HOW NASHVILLE BIOSCIENCES CAN FACILITATE EARLY STAGE TARGET PRIORITIZATION/TARGET DISEASE DEEP DIVES

New Approach to Reduce Clinical Development Cost and Time

Phenome Wide Association Studies (PheWAS) analyze the associations between single genetic variants and EMR-derived disease phenotypes. It is a quantitative technique that addresses which of many phenotypes are associated with a given gene.

This approach differs from that of genome wide association studies (GWAS), which asks which of many genes are associated with a given phenotype.

PheWAS is advantageous because it can exploit information from genomic databases linked to longitudinal EMRs. PheWAS enables identification of novel phenotypes associated with genes of interest and therapeutic indication expansion as well as provides genetic evidence for therapeutic efficacy. Therefore, it is a powerful approach to drug discovery and can advance precision medicine.

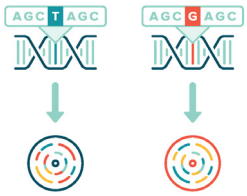
OVERVIEW

A top twenty pharmaceutical company was looking to prioritize 17 early stage targets for further clinical development. The company's portfolio included some therapeutics that were already marketed for various indications while others were in early-stage clinical development. For market therapeutics, the company was interested in indication expansion. We collaborated with the company to perform a pheWAS™ analysis in the BioVU population to identify disease phenotypes that represented possible indications for Celgene's therapeutics. We scored and prioritized associations from the 1,800 EMR-derived phenotypes based on statistical strength, literature support, and overall market attractiveness. Furthermore, we considered the company's interest in Oncology and Immunology and prioritized phenotypes that aligned with these therapeutic interests. By evaluating gene target – phenotype associations across multiple scientific and commercial criteria, we enabled portfolio prioritization. We ultimately identified 4 gene targets for in-depth scientific and clinical analysis. Based on this analysis, the company began pre-clinical testing for two of the targets as part of an indication expansion program.

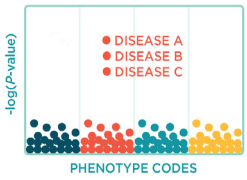
APPROACH

We surveyed the variants in each target that were available for pheWAS™ analysis and evaluated characteristics including the mutation type, minor allele frequency in the BioVU population, and known or predicted functional based on in silico prediction algorithms or published literature. We then performed a pheWAS™ computational analysis to test the associations between each variant in the targets of interest and a set of approximately 1,800 EMR-derived disease phenotypes. Phenotypes that demonstrated statistically significantly associations with variants in each target were evaluated across several scientific and commercial dimensions using a proprietary scoring system. Next, we worked with the company using an iterative and collaborative approach to select 4 targets and 8 priority phenotypes for deep-dive analysis. We first generated a cohort of patients with each disease and variant of interest and extracted both structured and unstructured data (e.g. ICD-9 and ICD-10 diagnosis codes, procedures, labs, and medications) from the de-identified EMRs for these patients. Using this information, we could validate and refine the diagnosis and characterize them according to specific clinical features of the disease. Next, we reviewed published literature to develop a mechanistic hypothesis for the role of the target in each priority phenotype. Additionally, the client provided some preliminary information regarding their existing knowledge of each target and results from pre-clinical or clinical studies. We incorporated this information and other feedback from the client into both the clinical and scientific deep-dive activities. Finally, we designed and recommended a set of feasible experiments to test our working hypothesis that could help the client substantiate the working hypothesis.

Assemble a large group of people with various small mutations and a diverse set of diseases



Identify mutations in the underlying gene for the drug target of interest



Use statistics to identify patterns between the selected mutations and associated diseases

OUTCOME

Our pheWAS™ analysis enabled the company to prioritize phenotypes for indication expansion using human genetic evidence. Furthermore, this approach allowed us to identify indications for novel targets in pre-clinical development. The company is currently pursuing several of these targets and indications.

ABOUT NASHVILLE BIOSCIENCES

Nashville Biosciences, a wholly owned subsidiary of Vanderbilt University Medical Center (VUMC), was created to harness the Medical Center's extensive genomic and bioinformatics resources for drug and diagnostics discovery and development.

Leveraging Vanderbilt University Innovation™, Nashville Biosciences serves as a commercial interface between outside companies and the formidable research capabilities represented by BioVU®, one of the world's most comprehensive genetic databases linked to de-identified medical records with years of longitudinal clinical data.

This unique asset is one of the largest and highest quality of its kind, providing an unprecedented opportunity to guide R&D activity in biotech, pharma, diagnostics, medical devices and other life sciences applications.

Nashville Biosciences

To learn more about Nashville Biosciences or to request a private demo of the organization's capabilities, please visit http://www.nashville.bio.