Precision Medication 2 (2025) 100052

Contents lists available at ScienceDirect

Precision Medication

journal homepage: www.keaipublishing.com/en/journals/precision-medication/

Advances and challenges in personalized diagnosis and therapies for the management of recurrent glioblastoma

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ARTICLE INFO

Keywords:
Clonal evolution
Multi-omics profiling
Liquid biopsy
Neoantigen vaccine
Radiogenomics
Precision radiotherapy
Adaptive clinical trials

ABSTRACT

Recurrent glioblastoma (rGBM) remains one of the most formidable challenges in neuro-oncology due to its aggressive evolution, treatment resistance, and profound intratumoral heterogeneity. Despite advances in multimodal first-line therapy, recurrence is nearly universal and represents a genetically divergent, therapy-adapted malignancy. This review dissects the evolutionary dynamics of rGBM, including clonal selection, therapy-induced mutagenesis, and proneural-to-mesenchymal shifts. It explores the translational potential of longitudinal sampling, circulating tumor DNA, and multi-omics profiling to dynamically monitor tumor progression and resistance emergence. Personalized therapeutic strategies are critically evaluated, including targeted inhibition of EGFR, PI3K/AKT/mTOR, and PDGFR pathways, immunotherapeutic approaches such as CAR T-cell therapy and neoantigen vaccines, and functional drug screening using patient-derived organoids. Moreover, the manuscript highlights innovations in AI-assisted therapy mapping, precision-guided re-irradiation, and adaptive trial designs that redefine individualized care in rGBM. Persistent challenges such as blood-brain barrier penetration, immune evasion, and lack of real-world clinical integration are also addressed. The convergence of high-throughput molecular diagnostics, AI analytics, and targeted therapies underscores a shift from static to dynamic, biomarker-guided interventions. Realizing the full promise of personalized medicine in rGBM demands systemic reforms, multi-disciplinary integration, and equitable clinical adoption.

Introduction

Glioblastoma (GBM), also known as Glioblastoma Multiforme, is the most prevalent and lethal primary malignant brain tumor in adults, accounting for nearly half of all malignant central nervous system (CNS) tumors. Classified as a World Health Organization (WHO) grade IV astrocytoma, GBM is characterized by aggressive infiltration of the brain parenchyma, robust angiogenesis, resistance to apoptosis, and profound genomic heterogeneity.[1] Despite multimodal therapy comprising maximal safe surgical resection, radiotherapy, and temozolomide chemotherapy, GBM remains largely incurable, with a median overall survival of 14–15 months and a 5-year survival rate of only 5–5.5 %.[2] The 2021 WHO CNS tumor classification introduced significant refinements by removing the term "IDH-mutant GBM" and reclassifying these as IDH-mutant astrocytoma's, reflecting a deeper understanding of the disease's molecular diversity.[3] These developments emphasize the need for molecular stratification in order to permit effective diagnosis and treatment and redirect attention to GBM heterogeneity as the major obstacle to therapeutic success. The tumor usually arises de novo in the cerebral hemispheres, often in the white matter, and grows extremely rapidly, usually becoming gigantic before clinical presentation as headaches, seizures, change of mental status, and weakness.[4]

The largest challenge to GBM treatment is its de facto universal recurrence. Around 90 % of GBM patients have tumor recurrence within two years, often at or near the primary location.[5] Recurrent glioblastoma (rGBM) is more resistant to treatment, has more aggressive biological characteristics, and is more genomically unstable. All of these are not an extension of the primary malignancy but an adaptively evolved, treatment-insensitive neoplastic phenotype.[6] Recurrence causes are incomplete surgical removal because of microscopic spread, drug resistance Temozolomide (TMZ) through mechanisms like O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status or mismatch repair deficiency, and immunosuppressive tumor microenvironment (TME) that

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https://doi.org/10.1016/j.prmedi.2025.100052
Received 7 July 2025; Received in revised form 8 August 2025; Accepted 18 August 2025
Available online 11 September 2025

can lead to immune escape. Recurrence diagnosis is still clinically problematic.[7] Symptoms are generally presentation-like, and distinction between actual growth of the tumor and pseudo-progression or radiation necrosis on imaging is challenging. Also, pre-existing treatment-altered changes can mask underlying tumor biology.[8] Molecular characterization upon recurrence is therefore required to reveal targets for therapy and evolve treatment strategy. The dynamic biology of the GBM, defined by spatial and temporal heterogeneity, requires serial and patient-specific molecular interrogation to inform treatment.[9]

Considering such intricacies, so-called personalized medicine or precision or individualized medicine has arisen as an inevitable paradigm. It consists of targeting the therapy to the patient's own molecular and clinical tumor profile, e.g., genomic mutations, epigenetic modifications, transcriptomic signatures, and immune contexture. GBM, with its active and complex molecular signature, was one of the earliest cancers to be mapped at extensive genomic scale by The Cancer Genome Atlas (TCGA), and found mutations in essential pathways like RTK/PI3K, p53, and RB1. But this genomics has not yet been reproducibly converted into successful clinical therapy against recurrence.[6,10] Such extreme inter- and intra-tumoral heterogeneity that it produces in rGBM equates to wide variability in treatment response, which causes resistance and unfavorable outcomes. Inability of the conventional "one-size-fits-all" methods to control recurrent GBM, therefore, reflects the imperative need for adaptive, biomarker-driven therapies.[11–13] Personalized medicine is not an evolutionary process in this case but an imperative clinical requirement. This review offers a detailed analysis of progress and setbacks toward the creation and provision of individual treatments for recurrent GBM based on molecular stratification, innovation in treatment, and translational challenges.

