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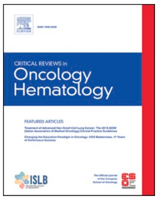

COST action CA22103 Net4Brain: Pan-European network advancing translational research in brain cancer

Terezia Kiskova-Simkova [a,*], Patrik Simko [a], Milica Pešić [b], Annalisa Occhipinti [c], Barbara Breznik [d,p], Anna Golebiewska [e], Alkinoos Athanasiou [f,g], Theodora Gazea [f], Aida Hajdarpasic [h], Thomas Booth [i,j], Tugba Bagci Onder [k], Yasin Kaymaz [l], Claudio Angione [m], Uchenna Ngameduru [n], Radim Jancalek [o], Xinzhong Li [n]

[a] *Department of Pathology, Faculty of Medicine, Pavol Jozef Safarik University in Kosice, Kosice, Slovakia*
[b] *Department of Neurobiology, Institute for Biological Research "Siniša Stanković" - National Institute of the Republic of Serbia, University of Belgrade, Despota Stefana 142, Belgrade 11108, Serbia*
[c] *School of Computing, Engineering and Digital Technologies, Teesside University, Middlesbrough, United Kingdom*
[d] *Department of Genetic Toxicology and Cancer Biology, National Institute of Biology, Ljubljana SI-1000, Slovenia*
[e] *NORLUX Neuro-Oncology Laboratory, Department of Cancer Research, Luxembourg Institute of Health, Luxembourg L-1210, Luxembourg*
[f] *Lab of Medical Physics & Digital Innovation, School of Medicine, Aristotle University of Thessaloniki, 54124, Greece*
[g] *2nd Department of Neurosurgery, Ippokratio General Hospital, Thessaloniki 54642, Greece*
[h] *Faculty of Medicine and Health Sciences, University of Buckingham, Buckingham, UK*
[i] *School of Biomedical Engineering & Imaging Sciences, King's College London, London, United Kingdom*
[j] *Department of Neuroradiology, King's College Hospital, London, United Kingdom*
[k] *Koç University School of Medicine, Istanbul, Türkiye*
[l] *Ege University, Faculty of Engineering, Department of Bioengineering, Izmir, Türkiye*
[m] *School of Computing, Engineering and Digital Technologies, Teesside University, Middlesbrough, United Kingdom*
[n] *School of Health and Life Sciences, Teesside University, Middlesbrough, United Kingdom*
[o] *Department of Neurosurgery, St. Anne's University Hospital Brno, Faculty of Medicine, Masaryk University, Brno, Czechia*
[p] *Faculty of Chemistry and Chemical Technology, University of Ljubljana, SI-1000 Ljubljana, Slovenia*

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ABSTRACT

Brain and central nervous system cancers remain the deadliest forms of cancer, with limited improvement in survival following treatment. The Net4Brain COST Action (CA22103) addresses the urgent need for coordinated and multidisciplinary approaches to understand the pathogenesis, optimize early diagnosis, and personalize treatment strategies. Net4Brain unites a pan-European network of experts in basic and clinical neuroscience, oncology, molecular biology, data science and bioengineering. Through five thematic Working Groups (WGs), innovative Young Researcher's Group and one dissemination WG, supported by Creative Group, the Action focuses on non-invasive biomarker discovery, preclinical modeling, tumor profiling, computational modeling, and treatment optimization. This initiative supports collaborative research, capacity building, and the development of a shared pan-European brain cancer centralized virtual database and biobank. Progress has been made in standardizing biomarker discovery, building innovative advanced preclinical models, and fostering integration of "omics" and imaging data for clinical applications. Net4Brain overcomes existing fragmentation in brain cancer research by providing a transdisciplinary platform for research and development, innovation, dissemination, and training, ultimately aiming to improve diagnostic accuracy, therapeutic outcomes, and patient quality of life. It also builds critical mass of knowledge/experts in the field of brain cancer and neuro-oncology.

1. Brain cancer: a persistent clinical challenge

Central nervous system (CNS) cancers represent a significant global health burden, characterized by a high mortality and debilitating symptoms (Zhang et al., 2025). Overall, the number of patients diagnosed with CNS cancer increased by 311 379 cases from 1992 to 2021,

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[*] Corresponding author.
E-mail address: terezia.kiskova@upjs.sk (T. Kiskova-Simkova).

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reflecting a substantial rise of 225.11% (Steindl and Valiente, 2025). As of 2024, the glioblastoma market size is estimated at more than two billion glioblastoma USD and is projected to grow during the forecast period 2025–2030, reaching value of four billion USD by 2030 (Yadav, 2025).

While incidence rates vary across regions and demographics, the overall burden is substantial, with increasing trends observed in certain populations (Filho et al., 2025), reflecting late diagnoses and limited access of treatment, such as Hungary (Elmadani et al., 2025). Brain cancers cause more than 18,000 deaths in Europe annually and are also the leading cause of cancer death in men aged 20–39 years as well as children (Siegel et al., 2025). However, the specific primary tumor type and the cause of death can vary by age group (Farrag et al., 2024).

Brain tumors are diverse, with different origins, characteristics, and clinical behaviors, including intrinsic tumors (mostly gliomas and glioneuronal tumors, also primitive, so-called embryonal tumors), extrinsic tumors (mostly meningiomas and schwannomas), as well as secondary brain tumors (metastatic) which originate elsewhere in the body and are the most common brain tumor in adults (Louis et al., 2021). Based on their histological characteristics, brain tumors are currently graded by the World Health Organization (WHO) into four grades (1, 2, 3 and 4) and they comprise more than 130 histological subtypes including newly defined tumor subtypes (Louis et al., 2021). Among all brain and CNS cancer types, glioblastoma represents one of the most aggressive and complex cancer types (Ismailov et al., 2025; Pouyan et al., 2025; Sipos et al., 2025).

To cure brain cancer, there are challenges in early diagnosis, patient stratification and treatment efficacy (Aldape et al., 2019; Mahima et al., 2024). Conventional treatment, such as surgery, radiotherapy, and chemotherapy, are often ineffective due to high tumor heterogeneity and resistance mechanisms (Zafar et al., 2025). There is an urgent need for precise diagnostic tools, better understanding of tumor biology and personalized treatment approaches (Krzyszczyk et al., 2018). Addressing these challenges requires continuous long-term efforts and multidisciplinary collaboration.

