Large-scale metabolic models are widely used to design metabolic engineering strategies for diverse biotechnological applications. However, the existing computational approaches focus on alteration of reaction fluxes and neglect the manipulations of gene expression to implement these strategies. Here I will show that the association of genes with multiple reactions leads to infeasibility of engineering strategies at the flux level, since they require contradicting manipulations of gene expression. I will then present a constraint-based approach, GeneReg that facilitates the design of feasible metabolic engineering strategies at the gene level and is readily applicable to large-scale metabolic networks. I will also show that GeneReg can identify feasible strategies to overproduce ethanol in Escherichia coli and lactate in Saccharomyces cerevisiae, but overproduction of the TCA cycle intermediates is not feasible in five organisms used as cell factories. Altogether, GeneReg points at the need to couple gene regulation and metabolism to design rational metabolic engineering strategies.