Tumor evolution in rGBM

Clonal selection and therapy-induced genetic drift

GBM exhibits profound inter- and intra-patient heterogeneity at genomic and phenotypic levels. This heterogeneity is the hallmark of resistance to treatment and recurrences of the tumor. Clonal evolution model, based on a Darwinian selection mechanism, believes that the tumor cells develop random genetic changes, and those that confer survival benefit under selective pressure like therapy are selected.[14] In glioblastoma, this clonal selection is continuous and dynamic, molding the tumor environment and allowing for the emergence of progressively more aggressive and treatment-refractory phenotypes with time. Standard therapies, particularly temozolomide (TMZ) and radiotherapy, impose significant selective pressures. Sub-clonal populations with pre-existing or acquired resistance mechanisms may survive initial treatments and subsequently dominate the recurrent tumor.[15] TMZ, for example, induces characteristic C > T base transitions through alkylation of DNA, resulting in a distinct hyper-mutational signature in some patients.[16] Comparative genomic analyses of paired primary and recurrent GBM samples have demonstrated increased mutational burdens and treatment-driven genetic drift in recurrent tumors. Additionally, recurrence often involves a shift in cellular architecture. Tumors may upregulate MGMT, diminishing TMZ efficacy, or adopt hypoxia-adapted phenotypes associated with radiation resistance.[17] Crucially, glioblastoma stem cells (GSCs) a subset of tumor cells with self-renewal capacity and multipotency are particularly resistant to conventional therapies. GSCs can persist following treatment, forming the nidus for recurrent disease. Their intrinsic chemo- and radio resistance, coupled with plasticity, allows them to initiate new tumor growth with greater resistance and altered biology.[18]

The transition to more aggressive phenotypes upon recurrence has also been linked to a proneural-to-mesenchymal shift, a process associated with epithelial-to-mesenchymal transition (EMT)-like programs and poor clinical outcomes. These shifts are not only genetic but also involve substantial epigenetic reprogramming and transcriptomic realignment, further complicating therapeutic targeting.[8] Hence, understanding and intercepting the evolutionary trajectory of GBM is essential to delaying or preventing recurrence.

Distinct molecular profiles in rGBM

Recurrent GBM is not simply a reappearance of the primary malignancy; rather, it often represents a genetically divergent, therapy-adapted disease state. Multiple studies have underscored significant molecular discrepancies between primary and recurrent tumors. For instance, the proportion of classical subtype GBMs decreases from 36 % at initial diagnosis to 22 % at recurrence, suggesting subtype switching or selective clonal depletion. Similarly, recurrent tumors show an increased frequency of IDH1 mutations (27 %) compared to primary tumors (14 %), although the relevance of this in IDH-wildtype GBM remains under investigation. Alterations in tumor suppressor genes also shift.[18,19] TP53 mutations, for example, become more prevalent in the classical subtype of recurrent tumors (80 %) versus their primary counterparts (44 %).[20] Meanwhile, EGFR amplification and mutations which define a large fraction of primary classical GBM appear reduced in recurrence (from 26 % to 18 %). Conversely, ATRX mutations increase in frequency in recurrent disease (18 % vs 10 %), potentially implicating chromatin remodeling as a resistance mechanism. These shifts may be partly driven by therapy-induced mutagenesis or selection of resistant clones. Initial chemoradiotherapy has been shown to induce mutations in DNA mismatch repair (MMR) genes, contributing to hypermutation and resistance to subsequent treatments, particularly alkylating agents.[21] Epigenetic alterations, including demethylation of the MGMT promoter or changes in histone modifications, further complicate the treatment landscape. Some recurrent tumors also display an immunosuppressive microenvironment, shaped by prior therapies, that impairs immune surveillance and facilitates tumor progression.[20] These findings underscore the necessity of re-biopsy and molecular profiling at recurrence, as the actionable targets and resistance mechanisms may have shifted dramatically since the initial diagnosis. A static, one-time molecular characterization is inadequate in the context of GBM's evolving nature.

Longitudinal sampling and its implications

The dynamic evolution of GBM mandates longitudinal sampling to capture the tumor's molecular adaptations in real-time. Unlike static tumor profiling at diagnosis, longitudinal sampling provides insights into the clonal dynamics, resistance mechanisms, and phenotypic plasticity of the tumor as it adapts to therapy.[22] This approach is critical for tailoring therapies to the evolving genetic landscape of recurrent GBM. Emerging technologies such as single-cell RNA sequencing (scRNA-seq), spatial transcriptomics, and high-throughput methylation profiling enable high-resolution mapping of intratumoral heterogeneity and clonal evolution.[22] Several studies have used these tools to track transitions in cellular states over time, identifying lineage trajectories and therapy-induced plasticity. For example, recent scRNA-seq analyses have revealed shifts from proliferative to mesenchymal states, emergence of novel cell populations, and reactivation of developmental pathways in recurrent tumors. In parallel, liquid biopsy approaches detecting circulating tumor DNA (ctDNA) and RNA offer minimally invasive methods to monitor molecular changes longitudinally. While still in early clinical stages for GBM, these methods hold promise for detecting emerging resistance mutations, predicting recurrence, and guiding treatment adaptation without the need for repeated surgical intervention.[23] Longitudinal data also help stratify patients based on response trajectories and predict those likely to develop resistance early. This real-time surveillance model transforms recurrent GBM management from reactive to proactive, allowing interventions to be adjusted before clinical progression becomes overt.

In summary, tumor evolution in GBM is a multifaceted process involving clonal selection, therapy-induced drift, and molecular reprogramming. Recurrence is not merely inevitable but biologically distinct, often more aggressive, and refractory to initial treatments. Understanding and intercepting this evolution through advanced profiling and adaptive therapeutic strategies is fundamental to the success of personalized medicine in recurrent glioblastoma.

Personalized targeted therapies for rGBM

Personalized targeted therapy seeks to inhibit molecular pathways or genetic alterations that are uniquely activated or dysregulated in a patient's tumor, offering a more refined approach than conventional chemotherapy. In GBM, particularly in the recurrent setting, this strategy has attracted considerable interest due to the disease's molecular complexity, resistance to standard therapies, and heterogeneity. Despite numerous molecular targets being identified most notably among receptor tyrosine kinases (RTKs), the PI3K/AKT/mTOR axis, and the MAPK pathway clinical translation has been fraught with setbacks, primarily due to biological redundancies, poor blood-brain barrier (BBB) penetration, and insufficient patient stratification.[24]

EGFR, PI3K/AKT/mTOR, and PDGFR: therapeutic targets and clinical challenges

Epidermal Growth Factor Receptor (EGFR) is one of the most frequently altered genes in GBM, with EGFR amplification and mutations including the oncogenic EGFRvIII variant occurring in a substantial subset of tumors. These alterations have prompted the development and clinical evaluation of several EGFR inhibitors, including gefitinib, erlotinib, lapatinib, afatinib, and cetuximab.[25] However, most clinical trials have failed to demonstrate a significant therapeutic benefit in either newly diagnosed or recurrent GBM. A critical reason for these failures is the lack of biomarker-driven patient selection, as well as pharmacologic limitations such as poor BBB permeability and limited efficacy in tumors not entirely dependent on EGFR signaling for survival. Additionally, EGFR overexpression or mutation correlates with poorer prognosis, highlighting the need for more effective targeting strategies (Table 1).[26]

The PI3K/AKT/mTOR signaling pathway plays a central role in regulating cell survival, metabolism, and proliferation. Aberrations in this pathway often involving PTEN loss, PIK3CA mutations, and mTOR activation are present in over 50 % of GBM cases and contribute to resistance to alkylating agents such as TMZ.[27] While early-generation pan-PI3K inhibitors such as wortmannin and LY294002 showed preclinical efficacy, they were discontinued due to toxicity and poor pharmacokinetics.[28] Newer agents like BKM120 (buparlisib) and PX-866 have entered clinical trials, with BKM120 currently in Phase II trials for rGBM.[29] Despite promising preclinical activity, their effectiveness in the clinic remains modest, reinforcing the need for combination therapies or better patient stratification based on pathway activation.

