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INTRAOPERATIVE MOLECULAR IMAGING OF GLIOMA MARGINS: COMPARATIVE INTEGRATION OF 5-AMINOLEVULINIC ACID, RAMAN SPECTROSCOPY, AND REAL-TIME TISSUE CLASSIFICATION

Abstract

Background. In high-grade and molecularly heterogeneous diffuse gliomas, neurosurgical decisions remain difficult because visual inspection and white-light microscopy underestimate infiltrative tumor, whereas fluorescence intensity varies with tumor biology, treatment history, pharmacokinetics, and optical conditions.

Materials and methods. A structured narrative review is proposed using clinical trials, prospective cohorts, diagnostic-accuracy studies, systematic reviews, and relevant technical investigations. Evidence is organized by biological plausibility, technical performance, patient selection, safety, clinical effectiveness, reproducibility, and implementation. A prospective comparative study is specified for adults undergoing resection of newly diagnosed or recurrent contrast-enhancing diffuse glioma, with 5-ALA fluorescence-guided surgery alone as the reference strategy.

Results. The synthesis addresses five domains: fluorescence-guided resection, spectroscopic detection of nonfluorescent infiltration, real-time tissue classification, sampling bias and histological ground truth, workflow and regulatory translation. The proposed primary endpoint is patient-level sensitivity for viable infiltrating tumor at the final resection margin without an increase in permanent neurological morbidity; secondary endpoints include specificity, positive predictive value, residual enhancing volume, sampling time, interobserver agreement, molecular subgroup performance, and cost per additional tumor-positive margin detected. Originality derives from linking technical accuracy to patient-centered outcomes, explicitly modeling uncertainty, and requiring external validation.

Conclusion. Standardized endpoints support reliable clinical comparison. Independent adjudication strengthens causal interpretation. Longitudinal follow-up clarifies therapeutic durability. Equity analysis supports responsible implementation. Transparent reporting improves scientific reproducibility. Patient safety remains the central priority. External datasets reduce optimistic performance estimates. Rigorous independent external validation remains essential.

Keywords: glioma; 5-aminolevulinic acid; Raman spectroscopy; fluorescence-guided surgery; molecular imaging; surgical margin; machine learning.

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ИНТРАОПЕРАЦИОННАЯ МОЛЕКУЛЯРНАЯ ВИЗУАЛИЗАЦИЯ ГРАНИЦ ГЛИОМЫ: СРАВНИТЕЛЬНАЯ ИНТЕГРАЦИЯ 5-АМИНОЛЕВУЛИНОВОЙ КИСЛОТЫ, РАМАНОВСКОЙ СПЕКТРОСКОПИИ И КЛАССИФИКАЦИИ ТКАНИ В РЕАЛЬНОМ ВРЕМЕНИ

Аннотация

Актуальность. При высокозлокачественных и молекулярно гетерогенных диффузных глиомах принятие нейрохирургических решений остается сложной задачей, поскольку визуальная оценка и микроскопия в белом свете недооценивают степень инфильтративного распространения опухоли. При этом интенсивность флуоресценции варьирует в зависимости от биологических характеристик опухоли, истории предшествующего лечения, фармакокинетики флуоресцентного препарата и оптических условий во время операции.

Материалы и методы. Предложен структурированный нарративный обзор, включающий клинические исследования, проспективные когортные наблюдения, исследования диагностической точности, систематические обзоры и релевантные технические разработки. Доказательства систематизированы по биологической обоснованности, технической эффективности, критериям отбора пациентов, безопасности, клинической результативности, воспроизводимости и возможности внедрения в практику. Разработан дизайн проспективного сравнительного исследования с участием взрослых пациентов, которым выполняется резекция впервые выявленной или рецидивной диффузной глиомы с контрастным усилением. В качестве референтной стратегии определена только флуоресцентно-навигационная хирургия с применением 5-аминолевулиновой кислоты.

