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62/795,705 23 January 2019 (23.01.2019) US(71) Applicant: **THE REGENTS OF THE UNIVERSITY OF MICHIGAN** [US/US]; Office Of Technology Transfer, 1600 Huron Parkway, 2nd Floor, Ann Arbor, MI 48109-2590 (US).(72) Inventors: **ATHEY, Brian, D.**; Palmer Commons, 100 Washtenaw Ave #2017, Ann Arbor, MI 48109 (US). **HIGGINS, Gerald, A.**; Palmer Commons, 100 Washtenaw Ave #2017, Ann Arbor, MI 48109 (US). **ADE, Alex**; Palmer Commons, 100 Washtenaw Ave #2017, Ann Arbor, MI 48109 (US). **KALININ, Alexandr**; Palmer Commons, 100 Washtenaw Ave #2017, Ann Arbor, MI 48109 (US). **REA-****MAROON, Narathip**; Palmer Commons, 100 Washtenaw Ave #2017, Ann Arbor, MI 48109 (US). **BURNS, James S.**; Palmer Commons, 100 Washtenaw Ave #2017, Ann Arbor, Michigan 48109 (US).(74) Agent: **RUETH, Randall, G.**; Marshall, Gerstein & Borum LLP, 233 S. Wacker Drive, 6300 Willis Tower, Chicago, IL 60606-6357 (US).

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(54) Title: METHODS AND SYSTEM FOR THE RECONSTRUCTION OF DRUG RESPONSE AND DISEASE NETWORKS AND USES THEREOF

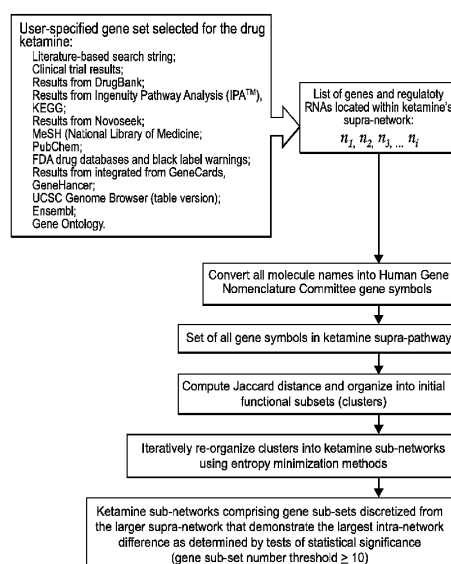


FIG. 12

(57) Abstract: Methods comprising an integrated, multiscale artificial intelligence-based system that reconstructs drug- specific pharmacogenomic networks and their constituent functional sub-networks are described. The system uses features of the functional topology of the three-dimensional architecture of drug-modulated spatial contacts in chromatin space. Discovery of a drug pharmacogenomic network is made through the selection of candidate SNPs by imputation, determination of the predicted causality of the SNPs using machine learning and deep learning, use of the causal SNPs to probe the spatial genome as determined by chromosome conformation capture analysis, combining targeted genes controlled by the same cell and tissue- specific enhancers, and reconstruction of the pharmacogenomic network using diverse data sources and metrics based on the results of genome-wide association studies. Knowledge-based segmentation methods are used to deconstruct the pharmacogenomic network into its constituent efficacy and adverse event sub-networks for applications in clinical decision support, drug repurposing, and *in silico* drug discovery.

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