Platelet-Derived Growth Factor Receptor (PDGFR), particularly PDGFRA, is another RTK commonly amplified or mutated in GBM. Its activation is typically mutually exclusive with EGFR alterations.[40] Single-agent PDGFR inhibitors have yielded minimal clinical benefit, in part because co-amplification of PDGFRA with EGFR or MET occurs in up to 43 % of tumors, necessitating multi-targeted inhibition to abrogate downstream PI3K pathway activity.[41] This highlights the intratumoral heterogeneity and coexistence of functionally distinct RTK-driven subpopulations, which complicates therapeutic targeting.

A consistent limitation across targeted therapy trials in GBM is the lack of biomarker-enriched designs, leading to suboptimal responses in unselected populations. Moreover, pathway redundancy and cross-talk within tumor signaling networks allow for bypass mechanisms, rendering single-agent therapies ineffective over time. Thus, failures in

Table 1
Overview of personalized therapeutics in GBM/rGBM.

Agent / Strategy	Target	Therapy Type	Clinical Stage	Remarks	Reference
Afatinib	EGFR	Tyrosine Kinase Inhibitor	Phase I/II	EGFR-mutated GBMs; limited by BBB penetration	30
Neoantigen Peptide Vaccines	Tumor-specific mutations	Personalized Vaccine	Pilot/Observational	Requires WES/RNAseq; immunogenic in subsets	31
Personalised WES-Guided Combo	Multi-gene mutation profile	Custom Drug Combinations	Pilot Studies	Exome data used to guide patient-specific multidrug regimens	32
IL13Rα2 CAR-T Cells	IL13Rα2	Cell-based Immunotherapy	Phase I	Demonstrated intracranial delivery and partial responses in rGBM	33
Organoid-Based Drug Testing	Functional Profile	Precision Testing Platform	Preclinical/Pilot	Predicts patient-specific drug response using ex vivo models	34
AI-Guided Therapy Mapping	Integrated Multi-omics	Decision Support Algorithm	Preclinical/Platform Studies	AI tools mapping molecular alterations to therapeutic suggestions	35
REYOBIQ™ (Rhenium – 186)	Intratumoral radiotherapy	Targeted Radiopharmaceutical	Phase II	Direct CNS delivery bypasses BBB; trial ongoing	36
BKM120 (Buparlisib)	PI3K Pathway	Small Molecule Inhibitor	Phase II	Used in PI3K-mutated tumors; limited single-agent efficacy	33
INSIGhT Trial Agents	Adaptive Genomic Targets	Multiple Personalized Drugs	Phase II Platform Trial	Bayesian adaptive platform matching patients to drug based on biomarkers	37
Bevacizumab + Genomic Strat.	VEGF	Monoclonal Antibody	Approved (rGBM)	Enhanced outcomes when guided by molecular markers	38
MET Inhibitor (e.g., Crizotinib)	MET Amplification	Tyrosine Kinase Inhibitor	Phase I	Beneficial in MET-amplified rGBM subtypes	38
EGFRvIII CAR-T Cells	EGFRvIII	Cell-based Immunotherapy	Phase I/II	Shown safety but limited efficacy due to antigen loss and tumor heterogeneity	39

targeted therapy trials do not necessarily invalidate the therapeutic targets themselves but rather reflect shortcomings in therapeutic design, delivery, and implementation.

Adaptive resistance and escape mutations

A hallmark of recurrent GBM is its ability to adapt and develop resistance to therapy through both intrinsic and acquired mechanisms. Adaptive resistance arises when tumor cells, under therapeutic pressure, undergo genetic, epigenetic, or transcriptomic changes that facilitate survival.[42] These changes are often not present or detectable at the time of initial diagnosis. Key mechanisms include upregulation of MGMT, which confers resistance to alkylating agents, and metabolic reprogramming that supports cell survival under hypoxic conditions particularly relevant for radioresistant phenotypes.[43] The inherent redundancy of oncogenic pathways enables GBM cells to activate alternative survival signals when one pathway is inhibited. For example, blockade of the EGFR pathway may inadvertently activate compensatory PI3K/AKT or MET signaling, allowing tumor cells to escape apoptosis. Glioblastoma stem-like cells (GSCs) are particularly problematic in the context of recurrence.[44] These cells are inherently resistant to radiation and chemotherapy due to enhanced DNA repair capabilities, quiescent cell cycle states, and high expression of drug efflux pumps. GSCs can persist following therapy and repopulate the tumor, contributing to the therapy-resistant phenotype of rGBM.[45]

In addition, transcriptomic plasticity enables glioblastoma cells to switch between cellular states under selective pressure. This includes the well-documented proneural-to-mesenchymal transition, which is associated with increased invasiveness, immune evasion, and resistance to standard treatments.[46] From an immunotherapeutic standpoint, this plasticity severely limits the efficacy of CAR T-cell therapies, as the heterogeneous antigen landscape makes it difficult to identify universal, durable targets. Furthermore, secondary mutations, such as EGFR T790M, have been linked to acquired resistance to tyrosine kinase inhibitors, further limiting long-term efficacy.[47]

Real-world precision targeting strategies

Recognizing the inadequacies of monotherapies and static treatment models, current research has shifted toward more dynamic, patient-specific therapeutic paradigms. A promising strategy involves target-enriched clinical trials, where patients are selected based on molecular profiling of their tumors.[48] The ATTRACT trial, for instance, is a randomized Phase II study initiated in July 2024 to evaluate the efficacy of ex vivo drug screening on patient-derived GBM cells. These cells are tested against a library of 28 FDA-approved drugs to guide personalized therapy regimens. Preliminary findings suggest that combination therapies based on whole exome sequencing significantly outperform monotherapies in reducing tumor burden and delaying recurrence.[49] Another notable development is REYOBIQ™ (rhenium Re186 obisbemeda) by Plus Therapeutics, a novel radiopharmaceutical in Phase II trials for rGBM. This agent delivers localized radiation via a single intratumoral injection, bypassing the BBB and minimizing systemic toxicity offering a targeted, precision-guided alternative to traditional external beam radiotherapy.[50] Advances in drug delivery systems, such as nanoparticles, micelles, and monoclonal antibodies, are also being explored to improve targeted delivery across the BBB. Nanocarrier platforms have demonstrated the ability to encapsulate chemotherapeutic agents like TMZ and selectively release them within the tumor microenvironment, enhancing therapeutic index while reducing off-target effects.[51]

