

The future of treatment for glioblastoma

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Story highlights

McCain returns to Arizona to continue recovering from side effects of chemotherapy treatment for glioblastoma

Ongoing clinical trials are shaping the future of glioblastoma treatment options

Clinic. He is grateful for the excellent care he continues to receive, and appreciates the outpouring of support from people all over the country. He looks forward to returning to Washington in January."



Related Article: Sen. John McCain has brain cancer, aggressive tumor surgically removed

"There are many exciting areas in research in primary brain cancers, and most clinical trials are in glioblastomas, in part because they are the most common primary brain cancers in adults," Holdhoff said.

(CNN) — Sen. John McCain [returned to Arizona on Sunday](#) to continue recovering from the side effects of chemotherapy for an aggressive type of brain cancer called [glioblastoma](#).

McCain, 81, was [diagnosed with the brain tumor in July](#) after surgery to remove a blood clot above his left eye.

Last week, [McCain received treatment at Walter Reed Medical Center](#) in Bethesda, Maryland for the side effects of his ongoing cancer therapy, [according to his office](#).

Then on Sunday, [McCain's office said in a statement](#) that he "will undergo physical therapy and rehabilitation at Mayo

Glioblastoma can be difficult to treat. Average survival for malignant glioblastoma tends to be about 14 months with treatment, according to CNN Chief Medical Correspondent Dr. Sanjay Gupta, a practicing neurosurgeon.

"The general approach is to offer patients a combination of radiation and chemotherapy as a first-line treatment," said Dr. Matthias Holdhoff, a medical oncologist and associate professor of oncology in the brain cancer program at Johns Hopkins University School of Medicine in Baltimore. He was not involved in McCain's care.

"Based on this, we're trying to build on that standard of care," he said.

So, in the future, there might be more cutting-edge treatment options for glioblastoma patients.

A 'quest for finding better treatments'

Clinical trials being conducted across the United States are exploring immunotherapies, vaccines and targeted therapies in addition to traditional treatments, said Dr. Manmeet Ahluwalia, a brain tumor oncologist, professor and director of the brain metastasis program at the Cleveland Clinic in Ohio.

He is not involved in McCain's care, but his team at the Cleveland Clinic has enrolled patients in a number of clinical trials for glioblastoma treatments.

According to the [National Institutes of Health's clinical trials database](#), 274 glioblastoma multiforme studies across the country are active or recruiting.



"The brain tumor community is very united in our quest for finding better treatments for our patients, and I think the progress will come through clearly planned and orchestrated clinical trials, looking at both approaches, immunotherapies ... and appropriate uses of targeted therapies, which will go and attack the genes that drive a particular tumor," Ahluwalia said.

As for potential vaccine options, "the hope is that we are using vaccines to keep the tumor from coming back," he said.

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These treatment options, which are still in early phases of research, are not yet approved and available for the general public. As the research is still ongoing, it remains unclear how much any of the potential treatments would someday cost.

Targeted cancer therapies

Targeted cancer therapies are drugs or other substances that block the spread of the disease by targeting and interfering with specific molecules involved in its growth and progression, according to the [National Cancer Institute](#).

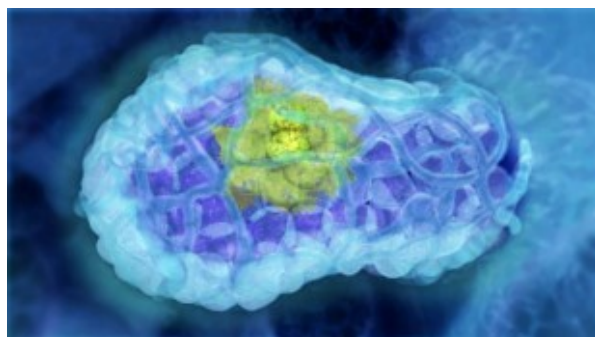
Though such therapies may sound promising in theory, study results have been unexpectedly disappointing, said Dr. Eric Holland, senior vice president and director of the human biology division at the Fred Hutchinson Cancer Researcher Center in Seattle.