Результаты. Синтез доказательств охватывает пять основных направлений: флуоресцентно-ориентированную резекцию, спектроскопическое выявление нефлуоресцирующей опухолевой инфильтрации, классификацию тканей в режиме реального времени, систематические ошибки при отборе образцов и гистологическую верификацию как эталонный метод, а также интеграцию технологии в операционный процесс и ее регуляторное внедрение. Предлагаемой первичной конечной точкой является чувствительность на уровне пациента при выявлении жизнеспособной инфильтрирующей опухолевой ткани по окончательному краю резекции без увеличения частоты стойкой неврологической заболеваемости. Вторичные конечные точки включают специфичность, положительную прогностическую ценность, объем остаточной контраст-накапливающей опухоли, продолжительность отбора образцов, межнаблюдательную согласованность, эффективность метода в различных молекулярных подгруппах и стоимость выявления одного дополнительного опухоль-положительного края резекции. Научная оригинальность заключается в объединении технической точности с клиническими исходами, значимыми для пациента, явном моделировании неопределенности и обязательном проведении внешней валидации.

Заключение. Стандартизированные конечные точки обеспечивают надежность клинических сравнений. Независимая экспертная оценка результатов повышает достоверность причинно-следственной интерпретации. Продолжительное наблюдение позволяет оценить устойчивость терапевтического эффекта. Анализ равноправия способствует ответственному внедрению технологии. Прозрачное представление результатов повышает научную воспроизводимость. Безопасность пациента остается основным приоритетом. Использование внешних наборов данных снижает риск завышенной оценки эффективности метода. Строгая и независимая внешняя валидация остается обязательным условием.

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Ключевые слова: глиома; 5-аминолевулиновая кислота; рамановская спектроскопия; флуоресцентная навигация; молекулярная визуализация; хирургический край; машинное обучение.

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GLIOMA CHEGARALARINI INTRAOPERATSION MOLEKULYAR TASVIRLASH: 5-AMINOLEVULIN KISLOTA, RAMAN SPEKTROSKOPIYASI VA REAL VAQT TO‘QIMA KLASSIFIKATSIYASINI QIYOSIY INTEGRATSIYA QILISH

Annotatsiya

Dolzarblik. Yuqori darajali va molekulyar jihatdan geterogen diffuz gliomalarda neyroxirurgik qaror qabul qilish murakkabligicha qolmoqda, chunki vizual baholash hamda oq yorug‘lik mikroskopiyasi o‘smaning infiltrativ tarqalish darajasini yetarlicha aniqlamaydi. Shu bilan birga, fluoressensiya intensivligi o‘smaning biologik xususiyatlari, avvalgi davolash tarixi, fluoressent preparat farmakokinetikasi va operatsiya vaqtidagi optik sharoitlarga qarab o‘zgaradi.

Material va usullar. Klinik tadqiqotlar, prospektiv kohort kuzatuvlari, diagnostik aniqlikni baholovchi tadqiqotlar, tizimli sharhlar va tegishli texnik izlanishlarni qamrab oluvchi strukturaviy narrativ sharh taklif etildi. Dalillar biologik asoslanganlik, texnik samaradorlik, bemorlarni tanlash mezonlari, xavfsizlik, klinik natijadorlik, takrorlanuvchanlik va amaliyotga joriy etish imkoniyatiga ko‘ra tizimlashtirildi. Kontrast to‘plovchi yangi aniqlangan yoki qaytalangan diffuz gliomani rezeksiya qilish rejalashtirilgan katta yoshli bemorlar uchun prospektiv qiyosiy tadqiqot dizayni ishlab chiqildi. Faqat 5-aminolevulin kislotasi yordamida amalga oshiriladigan fluoressensiya-navigatsion jarrohlik referent strategiya sifatida belgilandi.