Furthermore, personalized peptide vaccines targeting patient-specific neoantigens have shown promise in early-phase trials. One observational study reported a median overall survival of 31.9 months from initial diagnosis in patients receiving a personalized vaccine, with the best outcomes seen in those with robust vaccine-induced T-cell responses (53 months vs. 27 months in non-responders).[52] These findings emphasize the immunogenic potential of tailored immunotherapies and the critical role of host-tumor interactions in determining therapeutic outcomes. In summary, the failure of past targeted therapies in recurrent GBM is less a consequence of flawed targets than of insufficient personalization and incomplete understanding of resistance mechanisms. Emerging strategies that integrate molecular profiling, combination therapies, and novel delivery systems are reshaping the landscape of personalized treatment. As the field moves forward, biomarker-guided trials and adaptive treatment models will be essential to unlocking the therapeutic potential of personalized medicine for recurrent GBM.

While molecularly targeted therapies aim to inhibit aberrant signaling pathways in rGBM, the complexity of tumor-immune interactions and the immunosuppressive microenvironment present an additional therapeutic frontier.

Personalized immunotherapy in rGBM

Immunotherapy has changed the treatment of numerous malignancies; however, its effect on GBM, especially recurrent GBM, remains limited. The intrinsically TME of glioblastoma, intratumoral antigenic heterogeneity, and immune privilege of the CNS are among the major obstacles to immunotherapeutic responsiveness. But the arrival of personalized immunotherapy, through its coming together of molecular, antigenic, and immune profiling into the development and administration of immunologic therapy, offers new hope for the cure of rGBM (Fig. 1), a class with limited prospects for effective therapy.[53,54]

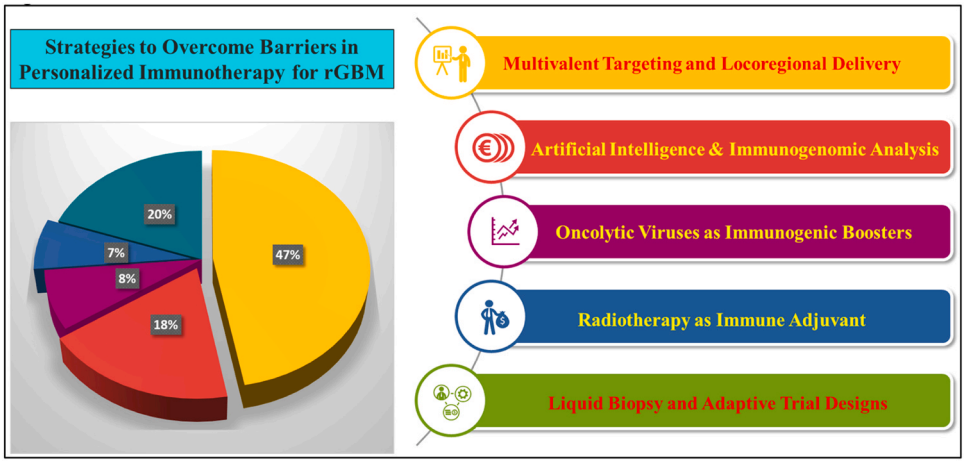

Fig. 1. Strategies to Overcome Barriers in Personalized Immunotherapy for rGBM.

Chimeric antigen receptor (CAR) T-cell therapy for recurrent GBM

CAR T-cell therapy, wherein patient-derived T cells are genetically modified to express artificial receptors that bind tumor-specific antigens, has registered modest but significant progress in rGBM. Clinical studies have assayed CAR constructs against the antigens EGFRvIII, IL13Rα2, and HER2, with early-phase studies showing safety and short-term clinical responses. Antigen heterogeneity, poor persistence of CAR T-cells, and immunosuppressive signaling of the TME have, however, bogged back the effectiveness of the treatments. For example, EGFRvIII-specific CAR T-cell therapy for rGBM patients led to antigen loss variants, emphasizing immune escape by antigen modulation as the prevalent mechanism of failure.[55] In addition, spatial and temporal heterogeneities of antigen expression require personalized, real-time identification of tumor antigens prior to treatment. The recent advances has been the development of multivalent CAR T-cell platforms for targeting multiple antigens to prevent clonal diversity and escape mechanisms. Artificial intelligence (AI)-driven modeling is being incorporated to fine-tune epitope selection, forecast escape mutations, and customize CAR constructs to the patient tumor profile. AI-driven methods are now used to fine-tune CAR T-cell affinity, toxicity risk, and antigen binding profiles to arrive at more potent and personalized constructs for clinical translation.[56]

Personalized vaccine strategies based on neoantigens

Neoantigens non-self, tumor-specific peptides of somatic mutation are the perfect targets for personalized vaccines. The neoepitopes are discovered by high-throughput sequencing of patient's tumor and normal matched tissue, followed by in silico predictions of MHC binding as well as by immunogenicity assays. In rGBM, several clinical trials have shown that personalized neoantigen vaccines induce polyclonal T-cell responses with memory. A phase II clinical observation trial on individualized peptide vaccines had total median survival of 31.9 months and strong vaccine-induced T-cell responders with survival durations of over 50 months, close to two times the historical controls.[57] These vaccines not only augment tumor-specific immunity but also enhance antigen spreading and T-cell repertoire diversity the key determinants to reach the heterogeneous and dynamic GBM tumor milieu. With the goal of amplifying immunogenicity, combination strategies pairing neoantigen vaccines with immune checkpoint inhibition or adjuvants (e.g., Poly-ICLC, GM-CSF) are currently the focus of intense investigation. Combinations aim to increase T-cell priming, augment effector populations, and abrogate immunosuppressive feedback loops.[37]

Immunogenomic profiling of recurrent disease

One of the hallmarks of rGBM is immunogenomic divergence from the primary tumor. Downregulation of Major Histocompatibility Complex (MHC) molecules, upregulation of PD-L1, and recruitment of immunosuppressive cell subsets, including tumor-associated macrophages (TAMs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs), are results of treatment-induced selection pressures.[58] These render conventional checkpoint blockade treatments ineffective and require personalized profiling upon recurrence. Advanced methods, such as single-cell RNA sequencing, spatial transcriptomics, and mass cytometry, are employed these days to deconstruct recurrent lesion immune landscape. These tools expose actionable immune targets and propose combinatorial approaches such as the combination of PD-1 blockade with CSF1R inhibition to rewire the pool of macrophages. Personalized immunotherapy in such cases is no longer a utopian fantasy but a living reality demanding re-biopsy and real-time immunogenomic evaluation for choosing effective interventions.[59]