"Individual drugs and combinations of them that hit more than one target have all been tried, and thus far, they've not really shown a whole lot of promise or certainly have not been as successful as we have liked," Holland said.

Some side effects of targeted cancer therapies include diarrhea; liver problems, such as hepatitis and elevated liver enzymes; skin problems; problems with blood clotting; and high blood pressure, according to the [National](#)

Immunotherapy

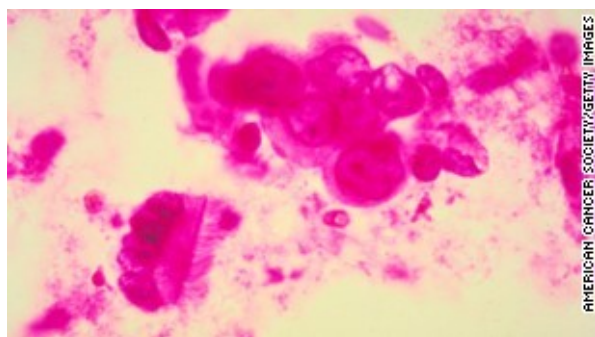
On the other hand, some studies have shown immunotherapies to work well against certain cancers, such as melanoma and lung cancer, he said. Yet more research is needed to determine the promise of immunotherapies for glioblastoma.



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glioblastoma," Ahluwalia said. "Immunotherapy has been shown to be promising in a number of other cancers, like lung cancer and melanoma. We are currently evaluating a number of such approaches. The ones which are most furthest along are some trials that are evaluating [nivolumab](#), which is an anti-PD1 therapy in combination with chemotherapy and radiation."

In other words, the [immunotherapy drug nivolumab](#) unleashes an immune system attack on cancer by blocking the activation of a protein called PD-1, which would otherwise inhibit that attack, according to MD Anderson Cancer Center. The hope is to extend the life of the patients with this treatment.



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Cancer [immunotherapy](#) is a type of treatment that harnesses the body's own immune system to recognize, target and attack the disease, similar to how the immune system helps the body fight infections and other diseases.

Some side effects of immunotherapies include skin reactions, flu-like symptoms, heart palpitations, sinus congestion, diarrhea or even fatal allergic reactions, according to the [National Cancer Institute](#).

Immunotherapies can come in many forms -- vaccines, antibody or cellular therapies, or drugs -- and can be received through an injection, a pill or capsule, a topical ointment or cream, or a catheter.

"There is a great deal of excitement about some of the immunotherapy-based approaches in treatment of

The diseases in which immunotherapies have shown promise, from skin to lung cancers, tend to involve tumor types that have many point mutations in them, Holland said. Point mutations are changes in specific locations in the tumor's DNA.

For instance, "in melanoma, it's the sun's damage to DNA, and smoking causes the lung damage" in lung cancer, Holland said.

When such genetic mutations occur in a tumor, they can cause the tumor to appear like a pathogen or foreign substance in the body, which the immune system can recognize and attack when triggered by an immunotherapy.

However, "brain tumors tend not to be that way," Holland said. "They tend to not be caused really by point mutations. They don't have a lot of point mutations in them."

Of all things, a [modified poliovirus](#) was found to infect and attack glioblastoma in [an experiment at Duke University](#).

In May 2012, the virus was injected directly into the tumor of a [glioblastoma patient as an investigational therapy](#). In the months following, the tumor started to shrink, without the use of chemotherapy or radiation.

Research focusing on [poliovirus immunotherapy and glioblastoma](#) remains ongoing.

While "it's certainly a very interesting concept ... this concept would also need to be rigorously tested further," said Holdhoff, who was not involved in the study. "We need to see how data will pan out when it's studied in a study that's looking at actual efficacy and overall benefit."

Cancer vaccines

Cancer vaccines, in particular, are another treatment approach in the immune space.



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Such vaccines are classified as active immunotherapies because they rely on activation of a patient's immune system to recognize and destroy a tumor, according to a 2014 paper in the [Journal of Immunology Research](#).

