Rabies diagnosis consists of either postmortem or antemortem procedures, or both. The first attempt of postmortem diagnosis of rabies, especially in dogs, was made by physical examination of stomach contents for ingested sticks and stones as stigmata of deranged behaviour.

Other techniques for the rabies diagnosis of infected animals evolved from Pasteur’s 1881 report that the disease-producing organisms were located in the central nervous system (CNS) of infected animals and that sub-meningeal inoculation of infected CNS material into rabbits caused their death. Pathological changes indicative of neuronal involvement were made in 1892, when Babès described accumulation of embryonal cells around blood vessels and neurones in the brain tissue undergoing chromatolytic degeneration which he called "rabidic tubercules". These lesions now known as Babès' nodules are also found in other viral encephalitides; their presence is not specific for rabies diagnosis.

Antemortem diagnosis of rabies in humans can aid health care personnel in providing the best clinical treatment for the patient and protection for others who may have been exposed to the disease. Antemortem diagnosis of rabies is a difficult procedure. The psychological impact on a patients family and hospital staff should not be underestimated when rabies is considered in the differential diagnosis. To make patient management even more difficult, negative findings on all tests, while certainly reducing the possibility that rabies virus is the cause of the illness, cannot rule out rabies infection.

Methods of antemortem diagnosis are based on clinical manifestation and previous studies of rabies pathogenesis. These studies showed that, after multiplication in the CNS, rabies virus moves centrifugally along the nerves to peripheral organs. Peripheral nerves, cornea, salivary glands, skin and other tissues near the CNS may be infected early in the disease.

The detection of viral antigen in immuno-fluorescent antibody stained impressions of corneal epithelium and frozen sections of skin biopsy or the isolation of a virus from the saliva and tracheal aspirates are reliable indicators of rabies infection.

Demonstration of a significant serum antibody titre to rabies virus in the absence of passive or active immunisation or the appearance of antibody in the cerebrospinal fluid is a definitive method for diagnosis. The antibody response to infection, usually found on day 8 to 10 after onset of the first symptom, may be absent even 24 days after onset on rare occasions.

Recent techniques, such as the detection of messenger and/or genomic RNA by in situ-hybridisation and polymerase chain reaction are good candidates for early detection of rabies infection. These techniques are still in the experimental stage, and when available may need well equipped laboratories and trained personnel to be applicable for routine rabies diagnosis.
Laboratory results from rather few cases of human rabies evaluated by the Rabies Laboratory at the Centers for Disease Control showed that no single ante-mortem diagnostic test was positive in every case.