

Department of Applied Mathematics and Statistics  
The Johns Hopkins University

SEMINAR

Rachel Karchin  
Dept. of Biomedical Engineering  
Institute for Computational Medicine  
The Johns Hopkins University

September 27, 2007  
304 Whitehead Hall  
Refreshments: 3:30 p.m.  
Seminar: 4:00 p.m.

**CLASSIFYING VARIANTS OF UNDETERMINED SIGNIFICANCE  
IN CANCER SUSCEPTIBILITY PROTEINS**

ABSTRACT

Some inherited DNA sequence variations in cancer predisposition genes create difficulties when clinically interpreting genetic tests. Although computational biology methods for predicting the impact of variants have been developed, they have not been readily applied by clinicians who counsel patients about cancer risk because (i) their outputs have not been validated with respect to molecular epidemiologic results and are difficult to interpret clinically and (ii) claims to general applicability on any gene/protein have been met with skepticism. I will present a method aimed at bridging this gap by integrating information about protein sequence and structure into a likelihood ratio that is easily interpretable by clinicians. Applying the method to Breast Cancer Type 2 Susceptibility Protein, I have computed likelihood ratios for 229 unclassified variants from high-risk breast/ovarian cancer families, yielding high positive and negative predictive values (PPV = 100%, NPV = 87%, N=20) when validated with available molecular epidemiological evidence.