Net4Brain (COST Action CA22103) was launched in October 2023 to address these unmet needs through the creation of a pan-European, transdisciplinary network. It brings together clinicians, researchers, data scientists, and industry partners to drive innovation in brain cancer research and treatment. The Action is structured around five scientific themes, each operationalized through a dedicated Working Group (WG), and a sixth WG focused on dissemination and stakeholder engagement. Net4Brain has more than 500 scientists from 45 countries (Fig. 1).

This COST Action aims to facilitate the translation of fundamental scientific discoveries into better clinical treatment and management of patients suffering from brain cancer. Net4Brain will enable these aims through the following main objectives: 1) to build a unique pan-European and multidisciplinary network focusing on brain cancer by combining state-of-the-art knowledge and innovative techniques; 2) to promote education and training in the areas of advanced neuroscience, neuroimaging, genetics and molecular biology, cell biology and disease (tumor) models, big data and computational techniques for the accurate early diagnosis, prognosis, patient stratification and treatment of patients with different types of brain cancer; and 3) to build an integrated pan-European brain cancer database and biobank platform for the benefit of the research and clinical community.

2. Research themes and activities

There are separate themes and activities within the WGs (Fig. 2), however, research topics often overlap, and sometimes even merge. Therefore, the individual WGs communicate with each other and frequently address shared scientific questions, complementing and supporting one another.

3. Non-invasive biomarker discovery (WG1)

Currently, most brain tumors are not diagnosed until they become symptomatic (Walter et al., 2019). They are initially detected by means of imaging studies, such as computer tomography (CT), magnetic

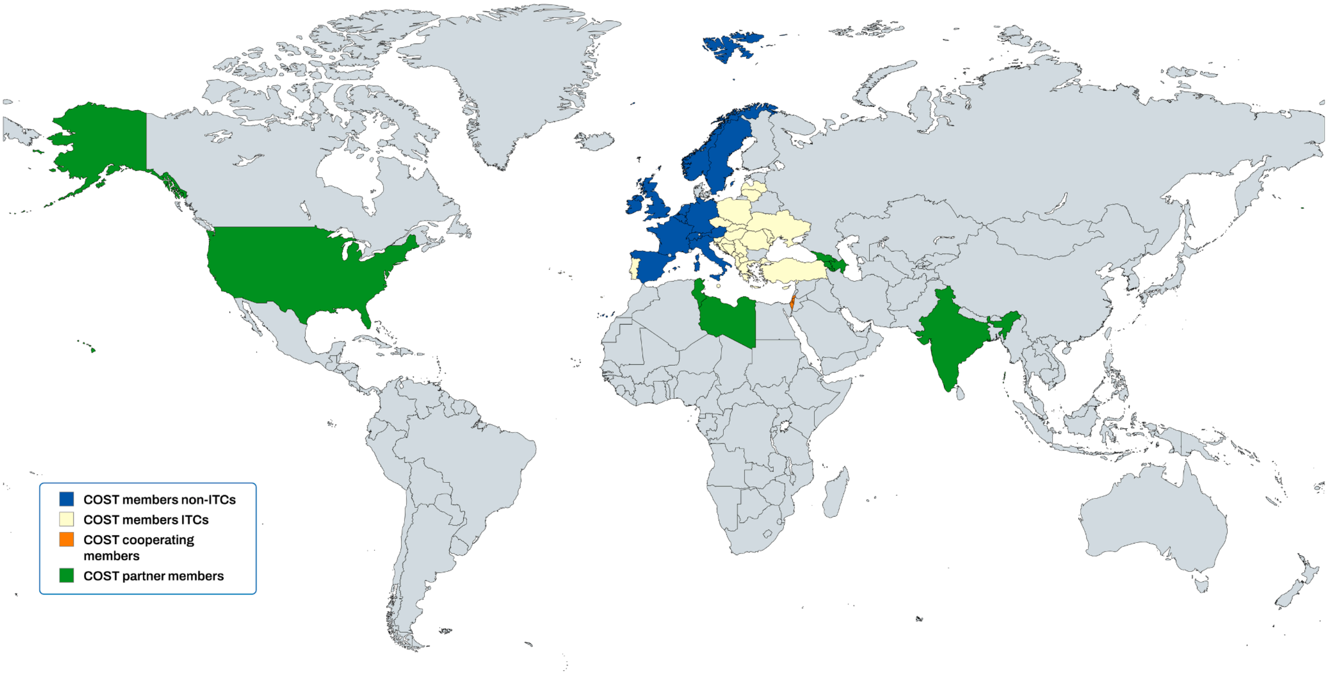

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Fig. 1. Geographical distribution of Net4Brain participants within and outside Europe. Inclusiveness Target Countries (ITC) are colored yellow, non-ITC countries are colored blue, COST cooperating members are labeled in orange and COST partner members are colored green.

