stakes algorithms should favor specificity and calibrated abstention. A false classification of lymphoma as glioblastoma could lead to unnecessary resection, while a false glioblastoma diagnosis of lymphoma could terminate surgery before adequate sampling of heterogeneous tissue.

Sampling Error and Tumor Purity. Every intraoperative platform is vulnerable to sampling error. Molecular accuracy cannot compensate for tissue obtained from the wrong location. A specimen may contain necrosis, blood, reactive brain, treatment effect, normal white matter, or only a small number of tumor cells. Tumor purity influences methylation and mutation calls. Low purity dilutes tumor-specific signal with normal glial, inflammatory, endothelial, or necrotic components. Some classifiers return a control-tissue label; others may assign a related but incorrect tumor class. The solution is not simply to collect larger tissue volumes. Small stereotactic biopsies may be located near deep eloquent or vascular structures. Excessive sampling increases hemorrhagic and neurological risk. Intelligent sampling should combine preoperative imaging, navigation, perfusion, spectroscopy, fluorescence, ultrasound, and intraoperative tissue analysis.

A staged strategy is preferable. The first sample establishes whether viable diagnostic tissue is present. A second sample can target a different radiological compartment if the initial result is necrosis, normal tissue, or low-confidence classification. The specimen reserved for permanent integrated diagnosis must remain adequate.

Table 3. Failure Modes of Intelligent Intraoperative Neuropathology

Failure mode	Mechanism	Potential consequence	Required safeguard

Nonrepresentative specimen	Tissue obtained from necrosis or reactive margin	Incorrect or inconclusive diagnosis	Navigation-linked multisite sampling
Low tumor purity	Dilution by normal or inflammatory cells	Low-confidence or wrong molecular class	Histological purity assessment and repeat sampling
Rare or unseen entity	Diagnosis absent from training reference	Forced classification into familiar class	Out-of-distribution detection and abstention
Domain shift	Different scanner, preparation, center, or population	Reduced external performance	Multicenter validation and local quality control
Label error	Incorrect reference diagnosis in training data	Systematic model bias	Integrated expert-reviewed ground truth
Algorithmic overconfidence	Poor calibration	Unsafe surgical action	Confidence thresholds and human verification
Spatial-label loss	Sample not linked to cavity location	Result cannot guide margin resection	Navigation coordinate and specimen map
Tissue consumption	Rapid test uses most available specimen	Inadequate final pathology	Predefined tissue-allocation protocol
Turnaround delay	Extraction or technical failure exceeds operative window	Result arrives after decision	Abort criteria and conventional fallback
Contamination	Cross-sample DNA or tissue carryover	False mutation or class	Unidirectional workflow and negative controls

Human–Machine Interaction and Diagnostic Confidence. A diagnostic algorithm should provide more than a class label. Clinically useful output includes the predicted class, confidence, alternative classes, quality-control metrics, tumor-purity estimate, time of analysis, test limitations, and whether the case lies outside the validated distribution. Confidence is not identical to probability of truth unless the model is calibrated. A reported confidence of 0.95 should correspond approximately to 95% correctness in similar external cases. Calibration can deteriorate after software updates, new scanners, altered tissue preparation, or changes in tumor prevalence. Abstention should be considered a successful safety outcome rather than a technical failure. A system that recognizes uncertainty protects the patient and prompts additional tissue sampling or conventional consultation. The neuropathologist remains responsible for integrating morphology, molecular findings, radiology, and clinical context. The neurosurgeon remains responsible for determining whether additional resection is anatomically and functionally safe. The algorithm supports both decisions but cannot assume either responsibility.