Natijalar. Dalillar sintezi beshta asosiy yo‘nalishni qamrab oladi: fluoressensiya asosida rezeksiya qilish, fluoressensiya bermaydigan infiltrativ o‘sma to‘qimasini spektroskopik aniqlash, to‘qimalarni real vaqt rejimida tasniflash, namuna olishdagi tizimli xatolik va gistologik tekshiruvni etalon mezon sifatida qo‘llash, shuningdek, texnologiyani operatsion ish jarayoniga va regulyator amaliyotga integratsiya qilish. Taklif etilgan birlamchi yakuniy ko‘rsatkich doimiy nevrologik asoratlar chastotasini oshirmagan holda yakuniy rezeksiya chegarasida hayotchan infiltrativ o‘sma to‘qimasini bemor darajasida aniqlash sezgirligidir. Ikkilamchi yakuniy ko‘rsatkichlarga spetsifiklik, musbat prognostik qiymat, kontrast to‘plovchi qoldiq o‘sma hajmi, namuna olish davomiyligi, mutaxassislararo muvofiqlik, turli molekulyar kichik guruhlardagi diagnostik samaradorlik va qo‘shimcha aniqlangan har bir o‘sma-musbat rezeksiya chegarasiga sarflanadigan xarajat kiradi. Tadqiqotning ilmiy yangiligi texnik aniqlikni bemor uchun klinik ahamiyatga ega natijalar bilan bog‘lash, noaniqlikni aniq modellashtirish va tashqi validatsiyani majburiy talab qilish bilan belgilanadi.

Xulosa. Standartlashtirilgan yakuniy ko‘rsatkichlar klinik natijalarni ishonchli taqqoslash imkonini beradi. Natijalarni mustaqil ekspert baholashi sabab-oqibat bog‘liqligini talqin qilishning ishonchliligini oshiradi. Uzoq muddatli kuzatuv terapevtik ta’sirning barqarorligini aniqlash imkonini beradi. Tenglik va adolatlilik tahlili texnologiyani mas’uliyatli joriy etishni qo‘llab-quvvatlaydi. Shaffof hisobot ilmiy natijalarning takrorlanuvchanligini yaxshilaydi. Bemor xavfsizligi asosiy

ustuvor yo‘nalish bo‘lib qoladi. Tashqi ma’lumotlar to‘plamlaridan foydalanish usul samaradorligini asossiz yuqori baholash xavfini kamaytiradi. Qat’iy va mustaqil tashqi validatsiya o‘tkazilishi muhim talab bo‘lib qolmoqda.
Kalit so‘zlar: glioma; 5-aminolevulin kislota; Raman spektroskopiyasi; flyuorestsent navigatsiya; molekulyar tasvirlash; jarrohlik chegarasi; mashinaviy o‘qitish.

Introduction. Neurosurgery is increasingly defined by the tension between anatomical precision and biological uncertainty. In high-grade and molecularly heterogeneous diffuse gliomas, the surgeon must act on information that is incomplete, time dependent, and distributed across imaging, physiology, pathology, electrophysiology, and patient-specific functional reserve. The conventional operative paradigm is therefore being replaced by a data-rich model in which preoperative planning, intraoperative sensing, and postoperative surveillance are treated as a continuous decision process. This evolution is clinically important because technical success cannot be reduced to target acquisition or implant placement; it must also preserve neurological function, reduce treatment burden, and improve survival or participation. Contemporary evidence supports this shift, but also shows that many innovations remain supported by retrospective cohorts, selected populations, and heterogeneous endpoints [21, 24, 31]. The central scientific problem is not simply whether a new device or algorithm performs accurately, but whether it changes a decision at the correct time and improves a patient-centered outcome. The specific rationale for intraoperative molecular imaging of glioma margins arises from a persistent limitation: visual inspection and white-light microscopy underestimate infiltrative tumor, whereas fluorescence intensity varies with tumor biology, treatment history, pharmacokinetics, and optical conditions. This limitation creates several forms of uncertainty. Anatomical uncertainty concerns where the clinically relevant target or boundary is located. Biological uncertainty concerns whether a visible or measurable abnormality represents viable disease, reversible dysfunction, treatment effect, or nonactionable tissue injury. Functional uncertainty concerns how much intervention can be tolerated without compromising language, cognition, mobility, independence, or quality of life. Finally, temporal uncertainty concerns how rapidly physiology, anatomy, or disease burden changes during and after treatment. Existing methods usually address only one of these dimensions. The proposed innovation-a multimodal margin-assessment strategy combining 5-ALA fluorescence, handheld Raman spectroscopy, quantitative optical calibration, and machine-learning tissue classification referenced to spatially matched histopathology-is intended to combine them within a single clinically interpretable framework [7, 14, 19].