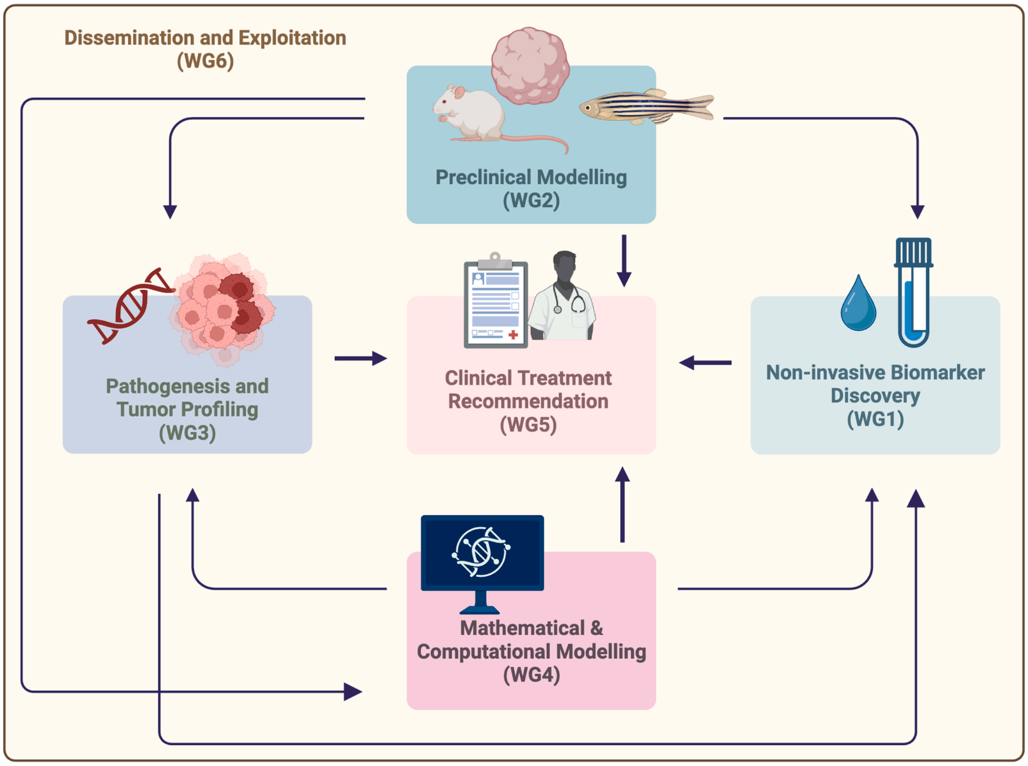

Fig. 2. Schematic organization of Net4Brain. Preclinical modeling as well as mathematical and computational modeling are the key stones for tumor profiling and biomarker discovery. Note the interaction between the Working Groups via various routes. Communication between the Net4Brain and the scientific community and wider public is ensured via Working Group 6.

resonance imaging (MRI), and positron emission tomography (PET) (Barańska et al., 2025). A definitive diagnosis typically requires a tissue biopsy for histopathological and molecular marker analysis. Typical treatments for aggressive brain cancers include surgery, radiotherapy (e.g., external beam fractionated radiotherapy), and chemotherapy (e.g., temozolomide) (Delaidelli and Moiraghi, 2024). These treatments may have short and long-term side effects, and in many cases these can be substantial (Brook, 2020; Weller et al., 2023).

Technological refinement and development of molecular diagnostics for brain cancer could pave the way to clinical implementation over the next decade (Zhan et al., 2025). Discoveries in the field of brain tumor biology over the last 15 years have identified a range of genetic and epigenetic alterations that are diagnostic and prognostic in brain tumors, such as *TP53* (tumor suppressor 53), *IDH1/2* (Isocitrate Dehydrogenase)*, NF1/2* (Neurofibromatosis type 1/2), *TSC1/2* (Tuberous Sclerosis Complex 1/2), *ATRX* (ATP-X-linked helicase II), *TERT* (Telomerase Reverse Transcriptase), *FRGR* (Fibroblast Growth Factor Receptor), the 1p/19q co-deletion, and methylation status in *MGMT (*O^6-methylguanine-DNA-methyltransferase) (Ruiz-Moreno et al., 2025). The use of more advanced technologies, such as next-generation sequencing (NGS) (Kwon and Yeung, 2024), RNA sequencing (RNA-seq) (García-Vicente et al., 2025), DNA methylation arrays (DNAm) (Ortega-Batista et al., 2025), and more recently, single-cell sequencing (scSEQ) and nanopore technology (Patel et al., 2025) are continuously improving the accuracy and speed of diagnostics, by interrogating either hundreds of disease-relevant genes or the genome-wide methylome. Recent advances in molecular classification based on transcriptomes including scSEQ and DNAm profiles have the potential to identify clinically relevant molecular subsets in brain tumors accurately, which may lead to the discovery of new types of precision medicine (Ortega-Batista et al., 2025; Ceccarelli et al., 2016; Maros et al., 2020; Martins et al., 2023). Already, there is a website-based application platform for Mobile Number Portability (MNP) which is a cloud-based software system that provides the necessary infrastructure and tools for users to upload their DNAm data and obtain the classification results which can be further integrated with the histological diagnosis (MNP, 2025).

Moreover, an interesting single-cell RNA (scRNA)-based study integrated scRNA sequencing data from 26 datasets, encompassing over 1.1 million cells from 240 patients, to construct GBmap, a harmonized single-cell atlas (Ruiz-Moreno et al., 2025). High-resolution spatial transcriptomics were employed to map the spatial organization of glioblastoma tissues. GBmap provides a novel platform for exploratory analysis with new data integration, hypothesis generation and testing.

Besides single-cell sequencing, many other sequencing and “omics” technologies are developing rapidly, such as single-nucleus sequencing (snSEQ) (García-Vicente et al., 2025), mass spectroscopy (Louati et al., 2025), single-cell proteomics (SCP) (Wu et al., 2025), single-cell metabolomics (SCM) (Zhang et al., 2025), or spatial transcriptomics (Ritter et al., 2025). These robust experimental technologies revolutionized the analysis of cellular heterogeneity and consequently allowed the identification of novel genes associated with cancer. These “omics” technologies on cells or tissues can be complemented by functional MRI (Yoon et al., 2024).

Relevant data have been deposited into the public domain for open access and reanalysis, such as ArrayExpress, GEO (Gene Expression Omnibus), CPTAC (Clinical Proteomic Tumor Analysis Consortium), TCGA (The Cancer Genome Atlas), CGGA (Chinese Glioma Genome Atlas), IvyGAP (Ivy Glioblastoma Atlas Project), GLASS (Glioma Longitudinal AnalySiS) or HGCC (Global Health Cost Consortium) (Tellam et al., 2015). Large-scale national biobank initiatives that employ whole-genome sequencing have become transformative resources for exploring human genetic variation and its impact on health and disease (Lee et al., 2025). The European Human Brain Project and the UK 500 K whole human genome sequencing project provide massive data resources with the potential to better understand, diagnose, treat and prevent life-changing diseases, including brain cancer (Lee et al., 2025).

Furthermore, the newly EU-funded Human Cell Atlas (HCA) organoid project is establishing single-cell transcriptomes, single-cell epigenomes and imaging data for several thousand organoids and matched primary tissue including brain tissue, which can serve as a baseline for medical studies including research on brain cancer.

The Net4Brain COST action emphasizes the discovery of liquid and imaging biomarkers for early detection, prognosis, and recurrence monitoring. This includes advanced profiling of blood-based markers such as ctDNA, circRNA, ecDNA, and tumor-educated platelets, as well as radiomic analysis of MRI and Raman Histology data using machine learning techniques. Radiogenomics approaches are also being developed to correlate imaging phenotypes with molecular signatures. Moreover, the European Cancer Imaging Initiative will be set up to develop an 'atlas' of cancer-related images and make anonymized images accessible, which will be an additional valuable resource for this Action.

Developments in radiogenomics provide non-invasive biomarkers that can lead to stratified treatment. A radiogenomics position statement on high-grade glioma is a WG1 objective leveraging the broad expertise within the Net4Brain consortium whose members range from clinicians to basic scientists, with experience stretching from imaging to molecular biology.

