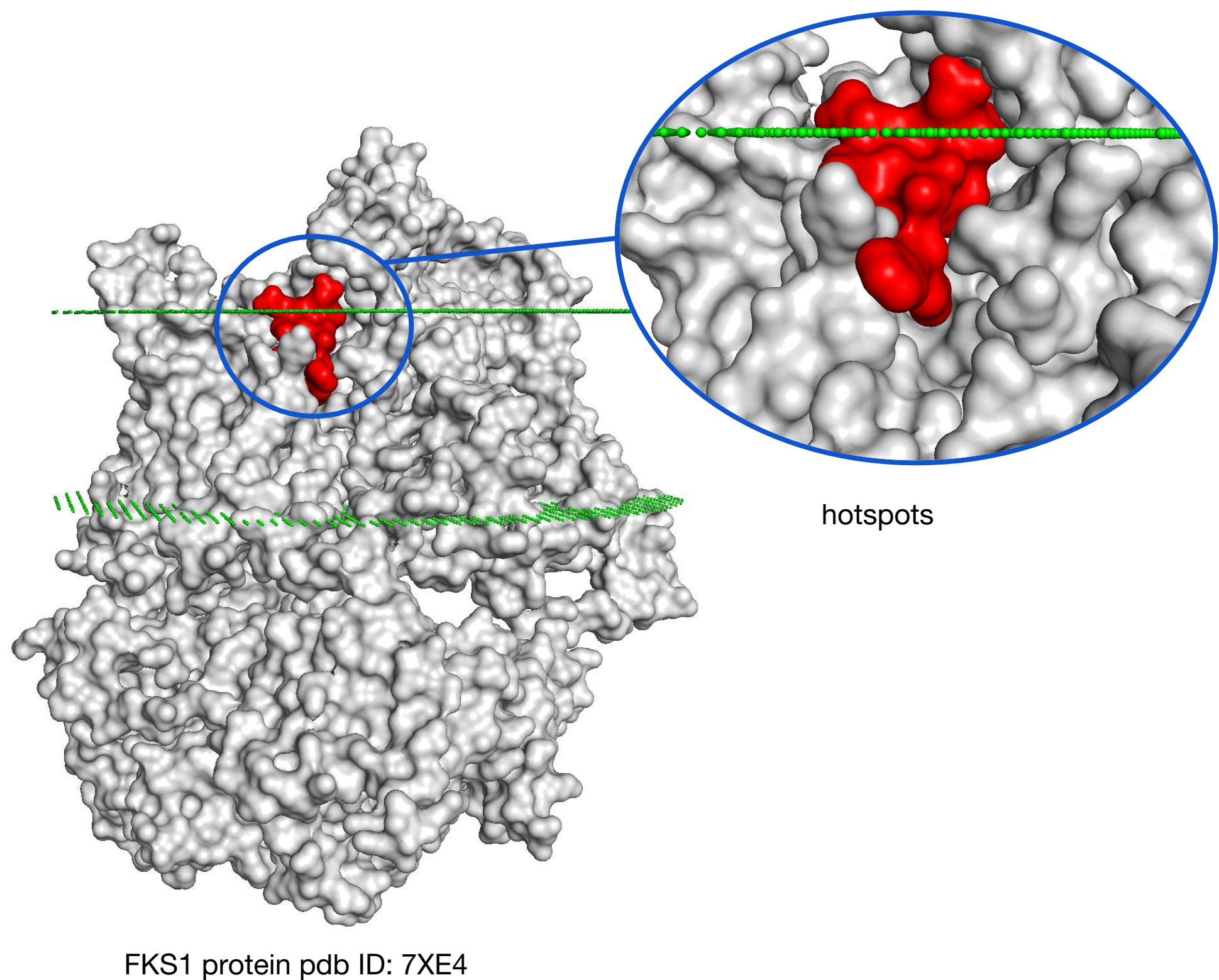