The potential advantages of this approach are mechanistically plausible. Relevant processes include protoporphyrin IX accumulation, vibrational molecular fingerprinting, optical calibration, machine-learning spectral classification, spatially registered histopathological validation. When these processes are measured independently, the clinician receives fragmented signals with different spatial resolutions, temporal resolutions, and error structures. Integration can theoretically reduce uncertainty by allowing one modality to compensate for the weaknesses of another. However, multimodal integration can also amplify hidden bias, propagate registration error, and create false confidence if outputs are presented without uncertainty estimates. For that reason, a clinically responsible system must reveal both its prediction and the conditions under which that prediction may fail. This requirement is particularly important in neurosurgery, where small errors can produce irreversible

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disability and where intraoperative decisions are often made under severe time constraints [4, 7, 14, 19]. Five evidence gaps justify a dedicated original investigation: small single-center cohorts, heterogeneous spectral preprocessing, limited recurrent-tumor data, absence of standardized margin definitions, uncertain impact on survival and neurocognitive outcome. These gaps are not merely methodological details. They determine whether results can be generalized across hospitals, whether a platform remains reliable after software or hardware changes, and whether the observed benefit reflects the technology rather than expert operator selection. A further problem is that technical publications often emphasize accuracy metrics while clinical publications emphasize outcome, leaving a translational gap between algorithmic performance and therapeutic value. The proposed study therefore uses patient-level sensitivity for viable infiltrating tumor at the final resection margin without an increase in permanent neurological morbidity as its primary endpoint and includes specificity, positive predictive value, residual enhancing volume, sampling time, interobserver agreement, molecular subgroup performance, and cost per additional tumor-positive margin detected as secondary endpoints. This endpoint architecture is intended to prevent a statistically impressive but clinically irrelevant result [1, 2, 10, 13].

Materials and methods. A structured narrative review with a prospectively defined translational framework was selected because the field contains randomized trials, observational cohorts, diagnostic-accuracy studies, engineering reports, and implementation analyses that cannot be combined responsibly through a single pooled effect estimate. Searches should cover MEDLINE, Embase, Scopus, Web of Science, the Cochrane Library, and major trial registries from January 2015 through July 2026, while allowing earlier landmark studies when they established the current standard. Core search concepts should combine the disease or procedure, the intervention components, and outcome terms related to safety, neurological function, accuracy, and effectiveness. Citation chaining should be used to identify technical validation papers that may not be indexed under conventional clinical terminology [1, 4, 7].

Eligible evidence should include adult or mixed-age human studies directly evaluating intraoperative molecular imaging of glioma margins; studies of adults undergoing resection of newly diagnosed or recurrent contrast-enhancing diffuse glioma; and investigations reporting at least one clinically interpretable outcome. Exclusion criteria should include purely conceptual commentaries without original data, nonvalidated simulations, duplicated cohorts, and reports in which the contribution of the target technology cannot be separated from unrelated interventions. For diagnostic and algorithmic studies, the reference standard, unit of analysis, handling of repeated measurements, and patient-level data split must be extracted. For therapeutic studies, eligibility criteria, crossover, rescue treatment, missing data, and outcome adjudication must be recorded. The distinction between internal validation, temporal validation, geographic external validation, and prospective clinical validation is essential [2, 5, 8].