Recent activities:

Net4Brain brings together scientists from Europe who, within WG1, have so far discussed common problems during several meetings. The first online WG1 meeting took place on 05.02.2024, where the leaders from the working group introduced the consortium of the WG1 objectives, preliminary plan, and introduction of WG1 members. From this first meeting we have had several more meetings before July 2025 annual meeting. One of the action points agreed in WG1 early on was development of two manuscripts. One manuscript for liquid biopsies and the other for radiogenomics. We have successfully created the radiogenomics manuscript and are in the last stages of submission. We will start the liquid biopsy manuscript this month. In addition, WG1 has reached out to all members of the consortium for a collaborative effort in identifying potential areas of collaboration and grant application.

4. Preclinical modeling (WG2)

Preclinical modeling plays a critical role in cancer research, serving as a tool for functional investigation of tumor biology as well as the assessment of the efficacy of novel therapies in experimental systems before they advance to human trials (Guo et al., 2024). Both *in vitro* and *in vivo* models are essential for understanding how specific pathways, molecules, and candidate drugs influence the development of tumors (Matye et al., 2024).

Brain tumor models are central to advancing our understanding of tumor biology and in shaping the development of effective antitumor therapies. An optimal model should fulfill multiple requirements, including representation of genetic alterations and the tumor microenvironment (TME), while also remaining cost-effective and technically accessible. Moreover, the closer these models mimic human diseases, the more reliable they become in predicting therapeutic responses, thereby closing the gap between laboratory discoveries and clinical application (Akter et al., 2021).

Preclinical models for brain cancer research involve a variety of patient-derived models and experimental systems. Patient tumor cells can be propagated short term as tissue slices or explants (Steindl and Valiente, 2025). Sustained in vitro modeling long-term can be maintained as tumor organoids (Golebiewska et al., 2020; Jacob et al., 2020; Majc et al., 2024; Soubéran et al., 2025), stem-like cultures (Campos et al., 2010; Ntafoulis et al., 2023; Xie et al., 2015) as well as traditional cell lines (Maturi et al., 2020; Torsvik et al., 2014). In vivo propagation is classically supported by transplantation in immunodeficient animals, leading to development of so called cell line-derived xenografts (CDXs) and patient-derived xenografts (PDXs) (Bougnaud et al., 2016; Oudin et al., 2021). Subcutaneous implantation is the most applied approach, as it is technically simple and allows for convenient longitudinal monitoring of tumor growth (Sheng et al., 2025). However, intracranial implantation appears superior, since so called patient-derived orthotopic xenografts (PDOXs) recreate heterogeneous tumors supported by the relevant TME components in the brain (Qi et al., 2024; Yabo et al., 2024).

Brain tumor research can be further supported by experimental models. Historically, chemically induced tumors (Leskanicova et al., 2024) and genetically engineered mouse models (GEMMs) have been developed in rodent systems (Brandner, 2024; Jiang et al., 2017), representing relative simple models that allows for in vivo modeling of primary brain tumors with similar histopathology, etiology, and biology as in humans. GEMMs provide powerful tools for dissecting the roles and behaviors of specific genes, making them essential to understand tumor initiation processes and gene dependencies in tumor progression. Beyond gene function, GEMMs also enable researchers to study tumor resistance in a physiologically relevant immunocompetent context, offering insights that cannot be captured through in vitro studies alone (Xu et al., 2024). Nowadays, modern modeling includes also genetic engineering of stem cells (Schmitt et al., 2021)and brain organoids (Bian et al., 2018; Lago et al., 2023; Ogawa et al., 2018). These models are further complemented by additional models base on zebrafish and fruit flies (Shahzad et al., 2021; Zottel et al., 2023).

In recent years, numerous adaptations have been developed to better mimic the 3D architecture and oxygen gradients in vitro. 3D growth, the use of serum-free or physiologically relevant media and controlled oxygen levels can be further supplemented by application of physical forces through methods such as hanging-drop cultures or bioreactor-based rotations (Golebiewska and Fields, 2023). Some organ-on-chips enable downscaling of patient tumor material (Ding et al., 2022; Jiang et al., 2020), other technologies aim to reconstruct hypoxic gradients, extracellular matrix environment, TME compartments for flexible treatment protocols (Bayona et al., 2025). The integration of advanced bioprinting techniques and organoid systems offers the possibility to recreate TME interactions, vascularization patterns, and immune cell infiltration, thereby providing a more holistic view of brain tumor biology. Advanced co-cultures with healthy brain organoids (Peng et al., 2025) or non-neuronal components (Klein et al., 2020; Salvato et al., 2025) will further allow to examine functional interactions with the relevant TME components. PDOX models can be further advanced by reconstitution of adaptive immune system via humanized mice based on mature blood cells or hematopoiesis from the CD34 + stem cells (Klein et al., 2020).

Net4Brain WG2 group includes experts in preclinical modeling, covering diverse experimental systems. We aim to evaluate the strengths and pitfalls of available protocols as well as to develop novel innovative strategies based on advanced co-cultures, organ-on-chip and humanized mice. A central objective will be the refinement of protocols for ex vivo brain tumor propagation, as current approaches fail to fully capture the cellular diversity and molecular heterogeneity of patient tumors. Achieving this will be crucial for developing preclinical models that more accurately mirror the complexity of human disease. These innovative systems will serve as versatile platforms for investigating tumor vulnerabilities, mechanisms of drug resistance, and therapeutic response. We aim to derive high-throughput methodologies for drug development pipelines (Ermini et al., 2025) as well as co-clinical trials to develop precision medicine and immunotherapeutic approaches.

Recent activities:

WG2 fosters exchange on preclinical modeling of brain tumors via regular meetings, workshops, lectures as well as STSMs. WG2 training so far included advance workshops on preclinical modeling with well removed external and internal speakers (23.05.2024, Berlin, Germany; 10.03.2025 online). WG2 members have opportunity to join regular online lectures, meetings and task forces (in vitro modeling, ex vivo advanced modeling, in vivo modeling). Several STSMs focused on the wet lab exchange programs, several trainees have been supported to join the CAJAL School of Cancer Neuroscience (September-October 2025, Bordeaux, France).