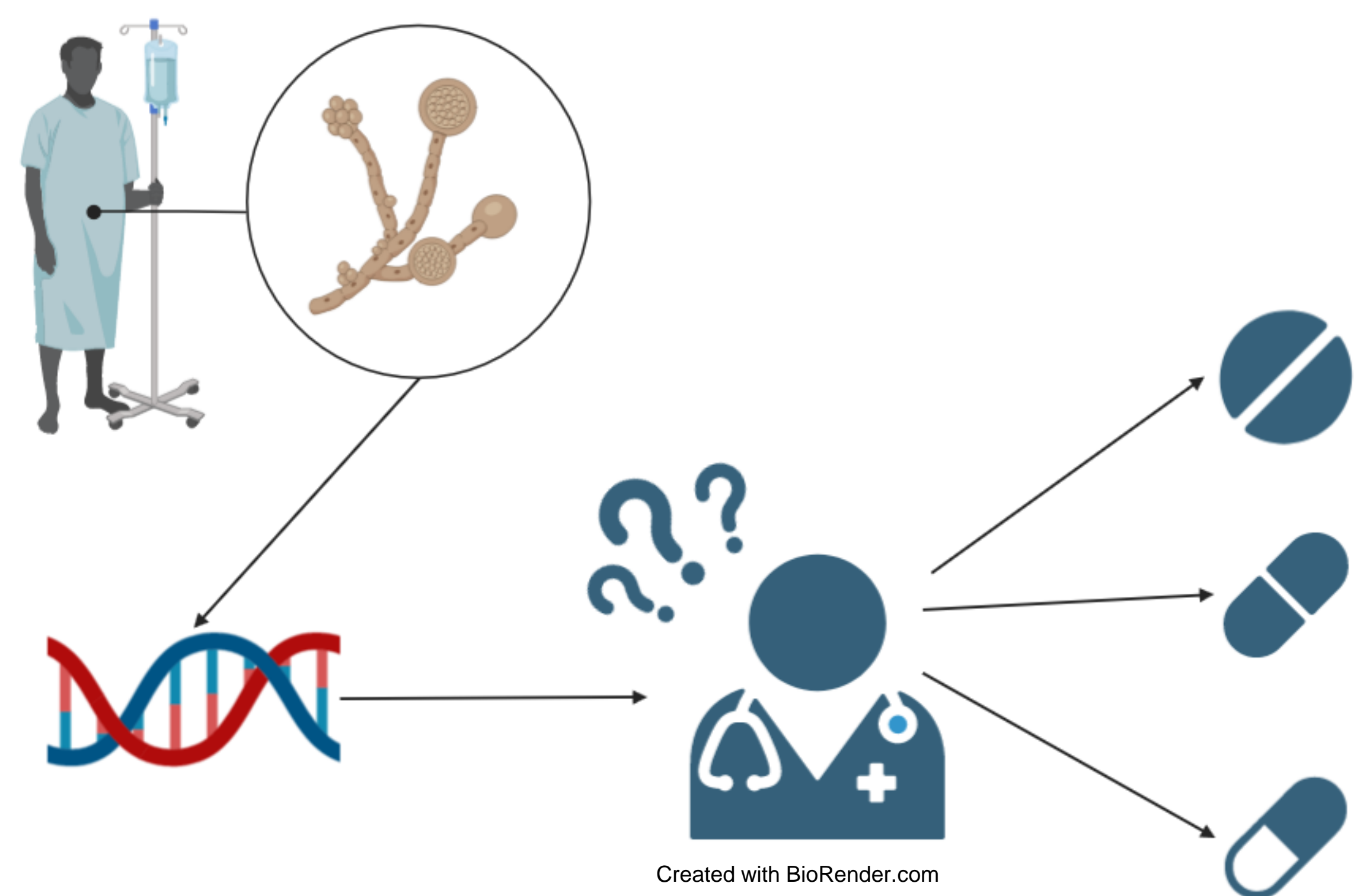