Data extraction should be organized into six domains: patient characteristics; disease or anatomical complexity; technical configuration; operator experience; safety; and clinical outcome. The technical domain should record hardware, software version, preprocessing, calibration, registration, data latency, and failure handling. The clinical domain should record patient-level sensitivity for viable infiltrating tumor at the final resection margin without an increase in permanent neurological morbidity and

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specificity, positive predictive value, residual enhancing volume, sampling time, interobserver agreement, molecular subgroup performance, and cost per additional tumor-positive margin detected. Risk of bias should be assessed with tools appropriate to study type, including RoB 2 for randomized trials, ROBINS-I for nonrandomized intervention studies, QUADAS-2 for diagnostic accuracy, and PROBAST or an equivalent framework for prediction models. Certainty should be interpreted according to consistency, directness, precision, and evidence of selective reporting [16, 23, 30]. The proposed original study is a prospective, multicenter, assessor-blinded comparative investigation involving adults undergoing resection of newly diagnosed or recurrent contrast-enhancing diffuse glioma. Participants should be enrolled consecutively to reduce spectrum bias. The intervention arm should receive a multimodal margin-assessment strategy combining 5-ALA fluorescence, handheld Raman spectroscopy, quantitative optical calibration, and machine-learning tissue classification referenced to spatially matched histopathology; the control arm should receive 5-ALA fluorescence-guided surgery alone. Randomization is preferred when clinical equipoise exists. If randomization is impractical, a pragmatic stepped-wedge or prospective registry design with propensity weighting and center-level random effects should be used. The primary endpoint is patient-level sensitivity for viable infiltrating tumor at the final resection margin without an increase in permanent neurological morbidity. Secondary endpoints are specificity, positive predictive value, residual enhancing volume, sampling time, interobserver agreement, molecular subgroup performance, and cost per additional tumor-positive margin detected. Outcome assessors should remain blinded to technical allocation whenever possible, and adverse events should be adjudicated by an independent committee. The statistical analysis plan should be finalized before database lock. Continuous outcomes should be analyzed with mixed-effects models that account for center and repeated measurements. Binary endpoints should be reported with absolute risk differences, relative risks, and number needed to treat or harm when appropriate. Ordinal neurological outcomes should be analyzed with proportional-odds models after testing the proportionality assumption. Time-to-event outcomes require Kaplan–Meier estimation and multivariable Cox models. Diagnostic models must report discrimination, calibration, decision-curve analysis, and performance across clinically relevant subgroups. Missing data should be addressed through multiple imputation when assumptions are defensible, accompanied by complete-case and worst-case sensitivity analyses.

Ethical oversight should recognize that advanced technology introduces risks beyond ordinary operative complications. These include privacy loss, cybersecurity failure, automation bias, inequitable performance, unplanned device downtime, and conflicts of interest arising from proprietary platforms. Consent documents should explain which decisions remain under surgeon control, whether data may be used for algorithm development, and how incidental findings will be managed. A data and safety monitoring structure should review not only adverse clinical events but also registration failures, algorithmic drift, protocol deviations, and cases in which the system recommendation was overridden. Such governance converts technological innovation into accountable clinical research [3, 6, 10].

Results. The structured synthesis is expected to identify a first domain centered on fluorescence-guided resection. Across contemporary studies, the most consistent observation is that richer biological or anatomical characterization improves stratification, but reported gains vary according to reference standards and population spectrum. Studies that use retrospective convenience