5. Pathogenesis and tumor profiling (WG3)

The 2021 WHO Classification of CNS tumors recognizes more than 100 distinct tumor types (Louis et al., 2021). Although histology remains a key diagnostic tool, molecular testing has become increasingly essential. For example, the combined loss of chromosome arms 1p and 19q is now required to classify IDH-mutant gliomas as oligodendrogliomas (Cahill et al., 2015). A deeper understanding of tumor pathogenesis and progression is essential for patient stratification and treatment, as it enables the identification of patients most likely to benefit from specific therapies while also enhancing insight into treatment-related toxicities, cancer recurrence, and drug resistance (Tremmel et al., 2025). Furthermore, brain tumor progression is shaped by genetic evolution and microenvironment interactions. Thus, the brain TME is emerging as a critical regulator of brain cancer progression, and the immune and vascular components of the TME are likely to have relevance for improving the treatment (Varn et al., 2022). These advances in accurate pathological diagnosis and TME-targeted interventions will become crucial for the optimal treatment of patients with brain cancer, allowing patient stratification and personalized medicine (Khan et al., 2023).

More recently, DNA methylation profiling has emerged as a powerful technique with high diagnostic precision. The integration of genetic (mutations, gene fusions) and epigenetic (CpG methylation) alterations has refined diagnoses and facilitated the identification of rare brain tumor subtypes with unique clinical outcomes, such as IDH-mutant gliomas represent a clinically and molecularly distinct subtype with a better prognosis compared to their IDH-wildtype counterparts. Looking ahead, molecular profiling is expected to play an even greater role in surgical neuropathology, though barriers such as cost, accessibility, and logistical complexity remain (Pratt et al., 2023). However, despite major advances in molecular profiling and classification of primary brain tumors, personalized treatment remains limited for most patients (Kuehn et al., 2024).

Single-cell resolution has proven to be of the utmost importance and can reveal a remarkable level of regional heterogeneity in cancer (Ortega-Batista et al., 2025). To obtain a complete understanding of brain tumor biology, this Action seeks to apply novel single-cell-based experimental techniques (e.g., single cell RNAseq, proteomics, and metabolomics), together with DNAm, and computational approaches to reveal how the brain TME contributes to drug resistance and tumor recurrence across brain tumor types, from low-grade to high-grade, and from predominantly pediatric (e.g., medulloblastoma) to those frequently seen in adults (e.g., glioma). Formalin-Fixed Paraffin-Embedded (FFPE) and fresh tissue samples will be obtained from public depositories such as EuroBioBank, UK Biobank, as well as cancer centers involved in this network. In addition, single-cell spatial epigenetic technologies will be developed to tag tissue epigenetic status *in situ* and decipher single-cell spatial chromatin accessibility, histone modifications, and transcriptional factor bindings. Both data-driven and hypothesis-driven approaches will be applied (the latter with power calculations to estimate sample size before data collection). Comprehensive bioinformatics analysis will then be carried out, including the development and application of machine learning techniques. Different research groups have been carrying on relevant work for many years, and their work will be enhanced via new collaborations within this Action.

Recent surveys among the action participants revealed a strong collective interest in molecular profiling techniques. Approximately 72% of the respondents expressed their willingness to actively contribute to WG3’s ongoing activities involving data sharing, analysis, and collaborative interpretation. However, it was also observed that nearly 80% of these researchers have not yet generated their own molecular profiling datasets. This finding highlights a substantial gap between theoretical interest and practical experience, emphasizing the need for capacity building and methodological training before experimental implementation and resource allocation. Accordingly, WG3 has prioritized initiatives that support the acquisition of foundational knowledge and skills in multi-omics data generation and analysis. To address these needs, WG3 has initiated the development of an umbrella database and data-sharing platform designed to consolidate publicly available datasets relevant to tumor profiling. This platform will employ automated public database scraping to collect metadata, dataset descriptors, and repository links from major international resources such as The Cancer Imaging Archive (TCIA), STEMRI Trial, EUCAIM, The Cancer Genome Atlas (TCGA), GBMseq, and the Chinese Glioma Genome Atlas (CGGA). Both image-based and non-image-based datasets will be indexed, enabling researchers to easily identify, retrieve, and compare relevant molecular and imaging data for exploratory or comparative analyses. In addition to aggregating public resources, the platform will also accept new dataset submissions from action members, contingent upon a standardized quality control and consistency assurance process. This ensures data reliability while maintaining full ownership rights and control for the contributors. By facilitating secure, traceable, and FAIR-compliant (Findable, Accessible, Interoperable, Reusable) data sharing, the platform aims to stimulate collaborative research, reproducibility, and cross-validation within the network. Ultimately, these initiatives will contribute to WG3’s overarching mission of enhancing our understanding of tumor pathogenesis through integrative profiling approaches, fostering collaborative data science, and supporting the European research community in building sustainable infrastructures for precision oncology research.

Recent activities:

The first WG3 meeting was held online in February 2024, during which the objectives of WG3 were introduced, along with the preliminary work plan, training school agenda, and introductions of the WG3 members. The second online meeting focused on the development of a dedicated database. The third meeting was largely devoted to the preparation of a manuscript on single-cell sequencing and spatial “omics“ technologies in brain cancer, which will constitute a key deliverable in the coming year. Recently, the WG3 members connected during the 2nd Annual Meeting in Bucharest in July 2025. Highlights included a keynote lecture by Dr. Gaetano Gargiulo (Max Delbrück Center, Germany), a session talk by Prof. Tugba Bagci-Onder (Koç University, Türkiye), and short talks by Prof. Milica Pesic (University of Belgrade, Serbia), Sagar Acharya (Medical University of Vienna, Austria) and Dr. Diana Aguilar Morante (Institute of Biomedicine of Seville, Spain). The session provided novel insights into the molecular mechanisms regulating the progression and therapy response of brain tumors.

As WG3 activities rely heavily on results from scientific research conducted on preclinical models, WG3 and WG2 collaborate closely. Reflecting this synergy, the leaders of both WGs, Dr. Barbara Breznik (National Institute of Biology, Slovenia) and Prof. Tugba Bagci-Onder (Koç University, Türkiye) successfully secured a bilateral grant to test novel epigenetic drugs on organoid models. This two-year project will facilitate researcher mobility between Slovenia and Türkiye, as well as the exchange of expertise between two state-of-the-art research hubs.

In addition, WG2 organized a virtual conference entitled *“Modeling Minds: Innovations in Preclinical Brain Cancer Research”* in March 2025, with strong participation from both WG2 and WG3 members. The meeting featured 10 presentations covering *in vitro* and *ex vivo* modeling, advanced co-cultures and organ-on-chip systems, and *in vivo* modeling. It concluded with a workshop that generated fruitful discussions on the challenges associated with GEMMs and PDOX models in brain tumor research.