Topographic Tumor Mapping. The full value of rapid tissue analysis emerges when diagnostic results are mapped back to the surgical cavity. Each specimen should carry a unique identifier, time stamp, side, depth, anatomical description, and neuronavigation coordinate. A

topographic map can distinguish viable tumor core, necrotic center, infiltrated margin, molecularly negative margin, and functionally constrained residual tissue. This creates a spatial record of why resection continued or stopped. Brain shift reduces the accuracy of preoperative navigation coordinates. Updated intraoperative MRI, ultrasound, or surface registration may improve localization. The tissue result itself remains correct for the specimen but may be incorrectly displayed if the anatomical coordinate has shifted. Molecular margins should not be interpreted as equivalent to surgically removable margins. Diffuse glioma cells extend beyond radiological and functional boundaries. The objective is not molecular sterility, which is biologically unrealistic, but reduction of safely resectable tumor burden.

Table 4. Clinical Questions and Appropriate Intraoperative Technologies

Surgical question	Preferred rapid method	Required confirmatory context	Potential surgical consequence
Is the biopsy neoplastic?	SRH with expert or AI review	Imaging and permanent pathology	Continue targeted sampling or terminate nondiagnostic trajectory
Glioma or lymphoma?	SRH classifier plus rapid targeted testing	Steroid history and conventional morphology	Resection versus diagnostic biopsy strategy
IDH-mutant or IDH-wild-type glioma?	Rapid PCR, mass spectrometry, or nanopore sequencing	Integrated final molecular testing	Informs provisional subtype and sampling
Is this margin infiltrated?	FastGlioma, SRH, rapid ddPCR, or mass spectrometry	Functional anatomy and location	Continue or stop resection
Which CNS methylation family is present?	Sturgeon, MethyLYZR, or Rapid-CNS²	Tumor purity and classifier confidence	Refine intraoperative diagnostic strategy
Is tissue recurrent tumor or treatment effect?	Multimodal SRH, molecular testing, and imaging	Permanent pathology	Extent of debridement and sampling
Is the specimen adequate for final testing?	SRH morphology and rapid purity assessment	Tissue-allocation protocol	Obtain additional viable tissue
Does the result justify an irreversible action?	Concordant multimodal evidence	Neuropathologist and neurosurgeon agreement	Proceed, pause, or obtain another sample

Discussion. The contemporary evidence indicates that intraoperative neuropathology is progressing from a single frozen-section answer toward a layered diagnostic system. Optical histology provides morphology within minutes. Artificial intelligence accelerates interpretation and quantifies infiltration. Nanopore sequencing provides epigenomic and copy-number information during surgery. Rapid PCR, ddPCR, and mass spectrometry answer focused molecular questions. These technologies

should not be considered interchangeable. SRH is particularly strong for immediate tissue morphology and infiltration. Nanopore sequencing is strong for integrated molecular classification. Targeted PCR is efficient when the clinically relevant alteration is predefined. H&E foundation models provide scalable decision support within existing pathology infrastructure. FastGlioma represents an important change because its output is not limited to a diagnostic category. The normalized infiltration score reflects a biological continuum and can be applied to multiple margin samples. Its prospective multicenter performance and head-to-head comparison with established adjuncts provide stronger evidence than many retrospective AI studies [5, 11, 16, 20]. Nevertheless, improved detection of tumor infiltration does not automatically improve patient outcome. A surgeon may detect additional tumor that cannot be removed safely. The relationship among diagnostic accuracy, extent of resection, neurological morbidity, progression-free survival, overall survival, cognition, and quality of life requires prospective interventional trials. The same distinction applies to rapid molecular diagnosis. Rapid-CNS² can generate methylation and copy-number information within the operation, but the molecular result improves care only when it changes an appropriate decision. Some tumors have the same immediate surgical strategy despite different subtypes. Other diagnoses, particularly lymphoma, diffuse midline glioma, or circumscribed pediatric tumors, may alter the value of aggressive resection [4, 7, 14, 19]. The most appropriate clinical trials should therefore measure decision impact rather than diagnostic accuracy alone. Relevant endpoints include frequency of additional sampling, avoidance of nondiagnostic biopsy, change in resection strategy, concordance with final integrated diagnosis, neurological outcome, residual tumor volume, operative time, and cost.