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samples commonly show higher performance than prospective consecutive cohorts. This difference is clinically meaningful because difficult cases, prior treatment, motion, artifact, and incomplete data are underrepresented in curated datasets. Accordingly, the likely result is not a universal performance value, but a gradient of reliability that depends on data quality, disease phenotype, and operator context [1, 2, 4]. A second domain concerns spectroscopic detection of nonfluorescent infiltration. The relevant literature suggests that intraoperative or procedure-time information is most valuable when it changes the operative plan rather than merely confirming a preoperative expectation. Clinically useful outputs therefore require low latency, stable registration, and a display format that can be interpreted without interrupting the procedure. The synthesis also indicates that human expertise remains necessary for resolving discordance between technology and anatomy. Systems designed as collaborative decision aids are more likely to improve workflow than systems designed as autonomous authorities. The proposed study will document every technology-related plan modification, the reason for the change, and whether the modification was subsequently supported by pathology, imaging, electrophysiology, or clinical outcome [5, 11, 16]. The third domain is real-time tissue classification. Evidence in this area shows that temporal change is a central feature of neurosurgical care. Anatomy deforms, physiological reserve fluctuates, tissue characteristics evolve, and device signals drift. Static thresholds or one-time images therefore have limited validity. A dynamic strategy should update its estimate as new data arrive and should retain an audit trail of how recommendations changed. The anticipated result is that dynamic monitoring will reduce selected technical errors, but it may also increase false-positive alerts. This trade-off must be quantified through sensitivity, specificity, false-alert burden, and decision-curve analysis rather than described qualitatively [8, 9, 25]. The fourth domain, sampling bias and histological ground truth, addresses the relationship between technical success and patient-centered benefit. Existing evidence often demonstrates improved localization, classification, or device accuracy without proving a reduction in disability or a durable improvement in survival. The proposed research framework therefore treats technical accuracy as an intermediate endpoint. The primary clinical endpoint remains patient-level sensitivity for viable infiltrating tumor at the final resection margin without an increase in permanent neurological morbidity. Secondary analysis will evaluate whether technical improvement mediates clinical benefit and whether the effect differs by baseline risk. This mediation-oriented approach can distinguish a technology that is accurate but clinically redundant from one that enables a beneficial change in treatment.

The fifth domain is workflow and regulatory translation. Implementation outcomes are expected to vary substantially between high-volume academic centers and lower-resource hospitals. Capital costs, maintenance, calibration, data storage, staffing, and training may determine real-world effectiveness more strongly than laboratory accuracy. The framework therefore includes acquisition cost, consumables, room time, failed-case cost, revision avoidance, and staff workload. Equity analysis should determine whether the innovation narrows or widens access. A platform that performs well only in a highly selected tertiary environment should not be described as universally transformative [2, 3, 18]. Taken together, the expected evidence pattern supports cautious optimism. A multimodal margin-assessment strategy combining 5-ala fluorescence, handheld raman spectroscopy, quantitative optical calibration, and machine-learning tissue classification referenced to spatially matched histopathology is likely to provide the greatest benefit in patients with high decision uncertainty and a realistic

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opportunity for management change. Benefit may be smaller in straightforward cases where standard practice already performs well. Harm may emerge from false reassurance, unnecessary extension of surgery, treatment delay, excessive alarms, or inappropriate extrapolation beyond the validated population. The originality tables below convert these observations into a testable study architecture and make clear which elements represent true innovation rather than repackaging of established practice.

Table 1. **Scientific originality matrix**

Domain	Current standard or limitation	Proposed original contribution
Optical signal	Subjective fluorescence intensity	Calibrated fluorescence plus quantitative Raman spectra
Margin validation	Selected biopsy specimens	Spatially registered circumferential margin sampling
Algorithm	Offline classification	Real-time uncertainty-aware tissue classification
Clinical endpoint	Diagnostic accuracy only	Accuracy linked to residual volume and 90-day function
Recurrent disease	Frequently excluded	Prespecified analysis of treatment effect and pseudoprogression

Table 2. **Proposed prospective study framework**

Element	Specification
Population	adults undergoing resection of newly diagnosed or recurrent contrast-enhancing diffuse glioma
Intervention	a multimodal margin-assessment strategy combining 5-ALA fluorescence, handheld Raman spectroscopy, quantitative optical calibration, and machine-learning tissue classification referenced to spatially matched histopathology
Comparator	5-ALA fluorescence-guided surgery alone
Primary endpoint	patient-level sensitivity for viable infiltrating tumor at the final resection margin without an increase in permanent neurological morbidity
Secondary endpoints	specificity, positive predictive value, residual enhancing volume, sampling time, interobserver agreement, molecular subgroup performance, and cost per additional tumor-positive margin detected

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Element	**Specification**
Design	Prospective multicenter randomized trial when equipoise permits; otherwise a stepped-wedge or rigorously adjusted prospective registry.
Validation	Internal, temporal, geographic, and subgroup validation with prespecified failure and uncertainty reporting.
Ethics	Independent safety adjudication, data governance, cybersecurity review, and transparent disclosure of proprietary interests.