6. Computational and mathematical modeling (WG4)

As healthcare systems worldwide grapple with rising costs, restricted access, and increasing demand for personalized care, machine learning is emerging as a powerful driver of transformation (Maleki Varnosfaderani and Forouzanfar, 2024). Medical imaging plays a fundamental role in current cancer detection. Using imaging data, deep learning (DL) based algorithms such as LYNA (LYmph Node Assistant) and FocalNet can detect breast cancer as accurately as radiologists (Ahn et al., 2023) and potentially improve the detection of prostate cancer (Rabaan et al., 2022; Riaz et al., 2024). As remarkable examples for brain cancer, the diagnosis of glioblastoma, the most aggressive brain cancer, could be significantly improved by applying DL on Stimulated Raman Histology (SRH) imaging (Asif et al., 2025; Hollon et al., 2020).

An open challenge is represented by how machine learning should be used in combination with current clinical practice. In 2025, Asif et al. revealed that ensemble machine learning approaches work better than individual models, particularly in identifying different types of brain tumors. Specifically, the combination of InceptionV3 + Xception hit an accuracy level of 98.50% in training and 98.30% in validation (Asif et al., 2025). In addition, the use of Nanopore technology aided by ML technology could reduce waiting times for an integrated diagnosis from 2 to 3 weeks to 2–3 days (Patel et al., 2022). Likewise, it was reported that benign and malignant brain tumors could be detected from 111,205 brain MRI data with an accuracy of 99% by applying ensemble ML approaches (Brunese et al., 2020).

Advances in deep learning combined with massive datasets may enable the development of new tools. NYUMets-Brain, the world’s largest, longitudinal, real-world cancer dataset consisting of the imaging, clinical follow-up, and medical management of 1429 patients, was built to detect small metastases. Using Segmentation-Through-Time, a deep neural network which explicitly utilizes the longitudinal structure of the data, obtained state-of-the-art results at small (< 10 mm^3) metastases detection and segmentation (Link et al., 2024). The authors further show that the monthly rate of change in brain metastases is a strong predictor of overall survival (HR 1.27, 95% CI 1.18–1.38) (Link et al., 2024).

Other promising tools include InnerEye, an open-source DL Toolkit from Microsoft that accelerates brain cancer treatment by cutting CT processing times during radiotherapy treatment planning by up to 90% (Escudero Sanchez et al., 2021).

Extensive efforts in machine learning, medical imaging, as well as multi-omics techniques are leading to new concepts (e.g., reinforcement learning, radiomics, digital twins), novel algorithms (e.g., GANs, Transformers) etc., aiming to convert traditional black-box machine learning into explainable and more usable tools. Guidelines for AI in healthcare are being studied for practical applications (Alzubaidi et al., 2021; Esteva et al., 2019; Liu et al., 2020).

Beyond machine learning, mechanistic mathematical models (Altrock et al., 2015; Azizi, 2025) offer other tools that can be used to construct prognostic and predictive biomarkers and find optimal treatment schedules. Such *in silico* models provide test beds for different treatment combinations and may help in raising hypotheses on game-changing therapeutic strategies, specifically for brain tumor studies (Collin et al., 2021). Computational and mathematical modeling in brain cancer applies mathematical techniques to understand tumor growth, invasion, and response to treatment, providing a framework for *in silico* (computer-based) experiments to generate new hypotheses and test existing ones before clinical trials. Mathematical models have been proven valuable for drawing inferences and making predictions in different fields of cancer research, but few mathematical works have considered brain metastases (Ocaña-Tienda and Pérez-García, 2024). By integrating mathematical insights with experimental data and clinical observations, mathematical modeling emerges as a powerful tool in oncology, contributing to the development of more effective and personalized cancer therapies that improve patient outcomes (Azizi, 2025).

Machine learning-based data integration platforms are developed to combine “omics”, imaging, and clinical data for diagnosis, stratification, and treatment optimization (Ozaki et al., 2024). Novel machine learning models (e.g., radiomics-integrated VCDN - Virtual Content Delivery Network) and mechanistic models are also used to simulate tumor dynamics, predict treatment response, and optimize radiotherapy schedules (Kocher et al., 2020; Xie et al., 2025).

Although classical machine learning approaches such as Support Vector Machine (SVM) and Random Forest (RF), as well as DL approaches, e.g. Convolutional Neural Network (CNN) and DeepCC, and subtype classification using a single type of “omics” or imaging data, have been successfully applied in cancer diagnosis and subtype classification, current existing methods may not be adequate to address the challenge of integrating genotypic data from patients, multi-omics data from drug treatments, pharmacology data from bioactivity and toxicity assays, as well as radiomics imaging data for diagnosis and classification of brain tumors. Therefore, developing new algorithms is still crucial. Pioneer studies have been conducted to integrate scRNAseq, miRNAseq, and DNAm data from TCGA using machine learning for pan-cancer classification and survival prediction where multi-omics and clinical data are both considered (Vatansever et al., 2021). This Action aims to extend such strategies by integrating genotype and radiomics data. Specifically, omics-specific DL models including radiomic models will be built-up for a single type or multiple types of brain cancer depending on the data availability, then the VCDN54 approach will be utilized to integrate these models for classification, and novel approaches will be developed for optimization. Biomarkers can be identified by their importance to classification performance which has the potential to interpret the results and understand the underlying cancer biology and pathology, especially when a correlation between radiomic and other “omics” biomarkers is detected (radiogenomics studies).

To make DL explainable and enhance its success in clinical practice, incorporating domain expertise is essential. Therefore, this Action also aims to encourage clinicians including neuro-oncologists and radiologists, to participate in the early development of machine learning algorithms including the whole training and validation process. Moreover, five mathematical models will be developed to understand and overcome resistance to therapies by integrating multi-omics data as well as biomarkers discovered in liquid biopsies: 1) to optimize the scheduling/therapy combinations allowing mitigation of the problem of the emergence of resistances; 2) to simulate tumor heterogeneity influencing the response to drug therapies in pre-clinical models developed during this Action; 3) to reveal “macroscopic” heterogeneity metrics correlating with tumor cell biology (genotypes and/or phenotypes i.e., invasive vs angiogenic growth); 4) to estimate prognosis in brain metastasis and understand the response of these secondary tumors to radiotherapy whilst focusing on primary lung and breast cancers. 5) to develop a tumor growth model (TGM) by estimating cell density. Although the generally limited data (and therefore sample size) due to the cost in biomedical research is one of the key challenges for the application of DL, it is believed through data integration, along with more data becoming available, that it may not be a significant concern in the future.

