

## Genetic Approaches to Repurposing Existing Drugs to Increase Drug Discovery

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## DESCRIPTION

Drug repurposing process of identifying new therapeutic uses for existing drugs, has emerged as an attractive approach for drug discovery in recent years. Compared to traditional drug development, repurposing offers several advantages, including reduced development time and cost, as well as a higher likelihood of success in clinical trials. While conventional drug repurposing has primarily relied on empirical observation and retrospective analysis of clinical data, next-generation drug repurposing is leveraging the power of human genetics to identify new targets for drug intervention.

Genome-Wide Association Studies (GWAS) have been at the forefront of this approach, as they have enabled the identification of genetic variants associated with disease susceptibility, progression, and response to treatment. By analyzing large cohorts of patients with a particular disease, GWAS can pinpoint the genetic variants that are more commonly found in affected individuals compared to healthy controls. These variants may be located in genes that are known to be involved in the disease, but they can also highlight previously unknown disease pathways and therapeutic targets.

Once genetic variants associated with a particular disease have been identified, the next step is to determine whether these variants are functionally relevant and whether they can be targeted with existing drugs. This involves a combination of experimental and computational approaches, such as *CRISPR/ Cas9* genome editing, gene expression profiling, protein-protein interaction assays, and network analysis. By integrating genetic and molecular data, researchers can identify novel drug-disease associations and predict the efficacy of repurposed drugs in clinical trials. One of the most promising areas of drug repurposing using human genetics is in the field of oncology. GWAS have identified hundreds of genetic variants associated with an increased risk of developing cancer, as well as with the response to chemotherapy and targeted therapies. For example, recent studies have shown that genetic variants in the *BRCA1* and

BRCA2 genes, which are known to be involved in DNA repair, can be targeted with PARP inhibitors in patients with breast and ovarian cancer. Similarly, genetic variants in the *KRAS* gene, which are commonly found in patients with pancreatic and lung cancer, have been shown to be sensitive to MEK inhibitors.

Beyond oncology, drug repurposing using human genetics is also showing promise in other disease areas, such as autoimmune and cardiovascular diseases. In rheumatoid arthritis, for example, GWAS have identified genetic variants in the *TNFAIP3* gene, which encodes a protein involved in the regulation of inflammation, as well as in the Human Leukocyte Antigen (HLA) region, which plays a key role in the recognition of self and nonself-antigens by the immune system. These variants are being investigated as potential targets for repurposing drugs used in other inflammatory conditions, such as psoriasis and Crohn's disease.

In cardiovascular diseases, GWAS have identified genetic variants associated with lipid metabolism, blood pressure regulation, and thrombosis. These variants are being used to identify new targets for drugs that can reduce the risk of heart attacks, strokes, and other cardiovascular events. For example, genetic variants in the *PCSK9* gene, which regulates the levels of Low-Density Lipoprotein (LDL) cholesterol in the blood, have led to the development of *PCSK9* inhibitors, a new class of drugs that have shown promising results in reducing the risk of cardiovascular events in high-risk patients. The advantages of drug repurposing using human genetics extend beyond the identification of new targets for drug intervention.

They also offer the potential for personalized medicine, as genetic information can be used to tailor treatments to individual patients based on their genetic makeup. This approach is particularly relevant for diseases that have a strong genetic component, such as rare genetic disorders and cancers with specific driver mutations. By matching patients to the most effective drug based on their genetic profile, healthcare providers can improve patient outcomes and reduce the risk of adverse events.

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