Primary central nervous system lymphoma (PCNSL) is a diffuse large B cell lymphoma that exclusively affects the brain, spinal cord, meninges or eyes.

**Epidemiology**
Annual incidence of PCNSL ranges from 0.3 to 0.6 cases per 100,000 persons. The incidence of this disorder has increased in the last few decades, with a 5-fold increase demonstrated in the USA between 1975 and 2017. Median age at diagnosis is 67 years, although disease can onset in childhood and adolescence. Incidence of PCNSL is substantially higher in people living with HIV compared with the general population, although incidence in people with HIV has reduced since the availability of combination antiretroviral therapy. The incidence of this disorder has increased in the last few decades, with a 5-fold increase demonstrated in the USA between 1975 and 2017. Median age at diagnosis is 67 years, although disease can onset in childhood and adolescence. Incidence of PCNSL is substantially higher in people living with HIV compared with the general population, although incidence in people with HIV has reduced since the availability of combination antiretroviral therapy.

- Chronic use of immunosuppressive therapies is a risk factor for PCNSL; disease biology and characteristics differ in PCNSL in immunosuppressed patients compared with in non-immunosuppressed patients.

**Mechanisms**
Several genetic alterations have been identified in PCNSL. Somatic mutations have been reported in IGHV4-34, BTG2, H1-4, MYC, PIM1 and KLHL14. Mutations in MYD88 and CARD11 have also been reported. MYD88, CARD11 and KLHL14 mutations can all activate NF-κB signalling. Moreover, MYD88 mutations can activate the B-cell receptor and toll-like receptors, block B-cell differentiation and apoptosis, lead to cell cycle dysregulation and can promote immune escape. Other genetic alterations in PCNSL include amplifications and deletions at various chromosomal regions. PCNSL cells interact with a range of other cell types, including T cells, endothelial cells, astrocytes and macrophages/microglia. These interactions drive neoplastic B cell proliferation and survival.

**Diagnosis**
The brain is the most commonly involved region of the CNS in PCNSL; however, patients can develop disease in multiple regions of the CNS.

- Brain involvement occurs in 92% of patients. The most common presentation is focal neurological defects (including sensory alterations, loss of reflexes and ataxia) but other manifestations can occur, for example, headache, behavioural changes and seizures.
- Ocular disease occurs in 15–25% of patients with PCNSL. Presentation typically comprises blurred vision, reduced visual acuity and eye floaters.

**Management**
Patients with PCNSL who are suitable for chemotherapy should receive methotrexate-based chemotherapy followed by consolidation with autologous stem cell transplantation (ASCT), whole brain radiotherapy (WBRT) or non-myeloablative chemotherapy. ASCT is the preferred consolidation approach; however, choice of consolidation therapy depends on several factors, including response and toxicity to methotrexate-based chemotherapy, patient age, and patient wishes. Patients who are not suitable for methotrexate-based chemotherapy can receive single drug chemotherapy, whole-brain radiotherapy or best supportive care. A standard of care for relapsed disease has not been established; accordingly, if available, patients with relapsed disease should be enrolled in appropriate clinical trials.

**Quality of life**
Quality of life of patients with PCNSL can be affected by several factors such as the invasive nature of the disease and treatment. Treatments of PCNSL (particularly WBRT) can affect neurocognitive function, which can affect quality of life. Neurological (including cognitive) deficits are common in patients with PCNSL and can improve after treatment of lymphoma; however, in some patients who received WBRT and combined chemoradiotherapy, cognitive outcomes can continue to worsen over time.

**Outlook**
New therapies or combinations of therapies are required for patients with PCNSL who have relapsed disease or who are not suitable for ASCT. Strategies to improve the penetration of drugs into the CNS are also required.