Recent activities:

To fulfill the aims of this part of the Action, in July 2024 a WG4 online meeting was held to discuss available expertise and plan for the next tasks. Another meeting in person was held in July 2025 to discuss new collaborations with other WGs. A new partnership was established through Net4Brain with the WG2 group, focusing on machine learning tools for segmentation, and organization of the tumor microenvironment.

A short-term scientific mission (STSM), offered via COST, was completed on machine learning for imaging in May 2025. The project aims to identify and create DL models on brain tumor data (MRI) that determine patient survival time and the probability of tumor recurrence.

The offered STSM project served as a bridge between two laboratories: the Department of Bioengineering and the Department of Mathematics & Computer Science at Ege University, and the lab supervised by Prof. Claudio Angione at Teesside University.

7. Clinical treatment recommendations (WG5)

New therapeutic approaches in brain cancer radiotherapy (RT) integrate techniques like particle therapy (protons and ions), which precisely target tumors, and FLASH radiotherapy, delivering ultra-high dose rates to protect healthy tissue. Nanomedicine enhances treatment by enabling targeted delivery of radiation and drugs, while imaging and AI improve treatment planning and delivery (Ćwiklińska et al., 2024; Webster et al., 2025). Clearly, these needed to be implemented within an evidence-based medicine (EBM) framework which is of considerable value for medicine and neuro-oncology (Van de Vliet et al., 2023). In this context, it is noteworthy that whilst using biomarkers in patients with cancer may help to select the optimal treatment, many patients do not undergo recommended biomarker testing (Brixner et al., 2025).

Net4Brain COST action aims to develop new therapeutic approaches in radiotherapy (RT). Novel pathological grading strategies will be exploited by combining radiomics and multimodal -omics techniques for RT. Specifically, to reduce treatment for less-aggressive brain tumors, it is very important to distinguish between low-risk of growth (LRG) and high-risk of growth (HRG) patients. For instance, the “Wait and See” following-up strategy can be directly applied to LRG patients. Among the HRG patients, (1) high-grade patients may need immediate surgery and/or RT; (2) low-grade with a low risk of recurrence (LRR) patients may just need routine “Wait and See” follow up; 3) low-grade with a high risk of recurrence (HRR) patients may need aggressive RT treatment and frequent following up. Combining radiomics with blood-based biomarkers and genotypic patterns supported by machine learning has the potential to provide more precision and robust grading, i.e., distinguishing LRG, HRG, LRR and HRR, for personalized treatment. In addition, brain metastasis prognosis models have a high chance of being applied in RT clinical practice. Moreover, new TGMs will be applied to optimize RT, e.g., to optimize the shape of the radiation beam as well as dose painting to significantly increase the number of tumor cells killed during RT treatment. Furthermore, it is reported that novel SSRT (Slow strain rate testing) has the potential to change clinical practice although its application is still in its infancy. Thus, this Action aims to develop clinically reasonable guidelines and protocols for accurate SSRT treatment based on patient stratification and prognostic biomarkers.

Recent activities:

Within this WG, several meetings were held to fulfill their aims. The first WG5 session was held during the 1st Annual Meeting in Ljubljana in July 2024: the WG5 session in the first Action meeting was chaired by Prof. Oliver Hanemman, Chair of Clinical Neurobiology at the University of Plymouth, and included general interest content around clinical treatment of brain tumors and translational research topics. The session served as the first steering meeting of the group, guiding the strategy for the following group events and actions. In October 2024, WG5 collaborative webinar titled “Bridging discovery and modeling with clinical treatment of brain cancer – what can clinicians expect?” involved the leaders of all the WGs of the Net4Brain Action and externals experts, such as the President of the European Association of Neuro-Oncology (EANO) Prof. Susan Short. The webinar aimed to offer an overview of the different brain cancer research aspects to interested clinicians and to trigger a discussion between researchers and clinicians pertaining to the expectations of the latter from the advances in basic research. The webinar dealt with biomarker discovery preclinical modeling, tumor profiling, diagnostic treatment strategies and computational modeling, attracting ~100 researchers and clinicians from the action members and beyond. Insights and updates from the webinar material have since been incorporated into the teaching curriculum in at least one medical school (School of Medicine, Aristotle University of Thessaloniki, in the Neurosurgery course). During the 2nd Annual Meeting in Bucharest in July 2025, the group-related content included the Mega-Talk by Prof. Thomas C. Booth dealing with consensus statements on machine learning models for adult HGG radiogenomics, and the WG5 session that was chaired by Assistant Professor of Neurosurgery Alkinoos Athanasiou (Aristotle University of Thessaloniki). The session served as the showcase for the actual reach of clinical treatment recommendations in the context of the Net4Brain action, including a keynote talk by Prof. Mauricio Reyes (University of Bern) on hypothesis-derived research in neurooncology, a talk by Professor of Neurosurgery Radim Jancalek (Masaryk University) on major clinical challenges in brain cancer research and a selection of short talks.

8. Dissemination and stakeholder engagement (WG6)

Outreach and dissemination are integral to Net4Brain activities including multilingual patient consent templates, training schools, and strong ties with patient organizations and industry. A publicly accessible pan-European brain cancer database is being established, aligned with FAIR data principles. Over the past two years, we have managed to set up and maintain a website not only for the members of the Action but also for the general public. We keep this website constantly updated. In addition to the website itself, we have also created Facebook, Instagram, and LinkedIn accounts. On these social networks, we share the latest activities and grant calls almost daily. We also regularly publish a newsletter – in spring, autumn, summer, and winter. There, we present news, members of the action, promotional activities, and successful projects. Within this group a Creative group of scientists is creating a net for collaboration in promotional and designing ideas.

9. Young researchers group

Supporting the next generation of scientists is a key pillar of Net4-Brain. The Young Researchers Group (YRG) have developed a structured platform for PhD students, postdoctoral fellows, and other early career researchers (ECRs) to engage in the Action’s scientific activities and to build capacity for future leadership in brain and CNS cancer research. By fostering cross-disciplinary exchange and peer support, the YRG ensures that young scientists contribute actively to Net4Brain’s research priorities while gaining skills, essential for independent careers.

The YRG focuses not only on advancing scientific knowledge but also on training, networking, and career development. Activities include keynote lectures by senior experts, interactive workshops on academic publishing, grant funding, and collaboration, as well as structured mentoring and peer-led discussions. A strong focus is placed on equipping ECRs with practical tools (e.g., publishing, project management, and communication skills) alongside opportunities to present their research and build international collaborations.