Hetairos demonstrates how routine morphology can encode molecularly associated information. Its breadth across 102 CNS tumor subtypes and validation across multiple continents are major strengths. Its top-prediction performance exceeded that of neuropathologists when both were restricted to histology alone [21, 24, 30]. This comparison should not be interpreted as replacement of neuropathologists. Human experts ordinarily use immunohistochemistry, molecular testing, clinical history, radiology, and knowledge of rare entities. The study demonstrates that morphology contains subtle patterns that can be extracted computationally and used to prioritize a differential diagnosis. Diagnostic confidence is central. Hetairos provided high-confidence predictions for only part of the cohort. Sturgeon abstained from cases that did not meet its confidence threshold. This behavior is clinically desirable. The most dangerous AI system is not the model that admits uncertainty but the model that produces a persuasive answer for every specimen. Rare tumors remain a persistent problem. The diagnostic spectrum of CNS tumors is broad, and many entities occur too infrequently to support conventional supervised training. Foundation models, hierarchical classification, synthetic augmentation, federated learning, and international data sharing may improve performance, but rare-class validation will remain difficult. Data governance is equally important. Histological images and genomic sequences contain sensitive patient information. Cloud-based analysis, remote neuropathology, software updates, and international model training require secure transfer, consent frameworks, audit trails, and protection against unauthorized access. Model updates can change performance. A new classifier version may improve common categories while reducing accuracy in a rare subtype. Clinical laboratories should validate software versions, document changes, and retain the ability to reproduce previous analyses. Another challenge is analytical contamination. Nanopore and

PCR workflows are sensitive to carryover DNA. The operating-room diagnostic pathway must use clean specimen transfer, unique identifiers, negative controls, physically separated pre-amplification and post-amplification zones, and documented chain of custody.

Tissue allocation should be defined before surgery. A small biopsy cannot be divided informally among frozen section, SRH, sequencing, culture, research, and permanent pathology. The definitive diagnosis must not be compromised by excessive rapid testing. An optimal workflow is sequential. Fresh tissue first undergoes a non-destructive or minimally destructive optical assessment. Representative regions are then allocated to rapid molecular testing and permanent processing. The neuropathologist reviews concordance among morphology, AI, and molecular results. Discordant findings require explanation rather than automatic averaging. An SRH image may show glioma while nanopore classification returns normal tissue because of low purity. Rapid PCR may detect IDH mutation in a sample whose morphology is dominated by reactive brain. These results can all be correct at different analytical scales. Spatial heterogeneity creates additional complexity. A glioblastoma may contain necrotic, proliferative, infiltrative, and treatment-resistant regions with different genomic and metabolic features. A single molecular classification identifies the tumor entity but does not describe every regional clone. Multi-region sampling can map this heterogeneity but must remain clinically justified. Excessive sampling increases time, cost, and risk. The central question is whether additional information can alter management. Intelligent intraoperative neuropathology may be particularly valuable in low-resource regions lacking continuous access to specialist neuropathologists. SRH images can be analyzed locally by AI and reviewed remotely. Portable nanopore systems reduce dependence on centralized sequencing infrastructure. However, high equipment cost and maintenance may widen disparities if platforms remain concentrated in wealthy centers. Open datasets, open-source models, shared regional laboratories, and portable technologies may improve accessibility.

Cost-effectiveness should include avoided repeat biopsy, reduced frozen-section labor, shorter diagnostic delay, optimized tissue use, potential reduction in residual tumor, and prevention of inappropriate resection. It should also account for equipment, consumables, technicians, computational infrastructure, quality assurance, and molecular confirmation. Regulatory evaluation should distinguish advisory tools from systems directly controlling surgical action. A classifier suggesting a differential diagnosis poses a different risk from a device defining the resection boundary in real time. The proposed SMART-PATH model addresses this difference by treating the diagnostic pathway as a closed loop rather than a machine output. Sampling strategy ensures that representative tissue is obtained and preserved. Multimodal acquisition combines optical, molecular, radiological, and conventional pathological information. Algorithmic confidence requires calibration, alternative predictions, and abstention. Rapid molecular testing addresses the specific intraoperative question rather than generating unnecessary data. Topographic mapping links every result to its surgical location. Pathology verification maintains expert integrated interpretation. Actionable interpretation defines which result can legitimately influence surgery. Team communication ensures that surgeons, neuropathologists, molecular scientists, and operating-room staff understand the result and its limitations. Human oversight preserves responsibility for the final clinical decision.

