The analysis of DNA sequence outcomes provides molecular insights into double-strand break (DSB) repair mechanisms. Using parallel in-pool profiling of Cas9-induced insertions and deletions (indels) within a genome-wide knockout library, we present a comprehensive catalog that assesses the influence of nearly every human gene on DSB repair outcomes. This REPAIRome resource uncovers uncharacterized mechanisms, pathways, and factors involved in DSB repair, including opposing roles for XLF and PAXX, a molecular explanation for Cas9-induced multinucleotide insertions, HLTF functions in Cas9-induced DSB repair, the involvement of the SAGA complex in microhomology-mediated end joining, and an indel mutational signature linked to VHL loss, renal carcinoma, and hypoxia. These results exemplify the potential of REPAIRome to drive future discoveries in DSB repair, CRISPR-Cas gene editing and the etiology of cancer mutational signatures.