The YRG organizes recurring online and in-person meetings, training schools, and workshops. Deliverables include (i) a sustainable platform for ECR engagement across Europe, (ii) integration of ECR contributions into Net4Brain outputs and guidelines, and (iii) a pipeline for future leadership within the Action. Partnerships with academic institutions, industry, and publishing groups will be explored to strengthen training and career support opportunities.

Recent activities:

The first Net4Brain Early Career Researchers (ECRs) Online Meeting took place on 28 October 2025. The program brought together PhD students, early career researchers, and senior experts to foster exchange, skill development, and community building. Highlights included keynote lectures by Prof. Bożena Kamińska-Kaczmarek (Nencki Institute of Experimental Biology, Warsaw) and Dr. Trygve Bakken (Allen Institute for Brain Science, Seattle), an Elsevier Author Workshop on academic publishing, short presentations by ECRs, and interactive breakout discussions covering topics such as publishing, funding opportunities, collaboration, and work–life balance. This event was part of a series of

YRG-led initiatives designed to empower the next generation of brain research leaders and to embed career development within the core mission of Net4Brain.

Looking ahead, the YRG is designed to serve as a sustainable framework for nurturing talent within and beyond the lifetime of the COST Action. Future initiatives will include annual ECR meetings, training schools, collaborative research exchanges, and partnerships with academic institutions, industry, and publishing groups. In this way, the YRG will not only strengthen the scientific and professional development of its members but also contribute to building a cohesive community of young researchers across Europe, ensuring continuity and innovation in brain cancer research.

10. Short term scientific missions

STSMs are exchange visits for researchers within their COST Action. STSMs are great opportunities for researchers to share techniques and gain skills that may not be available at their home institution or laboratory. Across 10 STSMs, Net4Brain has gathered researchers from Austria, the United Kingdom, Portugal, Spain, Germany, the Netherlands, Luxembourg, the Czech Republic, Slovenia, Greece, Türkiye, and Serbia to master cutting-edge methods in brain cancer research. These efforts cluster into four thematic areas: (1) quantitative imaging and data fusion, (2) advanced preclinical models, (3) machine learning prognostic modeling, and (4) molecular biosensor probe development - each delivering tangible advances.

10.1. Quantitative imaging and data fusion

Researchers have containerized a magnetic resonance spectroscopy processing model and implemented a workflow that produces absolute brain-metabolite concentration maps by integrating proton-density water mapping with multiparametric corrections, creating a shareable oncometabolic imaging system.

Routine anatomical scans were analyzed for radiomic features that predict spectroscopy signatures in glioblastoma, with machine learning classifiers achieving area-under-the-curve values of 0.60–0.70, thereby opening avenues for this to be a noninvasive biomarker.

Further, researchers have built a fully reproducible spatial transcriptomics pipeline that aligns single-cell molecular fingerprints onto three-dimensional tumor sections - combining high-resolution segmentation, Bayesian deconvolution and denoising - to reveal niche architecture, cellular plasticity and molecular heterogeneity for precision profiling.

10.2. Advanced preclinical models

Researchers established patient-derived glioblastoma organoids, screened repurposed drugs using sensitive luminescence assays and conducted live imaging to capture dose- and time-dependent morphological changes, guiding lipid-nanoparticle formulations for future *in vivo* work.

Other researchers have used immunodeficient mouse models, where safe dosing of a natural product, its hybrid compounds and an adamantane derivative were defined and shown to markedly suppress tumor growth, validating *in vitro* potency and informing plans for drug-resistant models.

A conversion of confocal to light-sheet microscopy enabled optimized tissue clearing, immunostaining, agarose embedding and high-resolution volumetric imaging of organoids. Standardizing workflows for invasion studies and biomarker mapping enhances consistency and comparability in biological research.

A comprehensive patient-derived xenograft organoid pipeline now encompasses tumor dissociation, three-dimensional culture, white blood cell isolation, microglia co-culture, flow cytometry phenotyping, and immunohistochemistry with confocal imaging. The research focused on modeling tumor–immune interactions in unprecedented detail.

10.3. Machine learning prognostic modeling

A hybrid DL framework now fuses three-dimensional postoperative magnetic resonance imaging with clinical metadata to predict survival time and recurrence in glioblastoma. Starting from a convolutional regressor with a 350-day error, researchers refined the model by combining neural networks with multilayer perceptrons, applying class balancing for underrepresented outcomes, tuning hyperparameters via particle-swarm optimization and introducing a mosaic strategy to include scans with missing image types—ultimately achieving 79.7% accuracy (F1 = 0.88) for recurrence prediction.

10.4. Molecular biosensor probe development

A chemo-enzymatic route was devised to synthesize alpha-fucosylated oligosaccharide probes by screening nine native fucosidases for transglycosylation activity. High-performance liquid chromatography–mass spectrometry identified four enzymes that reliably generate a protected fucosyllactose derivative, setting the stage for preparative-scale synthesis, structural confirmation by nuclear magnetic resonance and binding assays against galectin proteins. These probes will underpin an early-diagnosis glyco-biosensor for glioblastoma.

In summary, by transferring these state-of-the-art techniques to researchers across Europe, particularly in Inclusiveness Target Countries - Net4Brain has forged durable collaborations, standardized high-impact workflows and integrated multi-modal data. This interdisciplinary foundation positions the network to achieve translational breakthroughs in brain cancer detection, profiling, and personalized treatment.

11. Conclusion

Brain cancer presents persistent clinical challenges due to diffusely infiltrative tumor growth and the aggressive nature – especially in glioblastoma which is the most common form of glioma. Together with the therapeutic delivery constraints of the blood-brain barrier and tumor resistance to therapy, there are high relapse rates which result in a poor prognosis and a reduced quality of life. Key future directions in brain cancer research and care include developing earlier and more accessible methods of drug delivery across the blood–brain barrier and advancing novel targeted therapies that enhance efficacy while minimizing side effects. The aim of the Net4Brain COST Action is to build a comprehensive, pan-European network that translates scientific discoveries into improved clinical treatments for brain cancer by fostering research, training new experts, and developing innovative diagnostic tools and data resources. More information can be found on the official COST website, or by contacting the Action Leadership.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Grammarly to check for grammatical and stylistic errors and improve readability. After using this tool, the authors reviewed and edited the content as needed and they take full responsibility for the content of the published article.

Declaration of Competing Interest

No conflict of interest.

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