Table 5. Scientific Originality of the SMART-PATH Framework

Existing limitation	Conventional interpretation	SMART-PATH principle	Expected clinical contribution
Rapid diagnosis treated as a single test	One platform expected to answer every question	Optical, molecular, and pathological methods assigned complementary roles	Reduces inappropriate technology substitution
High accuracy assumed to justify action	Model performance equated with surgical usefulness	Decision impact and anatomical safety evaluated separately	Prevents diagnostically correct but unsafe resection
Margin samples analyzed without spatial mapping	Tumor-positive result lacks surgical context	Every specimen linked to navigation and cavity anatomy	Enables reproducible topographic interpretation
Confidence reported as an unverified score	High number assumed to equal certainty	Calibration, alternatives, and abstention required	Reduces overconfident misclassification
Low-purity samples treated as ordinary cases	Diluted molecular signal ignored	Histological purity and tissue adequacy assessed before interpretation	Improves molecular reliability
Algorithm and neuropathologist viewed as competitors	Automation framed as replacement	Human–AI concordance and discrepancy resolution formalized	Preserves integrated diagnostic responsibility
Tissue allocation performed ad hoc	Rapid testing may exhaust the sample	Predefined specimen-allocation hierarchy	Protects final diagnostic adequacy
Technical failure handled during surgery	Delays can disrupt operative strategy	Turnaround limits and fallback pathways established before incision	Maintains workflow continuity
Molecular positivity interpreted as a mandatory margin	Biological infiltration equated with removable tumor	Functional anatomy and neurological risk remain decisive	Supports maximal safe rather than indiscriminate resection

Limitations of Current Evidence. Many available studies evaluate diagnostic accuracy rather than patient outcomes. The evidence that a platform correctly classifies tissue does not establish that its use improves survival, neurological function, or quality of life. Several studies originate from highly specialized centers with expert neurosurgical oncology, neuropathology, optical engineering, and computational teams. Performance may be lower during implementation in centers with different case mix or technical support. Reference standards also vary. Some studies compare AI with frozen-section diagnosis, others with permanent H&E, WHO-integrated diagnosis, methylation class, or expert consensus. These endpoints are not equivalent. Publication bias may favor successful platforms. Negative studies, technical failures, low-quality images, and difficult rare cases may be

underrepresented. The rapid evolution of model architecture complicates long-term comparison. A platform can become obsolete before a randomized outcome trial is completed.

Future Directions. Prospective trials should randomize or pragmatically compare intelligent intraoperative workflows with standard care. The intervention should include predefined decision rules so that diagnostic information is translated consistently into surgical action. Margin studies should combine SRH, neuronavigation, intraoperative MRI or ultrasound, electrophysiological mapping, and postoperative volumetric analysis. Longitudinal follow-up should determine whether AI-guided additional resection improves disease control without increasing permanent deficit. Rapid sequencing studies should evaluate adult and pediatric tumors separately because their molecular spectra differ. They should include rare tumors, low-purity specimens, recurrent treated lesions, and inflammatory mimics. Multimodal foundation models may integrate SRH, H&E, MRI, age, location, genomic data, and operative context. Such models may outperform single-modality classifiers but introduce greater complexity and risk of hidden bias. Real-time uncertainty visualization is a priority. The surgeon should see not only the predicted label but also specimen quality, confidence range, alternative classes, and evidence that the sample is outside the model's validated distribution. Future platforms may perform continuous tissue interrogation through handheld Raman probes, endoscopic optics, mass-spectrometric surgical instruments, or intelligent ultrasonic aspiration. Direct in situ analysis would reduce sampling delay but must distinguish thermal, mechanical, and blood-related artifacts.

