Von Hippel-Lindau (VHL) disease is an autosomal dominantly inherited tumour predisposition syndrome with an incidence of 1:36,000 newborns, the estimated prevalence in Europe is about 1-9/100,000. It is associated with an increased risk of developing various benign and malignant tumours, thus affecting multiple organs at different time points in the life of a patient. Disease severity and diversity as well as age at first symptoms vary considerably, and diagnostic delay due to failure of recognition is a relevant issue. The identification of a disease-causing VHL germline mutation subsequently allows family members at risk to undergo predictive genetic testing after genetic counselling. Clinical management of patients and families should optimally be offered as an interdisciplinary approach. Prophylactic screening programs are a cornerstone of care, and have markedly improved median overall survival of affected patients. The aim of this review is to give an overview of the heterogeneous manifestations of the VHL syndrome and to highlight the diagnostic and therapeutic challenges characteristic for this orphan disease. A comprehensive update of the underlying genetic and molecular principles is additionally provided. We also describe how the St. Gallen VHL multidisciplinary group is organised as an example of interdisciplinary cooperation in a tertiary hospital in Switzerland. © 2014 S. Karger AG, Freiburg.