Discussion. The principal interpretation is that intraoperative molecular imaging of glioma margins should be evaluated as a sociotechnical intervention. The operative result emerges from interaction among the patient, surgeon, team, imaging or monitoring environment, software, hardware, institutional protocols, and rescue pathways. This explains why promising accuracy studies may not reproduce the same benefit after implementation. A technically excellent platform can fail if registration is unreliable, alerts are poorly prioritized, staff roles are unclear, or the output arrives too late to influence the decision. Conversely, a moderately accurate system can be clinically valuable when it addresses a high-impact uncertainty and integrates smoothly into workflow [1, 3, 5]. Patient selection is likely to be the main determinant of effect size. The target population is adults undergoing resection of newly diagnosed or recurrent contrast-enhancing diffuse glioma, but not every eligible patient has the same probability of benefit. Selection should incorporate baseline function, disease burden, anatomical complexity, comorbidity, prior treatment, expected survival, and the availability of an actionable alternative. The intervention should not be offered merely because the technology is available. A decision-impact criterion is more appropriate: the patient should have a plausible management fork that the new information can resolve. This principle limits exposure to unnecessary complexity and improves the efficiency of prospective trials [2, 4, 6]. The choice of comparator is equally important. The relevant comparator is 5-ALA fluorescence-guided surgery alone, delivered by trained clinicians under a standardized protocol. Comparing an advanced platform with poorly defined historical care exaggerates benefit and does not inform contemporary practice. Expertise bias should be addressed by documenting operator experience in both arms and by separating the learning phase from the evaluative phase. When blinding the surgeon is impossible, blinded endpoint assessment, objective imaging or physiological criteria, and independent adjudication become essential. These safeguards are particularly important when the intervention itself changes the amount or duration of surgery.

Safety must include both direct and indirect harm. Direct harm includes device- or procedure-related injury, infection, hemorrhage, neurological deficit, or treatment toxicity. Indirect harm includes delay, over-treatment, under-treatment, false reassurance, automation bias, and diversion of resources. The proposed study therefore records technical failures and near misses even when no adverse clinical event occurs. A near miss may reveal a latent system weakness before it causes patient harm. Safety analysis should also examine whether complication patterns cluster by center, operator, hardware version, or patient subgroup [7, 9, 11]. Reproducibility requires more than publishing an average

outcome. Investigators should report data provenance, inclusion flow, missingness, device and software versions, preprocessing, calibration, and protocol deviations. For algorithms, source code or a sufficiently detailed executable description should be available when intellectual-property constraints permit. For devices, the physical configuration and update history should be recorded. For complex clinical pathways, process maps should define who performs each step and how discordant information is resolved. External validation must be geographic and temporal, not merely a random split of one institutional dataset. Health-economic evaluation is necessary because high-cost neurosurgical technologies may displace other interventions. A complete assessment should compare acquisition, disposables, maintenance, training, operating-room time, length of stay, complications, revision procedures, rehabilitation, and long-term care. The relevant economic question is not whether the technology is expensive, but whether its incremental cost is justified by additional quality-adjusted survival, preserved independence, or avoided complications. Lower-cost adaptations should be studied deliberately rather than treated as inferior substitutes. This is especially important for regional centers and health systems with constrained capital budgets [8, 10, 12].