Conclusion. Intelligent intraoperative neuropathology is transforming brain-tumor surgery from provisional morphology-based consultation toward integrated optical, molecular, and computational diagnosis. Stimulated Raman histology produces high-resolution digital images of fresh tissue without fixation or staining. When combined with deep learning, it provides near-real-time tumor classification and can quantify diffuse-glioma infiltration. FastGlioma represents the most advanced prospective application of this concept. It produced predictions in less than ten seconds and achieved strong infiltration-detection performance across an international multicenter cohort. Rapid nanopore platforms extend intraoperative diagnosis from morphology to molecular classification. Sturgeon, MethyLYZR, and Rapid-CNS² demonstrate that sparse methylation and copy-number information can be interpreted during the operation. Rapid PCR, droplet digital PCR, and mass spectrometry offer focused alternatives for IDH, TERT promoter, tumor fraction, and oncometabolite assessment. Hetairos demonstrates that artificial intelligence can infer a broad range of methylation-associated CNS tumor subtypes from routine H&E slides, but such prediction remains an adjunct rather than a substitute for direct molecular testing. The principal limitations are sampling error, low tumor purity, rare entities, domain shift, technical contamination, loss of spatial context, miscalibrated confidence, and automation bias. A diagnostically accurate result does not automatically justify further resection. The decision must integrate functional anatomy, neurological risk, patient goals, and the biological meaning of residual infiltration. The proposed SMART-PATH framework integrates Sampling strategy, Multimodal acquisition, Algorithmic confidence, Rapid molecular testing, Topographic mapping, Pathology verification, Actionable interpretation, Team communication, and Human oversight. The future of intraoperative neuropathology is not an autonomous algorithm replacing the neuropathologist or neurosurgeon. It is a coordinated human–machine system that

delivers representative, spatially localized, uncertainty-aware and clinically actionable information while the surgical decision can still be changed.

References

1. Orringer DA, Pandian B, Niknafs YS, et al. Rapid intraoperative histology of unprocessed surgical specimens via fibre-laser-based stimulated Raman scattering microscopy. Nat Biomed Eng. 2017;1:0027.
2. Hollon TC, Pandian B, Adapa AR, et al. Near real-time intraoperative brain tumor diagnosis using stimulated Raman histology and deep neural networks. Nat Med. 2020;26:52–58.
3. Jiang C, Hou X, Kondepudi A, et al. OpenSRH: optimizing brain tumor surgery using intraoperative stimulated Raman histology. Adv Neural Inf Process Syst. 2022;35:28502–28516.
4. Kondepudi A, et al. Foundation models for fast, label-free detection of glioma infiltration. Nature. 2025. doi:10.1038/s41586-024-08169-3.
5. Pekmezci M, et al. Detection of glioma infiltration at the tumor margin using quantitative stimulated Raman scattering histology. Sci Rep. 2021;11:12162.
6. Di L, et al. Stimulated Raman histology for rapid intraoperative diagnosis of gliomas. World Neurosurg. 2021;150:e135–e143.
7. Scheffler P, et al. Intraoperative classification of CNS lymphoma and glioblastoma by AI-based analysis of stimulated Raman histology. Brain Spine. 2025;5:104187.
8. Vermeulen C, et al. Ultra-fast deep-learned CNS tumour classification during surgery. Nature. 2023;622:842–849.
9. Patel A, Göbel K, et al. Prospective, multicenter validation of a platform for rapid molecular profiling of central nervous system tumors. Nat Med. 2025. doi:10.1038/s41591-025-03562-5.
10. Brändl B, Steiger M, Müller FJ, et al. Rapid brain tumor classification from sparse epigenomic data. Nat Med. 2025. doi:10.1038/s41591-024-03435-3.
11. Jin D, et al. Hetairos is a histology-based artificial intelligence model for predicting central nervous system tumor methylation subtypes. Nat Cancer. 2026. doi:10.1038/s43018-026-01186-3.
12. Li J, Han Z, Ma C, et al. Intraoperative rapid molecular diagnosis aids glioma subtyping and guides precise surgical resection. Ann Clin Transl Neurol. 2024;11:2176–2187.
13. Maeda S, et al. Rapid intraoperative genetic analysis of adult-type diffuse gliomas using a microfluidic real-time polymerase chain reaction device. Neuro Oncol. 2025;27(12):3161–3172.
14. Shankar GM, et al. Rapid intraoperative molecular characterization of glioma. JAMA Oncol. 2015;1(5):662–667.
15. Livermore LJ, et al. Rapid intraoperative molecular genetic classification of gliomas using Raman spectroscopy. Neurooncol Adv. 2019;1:vdz008.

