Tobacco use disorder (TUD) is the most prevalent substance use disorder worldwide. Genetic factors influence smoking behaviors and although strides have been made using genome-wide association studies (GWAS) to identify risk variants, only a small amount of the variance has been accounted for. We leveraged five biobanks to perform a multi-ancestral meta-analysis of TUD (derived via electronic health records, EHR) in 740,937 individuals. We identified 72 independent risk loci; integration with functional genomic tools uncovered 330 potential risk genes, primarily expressed in the brain. TUD was genetically correlated with smoking traits and comorbid psychiatric traits from traditionally ascertained cohorts, externalizing behaviors in children, and hundreds of medical outcomes, including HIV infection, heart disease, and pain. This work furthers our biological understanding of TUD and establishes the use of EHR as sources of phenotypic information for studying the genetics of TUD.