Risks of gene therapy Depending on the type of gene therapy (ex vivo vs. in vivo, integrating vs. non-integrating vectors), several safety-related issues need to be taken into consideration and should be discussed with the potential patient.Studies in neonatal mice implicated that pathogenic AAV integration events might actively contribute to hepatocellular cancer development, although potential genotoxic events are highly dependent on factors including AAV integration preferences, vector design, vector dose and, in particular, recipient age at AAV injection [41,42,43].Also, the adaptive immune system can cause dangerous side effects via CD8+ cytotoxic T-cell responses, such as T-cell mediated hepatotoxicities associated with inflammatory reactions that have been observed in AAV9 vector therapy for spinal muscular atrophy.Uncontrolled immune responses are the main culprit with regard to most severe adverse events linked to AAV gene transfer, including fatal hepatotoxicity, dorsal root ganglia toxicity, and myocarditis.Uncontrolled innate immunes responses such as overactivation of the complement pathway with subsequent induction of thrombotic microangiopathy have been described following AAV gene therapy.Notably, the human body contains immune-privileged sites (e.g., the central nervous system) and immunosuppressive microenvironments (e.g., the liver) where AAV vectors are less likely to trigger strong responses than at other sites such as the circulation or the muscle [46].Integrating vectors such as retro- and lentiviruses that are primarily used for ex vivo gene therapy bear the risk of insertional mutagenesis due to their semi-random integration into the DNA.Since non-integrating vectors are applied in vivo, they carry the risk of evoking immune responses that are potentially life-threatening or might impair the long-term efficacy of treatment.However, clinical-scale production of lentiviral vectors is challenging