16. Sun Z, et al. Rapid detection of IDH mutations in gliomas by intraoperative mass spectrometry. Proc Natl Acad Sci U S A. 2024;121:e2318843121.
17. Hollon T, et al. Ultra-rapid droplet digital PCR enables intraoperative tumor quantification. Neuro Oncol Adv. 2025.
18. Golf O, et al. Towards real-time intraoperative tissue interrogation for REIMS-guided glioma surgery. Eur J Surg Oncol. 2022;48:2320–2329.
19. Ikeda JI, et al. Intraoperative integrated diagnostic system for malignant central nervous system tumors. Brain Tumor Pathol. 2024;41:1–12.
20. Zhang J, et al. Application of intraoperative rapid molecular diagnosis in precision surgery for glioma: mimicking the WHO CNS5 integrated diagnosis. Neurosurgery. 2023;92:762–771.
21. Capper D, Jones DTW, Sill M, et al. DNA methylation-based classification of central nervous system tumours. Nature. 2018;555:469–474.
22. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol. 2021;23:1231–1251.
23. Nasrallah MP, et al. Machine learning for cryosection pathology predicts the 2021 WHO classification of glioma. Med. 2023;4:526–540.
24. Blokker M, et al. Fast intraoperative histology-based diagnosis of gliomas with third harmonic generation microscopy and deep learning. Sci Rep. 2022;12:11334.
25. Hollon TC, et al. Artificial-intelligence-based molecular classification of diffuse gliomas using rapid, label-free optical imaging. Nat Med. 2023.
26. Orringer DA, et al. Rapid intraoperative histology and molecular assessment in neurosurgical oncology. Neurosurg Clin N Am. 2024;35:1–14.
27. Trevisi G, et al. Raman spectroscopy for intraoperative identification of glioma tissue: diagnostic accuracy and molecular applications. Neurosurg Rev. 2025.
28. Chen JS, et al. The intraoperative utility of Raman spectroscopy for neurosurgical oncology. Cancers. 2025;17:3124.
29. Reinecke D, et al. AI-driven label-free Raman spectromics for intraoperative spinal tumor diagnosis. NPJ Digit Med. 2026. doi:10.1038/s41746-025-02279-6.
30. LeCun Y, Bengio Y, Hinton G. Deep learning. Nature. 2015;521:436–444.
31. Fehlings, M. G., Tetreault, L. A., Riew, K. D., Middleton, J. W., Aarabi, B., Arnold, P. M., Brodke, D. S., Chiba, K., Dettori, J. R., Furlan, J. C., Harrop, J. S., Holly, L. T., Kalsi-Ryan, S., Kotter, M., Kurpad, S. N., Kwon, B. K., Martin, A. R., Massicotte, E. M., ... Wilson, J. R. (2017). A clinical practice guideline for the management of patients with degenerative cervical myelopathy. Global Spine Journal, 7(3 Suppl), 21S–27S.

32. Harrop, J. S., Aarabi, B., Dhall, S. S., Gelb, D. E., Hurlbert, R. J., Rozzelle, C. J., Ryken, T. C., Theodore, N., Walters, B. C., & Hadley, M. N. (2013). Management of acute traumatic central cord syndrome. Neurosurgery, 72(Suppl. 2), 195–204.
33. Rekate, H. L. (2009). A contemporary definition and classification of hydrocephalus. Seminars in Pediatric Neurology, 16(1), 9–15.

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