Bridging barriers to personalized immunotherapy

Although the potential of personalized immunotherapy in rGBM is boundless, there are many barriers still remaining to restrict its clinical use and transfer to the broader population. Among the most important barriers is the extensive intratumoral antigenic heterogeneity of GBM. In contrast to hematologic cancers, in which uniform presentation of targets such as CD19 enables serial CAR T-cell activation, GBM tumors typically possess an antigenic mosaic. This supports immune evasion by clonal growth of antigen-negative variants, particularly following monovalent targeting interventions like single-antigen CAR constructs. Secondly, the BBB also poses a physiological barrier that restricts trafficking and intratumoral delivery of systemically delivered immunotherapeutic compounds like engineered T-cells and monoclonal antibodies.[59,60] The GBM's suppressive TME also plays its part. Recurrent tumors also tend to be enriched in M2-polarized TAMs, Tregs, and MDSCs, which all inhibit effector T-cell function and suppress antitumor immunity. To this, most GBM tumors are immunologically "cold" they have no pre-existing T-cell infiltration and have too few neoantigens to induce vigorous immune responses. Furthermore, GBM's ability to modulate expression of immune checkpoint ligand (e.g., upregulation of PD-L1) upon therapy further contributes to immune evasion. These features, collectively, make GBM particularly effective in being immune-resistant to both innate and adaptive immune modulating therapeutic interventions and necessitating more sophisticated and adaptive immunotherapeutic modalities.[61,62]

Future directions

Addressing all these challenges needs a multi-disciplinary approach blending cutting-edge technology with translational immunobiology (Fig. 2). One of the encouraging approaches is the creation of multivalent or multiplexed therapies, like CAR T-cells targeting more than one antigen at a time or bispecific T-cell engagers (BiTEs) used for redirecting endogenous T-cells against tumor cells via dual-antigen binding. Furthermore, locoregional delivery strategies, such as intratumoral or intraventricular injection of CAR T-cells and immune modulators, are also investigated to circumvent the BBB and enhance drug bioavailability within the microenvironment of tumors.[63,64]

The use of artificial intelligence and machine learning in immunogenomic analysis and treatment matching is another new frontier in personalized immunotherapy. The technologies can detect patterns from single-cell and high-dimensional sequencing data to facilitate target selection, resist mechanism prediction, and fusion treatment. Oncolytic viruses that are engineered to infect tumor cells and trigger immune responses also increase as weapons to "heat" up cold GBM tumors and boost immunogenicity. Additionally, application of radiotherapy as an immune adjuvant with the ability to cause immunogenic cell death and unveil neoantigens can work in synergy with immunotherapeutic strategies.[65] For these improvements to be achieved, follow-up clinical trials need to utilize adaptive, biomarker-stratification designs, grouping patients according to immune and genomic status instead of traditional histopathology alone. Concomitant with this, ctDNA and T-cell receptor sequencing liquid biopsy platforms provide noninvasive platforms for monitoring the live immune status, adjustment of therapy, and detection of early resistance.[65–67] Eventually, immunotherapy customization in rGBM will require not only targeted therapies but also targeted trial design and biomarker platforms, together with dynamic characterization of the tumor and immune system and translational feedback.[68,69]

While immunotherapeutic approaches offer tailored solutions to overcome immune evasion, functional testing platforms like patient-derived organoids address therapeutic resistance and drug response variability at the *ex-vivo* level. Fig. 3

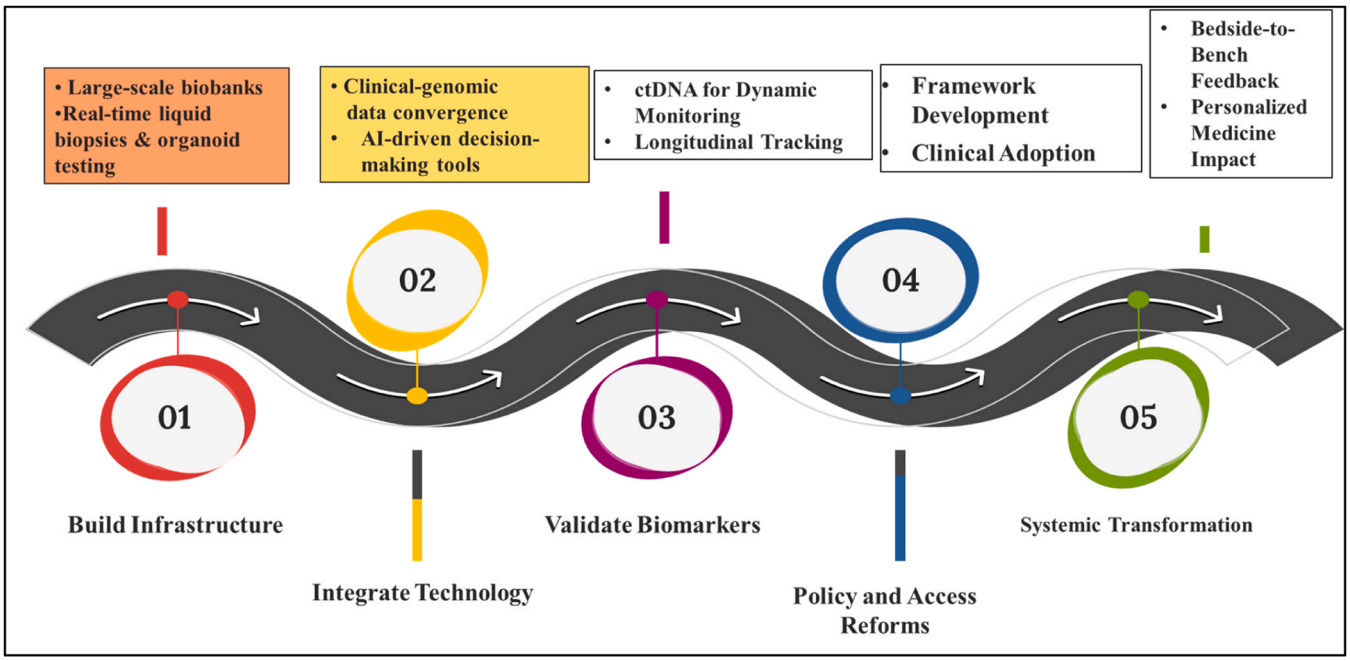

Fig. 2. Roadmap for translating personalized medicine into clinical impact for rGBM.

