A New Framework for the Use of Variant Interpretation Tools in Clinical Practice

Predrag Radivojac, Ph.D.
Professor of Computer Science
Associate Dean of Research
Northeastern University

WHEN & WHERE

November 14, 2024
11:00 a.m. – 12:00 p.m.
Peter Kiewit Institute 158 (UNO)

Current ACMG/AMP guidelines for the use of sequence variants for genetic diagnosis and treatment permit the use of in silico predictors as supporting evidence. These criteria, however, lack quantitative support and leave clinicians and scientists without standards for applying these criteria, leading to large interpretation variability. To address this, we introduced a novel criterion that can be used to calibrate any computational model or any other continuous-scale evidence on any variant type. We used it to estimate score intervals corresponding to the strengths of evidence for pathogenicity and benignity for missense variant interpretation tools. We found that most tools achieved the supporting evidence level for both pathogenic and benign classification using newly established data-driven thresholds. Importantly, some in silico methods can also provide Moderate and Strong evidence levels. Based on these findings, we provided recommendations for quantitative revisions of the PP3 and BP4 criteria within ACMG/AMP guidelines and the future assessment of in silico methods for clinical interpretation. At the end, we will discuss our most recent methods and findings for a formal consideration of interdependent evidence types for rare disease genetic diagnosis and population screening.

Light refreshments will be provided.

For more information, contact: dghersi@unomaha.edu or afruhling@unomaha.edu