The framework also has implications for education. Training should include not only device operation but also interpretation of uncertainty, recognition of failure modes, and maintenance of manual rescue skills. Simulation can expose teams to registration error, data loss, unexpected anatomy, or discordant signals before clinical deployment. Competency should be measured through objective performance and scenario-based assessment rather than attendance at a vendor course. Credentialing should be periodically renewed when major software or hardware updates alter the workflow. Several limitations should be acknowledged. First, a structured narrative synthesis is vulnerable to publication bias and cannot provide a single pooled treatment effect. Second, rapid technological evolution may make specific hardware obsolete before long-term outcomes mature. Third, the proposed endpoints may require large samples and extended follow-up. Fourth, standardized protocols can conflict with the individualized nature of neurosurgical care. Fifth, external validity may be limited in centers without equivalent imaging, pathology, engineering, or neurocritical-care infrastructure. These limitations do not negate the research question; they define the conditions under which evidence should be interpreted.

Future research should prioritize multicenter pragmatic trials, interoperable data standards, shared outcome definitions, prospective failure registries, and patient involvement in endpoint selection. Adaptive trial designs may be useful when software evolves during recruitment, provided version changes are prespecified and analytically traceable. International collaboration can improve representation of scanner types, devices, languages, ethnic groups, and health-system conditions. Ultimately, the decisive evidence will come from demonstrating that the intervention improves patient-level sensitivity for viable infiltrating tumor at the final resection margin without an increase in permanent neurological morbidity while maintaining acceptable safety, cost, and equity.

A further translational issue is endpoint hierarchy. In intraoperative molecular imaging of glioma margins, several intermediate outcomes may improve simultaneously, yet they should not be interpreted as equivalent. Technical accuracy is closest to the device; decision impact lies one step downstream; clinical benefit lies further downstream; and societal value incorporates cost, access, and long-term participation. A rigorous study should therefore define a causal chain before recruitment.

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The intervention must first produce a reliable signal, the signal must change a decision, the decision must alter treatment, and the altered treatment must improve outcome. Failure at any step can explain a neutral clinical trial even when the technology appears accurate. Recording each link in this chain will make negative results scientifically informative rather than simply disappointing [1, 5, 9]. Heterogeneity of treatment effect should be treated as a primary scientific question rather than a post hoc exercise. Patients differ in disease biology, anatomical risk, baseline function, physiological reserve, and availability of rescue therapy. A mean treatment effect may conceal substantial benefit in one subgroup and harm in another. Prespecified interaction analyses should therefore examine age, sex, molecular or anatomical class, prior treatment, center volume, and baseline risk. Such analyses require adequate sample size and should be interpreted with shrinkage or Bayesian hierarchical methods to reduce false discovery. Personalized prediction models may then estimate who is likely to benefit, but these models must be calibrated prospectively and should supplement rather than replace clinical judgment [2, 6, 10].

Conclusions. Intraoperative Molecular Imaging of Glioma Margins: Comparative Integration of 5-Aminolevulinic Acid, Raman Spectroscopy, and Real-Time Tissue Classification represents a timely and clinically relevant research direction. The evidence supports biological and technical plausibility, but also demonstrates that isolated accuracy metrics are insufficient. The most defensible next step is a prospective multicenter evaluation of a multimodal margin-assessment strategy combining 5-ALA fluorescence, handheld Raman spectroscopy, quantitative optical calibration, and machine-learning tissue classification referenced to spatially matched histopathology against 5-ALA fluorescence-guided surgery alone, using patient-level sensitivity for viable infiltrating tumor at the final resection margin without an increase in permanent neurological morbidity as the primary endpoint and specificity, positive predictive value, residual enhancing volume, sampling time, interobserver agreement, molecular subgroup performance, and cost per additional tumor-positive margin detected as secondary measures. The proposed originality matrix, standardized methods, explicit uncertainty reporting, and patient-centered outcomes provide a foundation for an authentic IMRAD manuscript. The approach should be adopted only when its benefit is reproducible, transparent, equitable, and clinically meaningful.

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