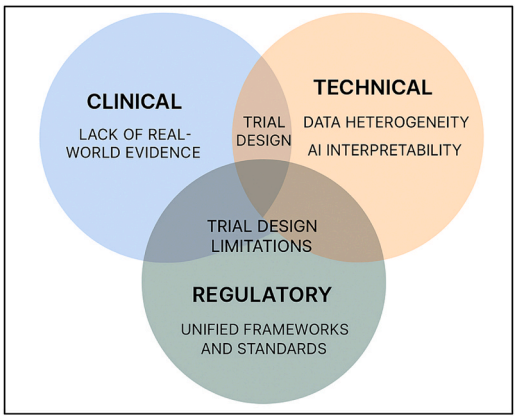

Fig. 3. Translational bottlenecks in rGBM precision medicine.

Organoid-driven therapeutic testing in recurrent glioblastoma

Treatment of recurrent glioblastoma is hindered by the tumor's extreme heterogeneity, dynamic behavior, and absence of predictive treatment biomarkers. These limitations have spurred the creation of patient-derived glioblastoma organoids (GBOs) as an *ex-vivo* model system for therapeutic testing. Organoids are three-dimensional, self-organized cultures of patient tumor tissue that are representative of important architectural, genetic, and phenotypic tumor features of the parent tumor, including cell heterogeneity and tumor microenvironmental signals.[70,71] Organoids provide a novel platform for high-throughput drug discovery, resistance, and precision oncology. Organoid models are especially useful for rGBM. Recurrent tumors contain treatment-induced mutations and epigenetic changes that distinguish them from primary tumors. Therefore, through the utilization of GBOs derived from recurrent tissue, drug response testing would be indicative of the evolutionary status of the tumor at that given time. It is possible to culture and expand patient samples' GBOs in simulating treatment resistance profiles as well as assessing drug efficacy is possible. Such models-maintained heterogeneity of RTK amplification and mesenchymal transition states that are typically enriched in recurrent lesions. In addition, co-culture of GBOs with immune or endothelial cells has further extended their use for the evaluation of immunotherapeutic and anti-angiogenic drugs.[72,73]

Notably, *ex-vivo* drug testing within GBOs could facilitate personalization of combination treatment design, especially to detect synergistic activity that could potentially be obscured in single-agent trials. Consistent drug sensitivity profiles of GBOs in a preclinical trial-simulation experiment were highly associated with clinical response in patients, implying them as a predictive biomarker for treatment selection. This strategy is being brought to the clinic in the form of clinical trials, including the Advanced Brain Tumor TheRApy Clinical Trial (ATTRACT) which stratifies patients based on ex vivo drug sensitivity against a library of FDA drugs.[74] Technologically, GBO platforms have progressed to support automated high-content imaging, drug penetration assays, and single-cell transcriptomic analysis, making them increasingly precise and scalable. Some limitations exist nevertheless: First, patient-derived organoids fail to establish viable cultures in 20–30 % of biopsies due to tissue quality or growth limitations. Second, AI models often lack generalizability because they are trained on primary tumor datasets, not treatment-evolved rGBMs. Third, integration into real-time clinical workflows is limited by data interoperability challenges and the absence of regulatory-approved decision-support systems.[75]

Despite these restraints, the application of GBO testing in clinic decision-making is a worthwhile step towards functional precision oncology in rGBM. By providing quick, patient-specific insight into drug effectiveness, organoids are a translational bridge between molecular diagnosis and therapy delivery minimizing empiricism and enhancing chances of treatment success. As culture methods improve and co-modeling schemes advance, utilization of organoids in recurrent GBM will advance from bench to bedside.[76,77]

Liquid biopsy and circulating tumor DNA in recurrent glioblastoma

Recurrent glioblastoma is a chronic, dynamic disease process frequently characterized by molecular divergence between the original tumor and recurrent tumors as a consequence of therapeutic-driven selective pressures. Liquid biopsy, the measurement of tumor-derived biomarkers in blood or cerebrospinal fluid (CSF), offers an appealing alternative to real-time, non-invasive monitoring of tumor evolution,

drug resistance, and disease progression.[78,79] Among the most investigated glioblastoma biomarkers are extracellular vesicles (EVs), circulating tumor cells (CTCs), and ctDNA, all of which may harbor genomic and transcriptomic data representative of the tumor milieu at the time.[80] Liquid biopsies provide a repeated and minimally invasive strategy for longitudinal molecular annotation compared with invasive, spatially localized, and frequently unobtainable solid tumor biopsies at recurrence. ctDNA has been most hopeful in rGBM since it is able to carry actionable mutations like EGFR amplification, TERT promoter mutation, or PTEN loss that are longitudinally measurable. In addition, it has been demonstrated that ctDNA levels are associated with tumor burden and also predict radiographic progression, an early surrogate warning indicator for recurrence.[81,82]

Emerging technologies in ultra-sensitive detection methods, including digital droplet PCR (ddPCR) and next-generation sequencing (NGS), have increased the analytical sensitivity of ctDNA assays to identify low-frequency mutations in plasma and CSF. Interestingly, liquid biopsies based on CSF were significantly more sensitive than plasma to identify ctDNA in glioma, possibly due to the blood-brain barrier's inhibitory effect on DNA release into systemic circulation. But advances in plasma ctDNA enrichment techniques and targeted sequencing panels are increasingly contributing to the diagnostic value of blood-based testing.[79,83] Besides detection, liquid biopsy also enables prediction and adjustment of resistance and therapy. In targeted or immunotherapy patients, resistance-related mutations (e.g., secondary EGFR mutations, downregulation of expression of neoantigen, or mismatch repair deficiency) can be identified with ctDNA, allowing timely treatment substitution. Finally, integrated ctDNA analysis with T-cell receptor (TCR) sequencing or cytokine profiling may provide information on the immune status of the patient, another level of individualization of immunotherapy approaches.[84,85]