As a treatment, cancer vaccines are intended to treat an existing cancer by strengthening the body's natural immune response against the cancer, according to the [National Cancer Institute](#).

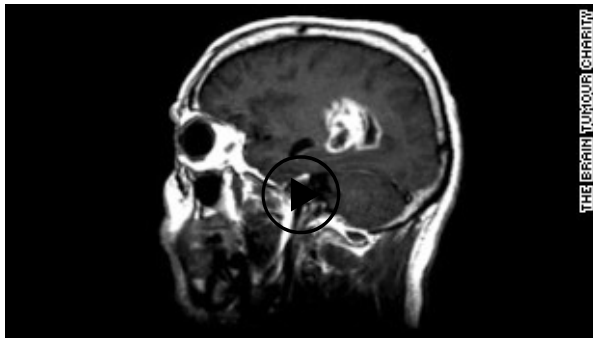
"Vaccines will target a very specific antigen, and it could be, for example, a mutation that's found in the tumors, and that would make that tumor cell recognized by the immune system, and you could vaccinate against it," Holland said, adding, "It's not completely clear how well those work."

Tumor treating fields

A novel treatment approach for recurrent glioblastoma also includes [tumor treating fields](#), a sci-fi-like therapy involving alternating electric currents, used in combination with chemotherapy.

The noninvasive treatment, [which transmits cancer-fighting electric fields through the patient's skin](#) around a region of the body containing a tumor, can be used to treat other types of cancer as well.

It works by sending [low-intensity electric fields](#) through the scalp, or other areas, that interfere with cell division in an effort to stop the cancer from spreading.



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For glioblastoma, [patients wear a device](#) that delivers the treatment on their shaved scalps. Adhesive bandages can hold such devices in place.

In 2015, researchers attending the [American Society of Clinical Oncology's annual meeting](#) presented data demonstrating that a tumor treating fields device could extend glioblastoma survival by more than two months when added to chemotherapy, though it was costly. At the meeting, treatment with a tumor treating fields device was estimated at \$20,000 per month.

A more recent study [published in the journal JAMA](#) found that adding tumor treating fields to the standard chemotherapy treatment of glioblastoma patients -- compared with chemotherapy alone -- could result in longer survival.

The study involved 695 cancer patients who had completed initial radiochemotherapy but still showed evidence of progressive disease. Patients were enrolled in the study from 2009 to 2014 and then followed up through 2016.

After a 40-month followup with the patients, the researchers found the addition of tumor treating fields, compared with chemotherapy alone, resulted in longer survival from the time of the study, 6.7 months versus 4 months, and longer overall survival, 20.9 months versus 16 months.

Yet the study had some limitations, including a possible placebo effect: Patients knew whether they were receiving the additional tumor treating fields treatment, due to continuously carrying the device.

"These findings are in contrast to the more than 23 randomized trials conducted over the last decade that have evaluated novel agents or intensified treatment strategies (eg, dose-dense temozolomide, cilengitide, nimotuzumab, bevacizumab, and rindopepimut) for treatment of patients with newly diagnosed glioblastoma and have failed to demonstrate improved survival. Innovative treatments for glioblastoma are needed," the researchers wrote in the study.

Many of these cutting-edge treatments, however, come with challenges.

Challenges and enthusiasm

No matter the treatment option, Holland said, crossing the [blood-brain barrier](#) remains to be a challenge for any brain cancer treatment approach.

The barrier includes a network of blood vessels and tissue that not only helps keep harmful substances from reaching the brain, it might block medicines from entering the brain.

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"It's certainly one of the biggest challenges," Holland said.

"Of all the drugs that are out there, really it's a small percentage of them that can get into the brain in any reasonable concentration that would be effective."

Nonetheless, Holdhoff, the oncologist at Johns Hopkins Medicine, said that the significant interest in glioblastoma treatment research shows no signs of slowing down.

"There is a great need for more research, and there is great enthusiasm across the board to improving on our standard of care," he said.