Notably, liquid biopsy has also been investigated as a tool for stratification and monitoring in clinical trials of rGBM. The incorporation of molecular response measures from ctDNA into trial end points may speed up drug development and permit dosing schedules to be modified depending on tumor kinetics. Despite its potential, liquid biopsy for GBM is problematic. Among these are the limited availability of ctDNA in peripheral blood, platform technical heterogeneity, and lack of standard protocols.[86,87] In addition, the benefit of liquid biopsy in the clinic needs to be measured using prospective, large-scale studies that link ctDNA kinetics to survival and treatment response. But with advancing analytical technology and improved clinical uptake, liquid biopsy will be the linchpin of personalized disease surveillance and therapy titration for rGBM (Table 2). It captures the constantly evolving molecular blueprint of the tumor and brings new promise for regimens tailored to the individual patient.[88]

Artificial intelligence and multi-omics in recurrent glioblastoma

The combination of artificial intelligence and multi-omics profiling is revolutionizing the biology of personalized medicine in oncology at warp speed, and rGBM has much to benefit from this technological convergence. Owing to the gross heterogeneity, adaptive resistance, and dynamic evolution of GBM, conventional linear approaches to diagnosis and treatment planning fall short.[89–92] Artificial intelligence allows complex, high-dimensional genomic, transcriptomic, proteomic, metabolomic, and radiomic data to be analyzed, with a systems-level understanding of tumor biology and patient-specific vulnerabilities. In rGBM, artificial intelligence-based models are being constructed that can predict therapy resistance, survival, and therapy response. Genomic data-trained machine learning models have been successful in identifying predictive sets of mutations for TMZ resistance, immune checkpoint inhibitor response, and radiotherapy failure. Deep learning pipelines employing DNA methylation profiles, mutational signatures, and scRNA-seq have, for example, been employed for classifying GBM subtypes with varying recurrence risk and therapeutic sensitivity.[93]

One of the most exciting uses of AI is to model evolutionary lines of tumor clones from serial liquid biopsies or multi-regional tumor sampling. These models can predict the development of resistance clones and propose therapeutic alterations prior to such radiologically detectable clinical evolution. Furthermore, AI is employed to predict patients' best drug combinations using compounding of mutation burden, pathway activation scores, immune infiltration scores, and drug sensitivity profiles from organoid screen or patient-derived xenografts. Radiogenomics, a discipline that bridges imaging and genomics, is also using AI for non-invasive prediction of molecular changes.[94–98] MRI analysis with the aid of AI has been applied to infer IDH mutation status, MGMT methylation, and even EGFR amplification so that molecular characteristics can be preoperatively prebiased without the need for surgical tissue. These methods are very useful in rGBM where repeated biopsy may not be possible. Additionally, AI has the ability to maximize study design and conduct of individualized clinical trials. Adaptive trial platforms utilize patient information in real-time to modify enrollment, dosing, and combination plans by estimated probability of benefit. AI has the potential to facilitate the interpretability of high-dimensional immune data, for example, multiplex immunofluorescence or CyTOF, in order to enhance identification of patient-specific candidates for immunotherapy.[99]

Although promising, there are serious challenges that it faces. They include standardization of data, model interpretability, clinical validation, and integration with existing electronic medical records. Furthermore, the majority of artificial intelligence models are trained in comparison to de novo GBM diagnostic datasets, and customized training against recurrent disease cohorts is presently lacking. Policy and ethics for AI-based clinical decision-making within neuro-oncology are also in development. But the convergence of multi-omics analyses with AI represents a turning point in the tailoring of rGBM treatment. By facilitating real-time data-driven prescribing, AI holds the prospect of enhancing precision, minimizing trial-and-error therapy, and eventually spurring better patient outcomes in an arena that has historically been difficult to treat through standard approaches.[100]

Despite the promise of AI-integrated multi-omics in rGBM management, significant bottlenecks hinder clinical translation. A major hurdle is data heterogeneity lack of standardized formats and protocols across omics platforms, imaging systems, and clinical reporting. This compromises reproducibility and cross-institutional collaboration. Most AI models are trained on primary GBM datasets, reducing their predictive validity in rGBM. The 'black-box' nature of many deep learning algorithms poses interpretability issues, limiting clinician trust and regulatory approval. Integrating AI pipelines with real-time electronic health records (EHRs) and adaptive trial workflows remains technically and logistically challenging. Furthermore, the absence of unified ethical and governance frameworks for AI-guided therapy hinders widespread adoption. Addressing these constraints requires collaborative efforts between bioinformaticians, clinicians, and regulators to ensure transparency, generalizability, and safety of AI-driven interventions.[101]

Table 2
Recent sensitivity/PPV data from CSF vs. plasma vs. imaging.

Modality	Sensitivity	Specificity	Invasiveness	Remarks
CSF ctDNA	58–85 %	High	Moderate	High detection rate in gliomas; invasive
Plasma ctDNA	10–20 %	Moderate	Low	Limited by BBB; low yield
MRI (with perfusion)	70–90 %	Moderate	Non-invasive	Affected by pseudo-progression

Re-irradiation in a personalized context

Re-irradiation is one of the options available to treat rGBM patients, especially when previous systemic treatment has failed or is no longer an option. Re-irradiation in GBM earlier had been held back because of cumulative neurotoxicity concerns, more so after previous high-dose exposure of the surrounding normal brain tissue. But with the advancements in radiotherapy modality, imaging, and patient preference, added to molecular stratification and radiogenomics, re-irradiation has been rekindled as individualized, targeted therapy for rGBM.[102–105] Contemporary re-irradiation is based on hypofractionated stereotactic radiotherapy (SRT), fractionated stereotactic radiotherapy (FSRT), and proton or heavy-ion treatment to provide highly conformal irradiation to tumor targets with sparing of normal brain tissues. The capacity to treat with precise high-dose radiation is especially useful in recurrent disease with ill-defined tumor borders and infiltrative behavior. According to reports, selected patients receiving re-irradiation have been observed to experience median overall survival advantages of 6–12 months, particularly when combined with systemic therapy such as bevacizumab or targeted agents.[106]

Radiogenomics evolution the combination of imaging phenotypes with genomic and epigenetic characteristics has added new dimensions to patient individualization in re-irradiation. For instance, MGMT promoter methylation or IDH mutations can convey tumor radiosensitivity, and this indicates that molecular subtypes can guide dose adaptation and patient selection. Genotype- and imaging biomarker-guided re-irradiation were linked with safe profiles and long progression-free survival, further illustrating the clinical value of combining molecular and radiographic information.[107,108] Furthermore, functional imaging modalities like amino acid PET and advanced MRI sequences (e.g., perfusion-weighted imaging, diffusion tensor imaging) are being utilized to more accurately discriminate between active tumor and treatment-induced necrosis, improving target delineation. Integration of radiomic features into treatment planning algorithms allows for recurrence risk and biologic aggressiveness stratification by the clinician, and has implications for high-risk volume dose intensification.[109–111]

The advent of biologically guided radiation therapy (BGRT) is also significant. It treats patients with adaptive real-time adaptation of radiation delivery to biological markers, e.g., tumor hypoxia or proliferative indices identified by imaging or circulating biomarkers. This type of adaptation can potentially neutralize treatment resistance in rGBM, where radiotherapy failure is largely fueled by hypoxic foci and metabolic heterogeneity. Although promising, re-irradiation needs to be individually managed cautiously considering previous dose received, tumor site, and patient performance status.[112,113] Long-term neurocognitive toxicity, radiation necrosis, and vascular toxicities continue to be major challenges. Incorporating artificial intelligence and predictive modeling to quantify cumulative dose distribution, normal tissue tolerance, and recurrence kinetics would further boost the safety and benefit of re-irradiation. In general, re-irradiation of rGBM is transitioning from a salvage operation to a precision medicine treatment strategy, yet aided increasingly by genomic, radiomic, and AI paradigms. When administered as part of an individualized, multidisciplinary therapeutic regimen, it produces significant prolongation of survival and quality of life in carefully selected patients with recurrent disease.[114]

Challenges and future roadmap

Despite significant advances in individualized therapy for recurrent glioblastoma, its widespread use remains hampered by a variety of interconnected factors. Among the most critical of them is the intrinsic and acquired heterogeneity of the tumor rGBM evolves at a high level under the pressure of prior treatment, often leading to extensive genetic and phenotypic divergence both within and between patients. Sophistication diminishes the validity of molecular profiling based on single biopsy, especially when recurrent tumors are not accessible by surgery or divergent clones co-exist in a single lesion. Without standardization across genomic platforms, bioinformatics pipelines, and interpretation criteria, reproducibility of decision-making that is driven by omics is further incapacitated.[115–117] Technically and infrastructurally, incorporation of multi-omics analysis, real-time liquid biopsy, or drug testing with organoids into standard-of-care clinical practice remains logistically complicated and dependent on multidisciplinary leadership, high-computing capacity, and institutional preparedness. Ethical and equity issues also arise, with disproportionate access to such patient-level technologies and frequently restriction of access to research-rich or resource-concentrated locations, risking the exacerbation of care inequities.[104–107] Furthermore, novel adaptive trial designs, such as basket and n-of-1 trials, even though they are scientifically promising, represent a challenge to traditional regulatory paradigms and raise alarm about informed consent and ongoing safety surveillance. It will overcome these constraints by using a multi-faceted approach directed towards building large-scale biobank and multi-omics sequencing infrastructures, the linking of AI-based clinical decision-making tools, the validation of dynamic biomarkers like circulating tumor DNA for monitoring response, and the ownership of regulatory, ethical, and economic frameworks to enable biomarker-guided therapies as well as offer extensive clinical access. Only through such systemic reform will personalized medicine move from bedside to bench and bestow actual survival benefit on patients with recurrent glioblastoma. Overcoming these challenges requires system-level interventions. Standardization can be facilitated by adopting global frameworks like the Global Alliance for Genomics and Health (GA4GH) to unify omics data protocols. To mitigate training bias, federated AI models enable privacy-preserving learning across decentralized datasets, thus enhancing generalizability without data sharing. Regulatory innovations like 'sandbox' environments can be used to test adaptive trial designs in real-time, enabling more flexible and rapid patient-specific interventions. Further, integration of real-world evidence and pragmatic clinical trial networks can support dynamic biomarker-based treatment pathways. Crucially, robust public-private partnerships between academic institutions, government bodies (e.g., NIH, FDA), and industry stakeholders are essential to co-develop ethical, scalable, and equitable precision medicine platforms for rGBM.[39,95,118–120]

Translating precision oncology for recurrent glioblastoma into standard clinical care requires a multi-dimensional strategy addressing financial, infrastructural, and regulatory barriers. From a cost perspective, whole exome sequencing (WES)-guided treatment selection has shown emerging cost-effectiveness, particularly in high-burden cancers such as rGBM.[121] By enabling more targeted use of therapeutics and reducing trial-and-error prescribing, WES-guided approaches can decrease unnecessary toxicity and resource utilization. To overcome reimbursement challenges associated with next-generation sequencing (NGS), institutions are exploring value-based frameworks in which payers reimburse genomic testing based on clinical utility or treatment outcomes. Bundled models that integrate sequencing, interpretation, and trial matching into a single reimbursable service are also gaining traction. On the regulatory front, adaptive licensing strategies such as the FDA's Real-Time Oncology Review (RTOR) and the European Medicines Agency's adaptive pathways can expedite approval of biomarker-guided interventions. These frameworks support conditional authorization while continuing evidence generation. Equally important is addressing disparities in access to precision medicine especially in rural and under-resourced regions through telemedicine platforms. Virtual molecular tumor boards, remote genomic consent, and decentralized clinical trials now offer viable solutions to expand access to biomarker-matched therapies. Taken together, these strategies create a pragmatic roadmap toward equitable and sustainable clinical integration of individualized care for patients with recurrent glioblastoma.[122,123]

Conclusion

Recurrent glioblastoma is one of the most resistant problems in neuro-oncology, and it is characterized by resistance to treatment, molecular adaptation, and poor prognosis. While conventional treatments have only moderate effectiveness at recurrence, the dawn of personalized medicine has created a paradigmatic revolution based on tailor-making therapy approaches against the adaptive tumor biology of the individual patient. From neoantigen- and targeted immunotherapy to drug screening with organoids, AI-directed treatment mapping, and precision-guided re-irradiation, the horizon for rGBM care is aimed towards increasingly dynamic, adaptive, and biologically guided medicine. With the promise of encouraging preclinical and early clinical trials, adoption of these personalized therapies in daily practice is thwarted by biological complexity, logistics, access disparities, and calls for standardization. In the years ahead, rGBM science will have to adopt real-time analysis of molecules, liquid biopsy monitoring, functional model systems, and AI-facilitated trial designs to turn responsive and stratified care into a reality. Finally, overcoming the distinct hurdles of rGBM will necessitate not just technological advancement and therapeutic advances but also reborn clinical paradigms that stress precision, adaptability, and equity in cancer treatment.

Declarations

Not applicable.

Authors' contributions

Sagar Trivedi: Writing – Review & Editing; Manisha Kawadkar: Literature Review, Data Curation, Formal Analysis; Diksha Pawar and Ujban Hussain: Review & Editing, Critical Revisions; Rishabh Agade: Resources validation.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Sagar Trivedi reports was provided by GH Raisoni University. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Authors' other information

Not applicable.

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