# Can We Predict Antifungal Resistance ?

Mathieu Giguère, Romain Durand, Alexandre K Dubé, Christian R Landry

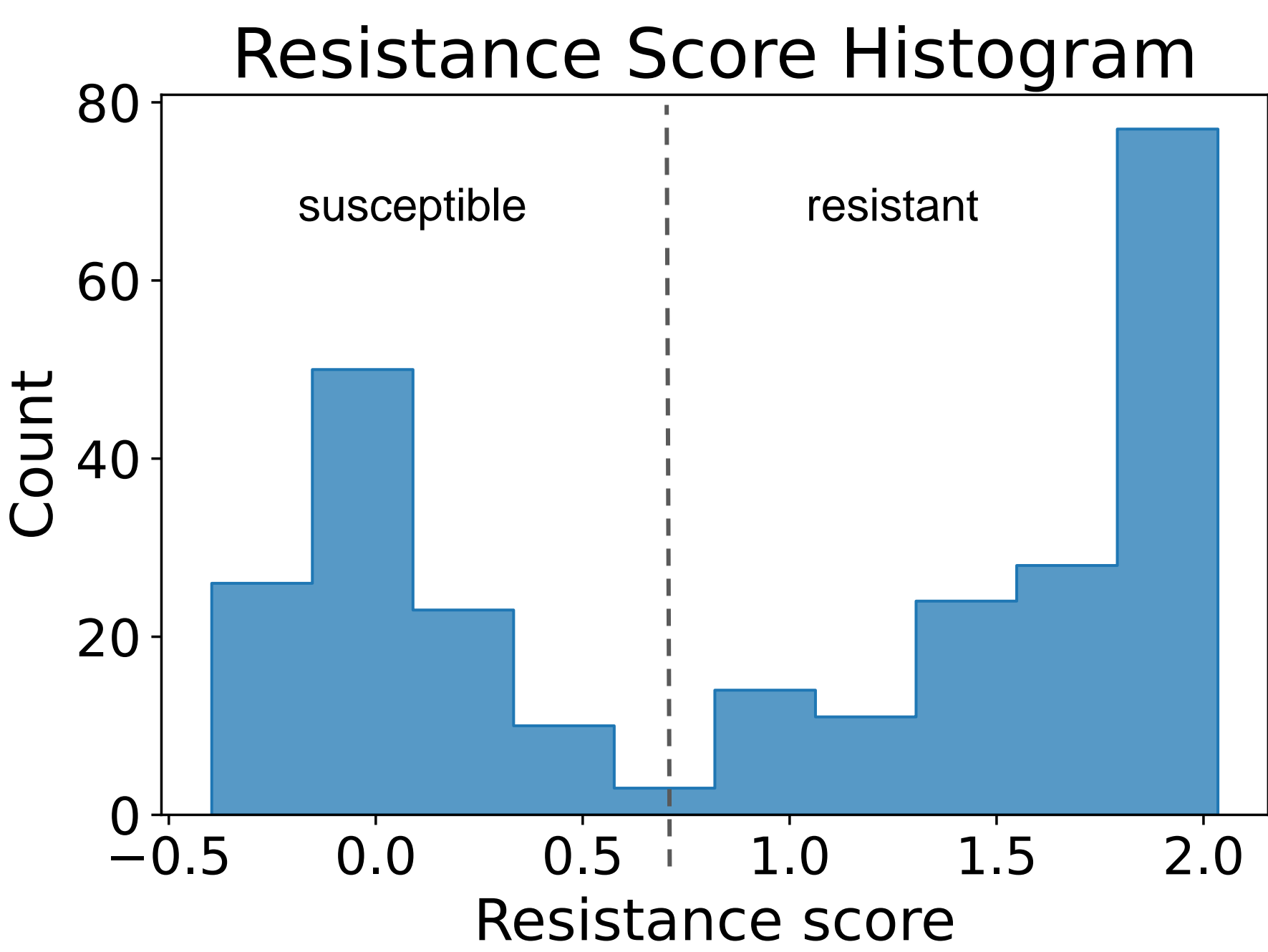
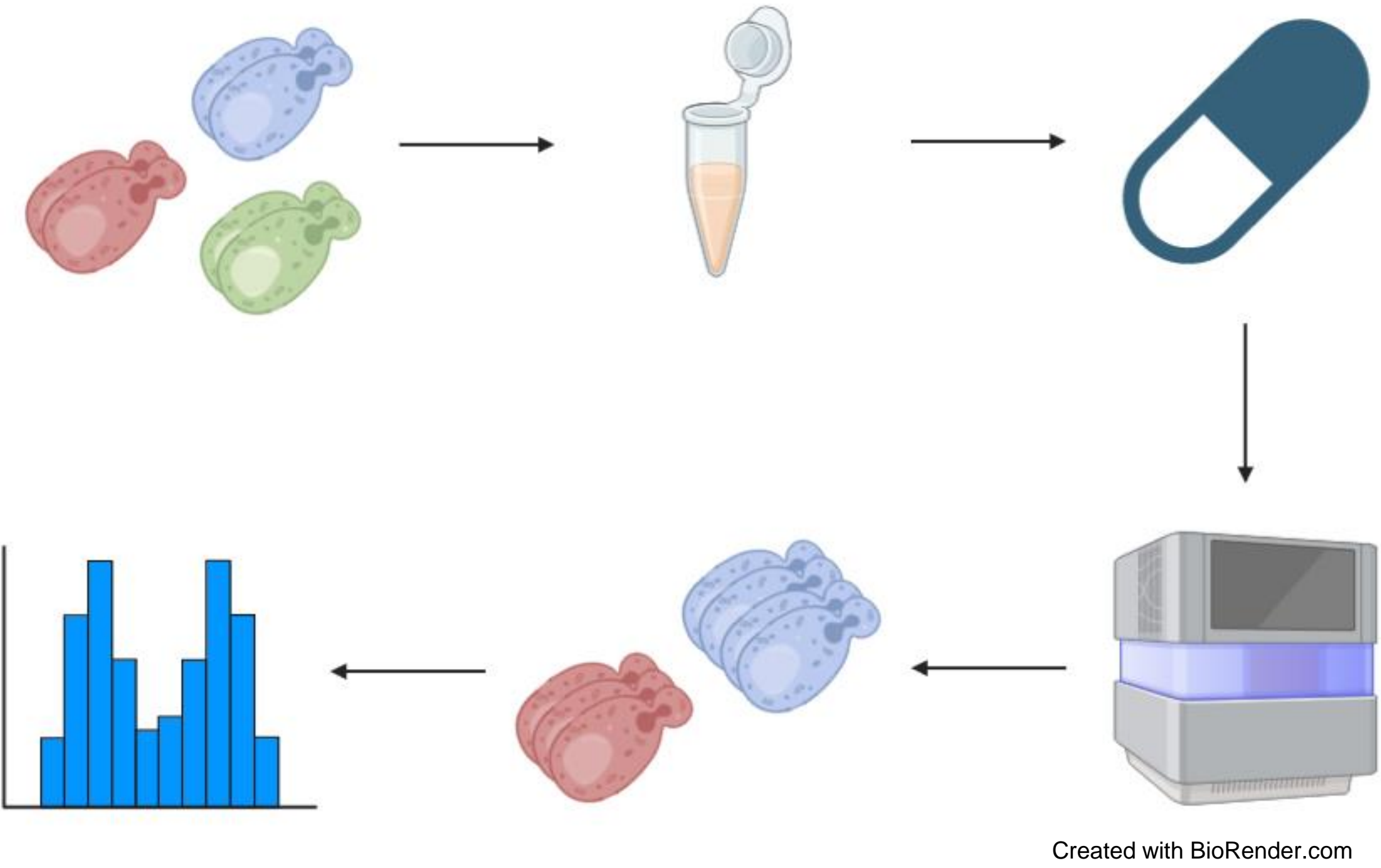
## Introduction

- Patients suffering from a generalized fungal infection face a high mortality rate.
- Caspofungin is an antifungal drug that targets and inhibits FKS proteins. These proteins synthesize an essential component of the fungal cell wall.
- Mutations in the *FKS* gene sequences that confer resistance are often located in specific regions hence referred to as hotspots.<sup>1</sup>
- We want to develop a tool that uses the amino acid sequence of a fungal pathogen's FKS hotspot to predict its resistance to antifungal drugs.

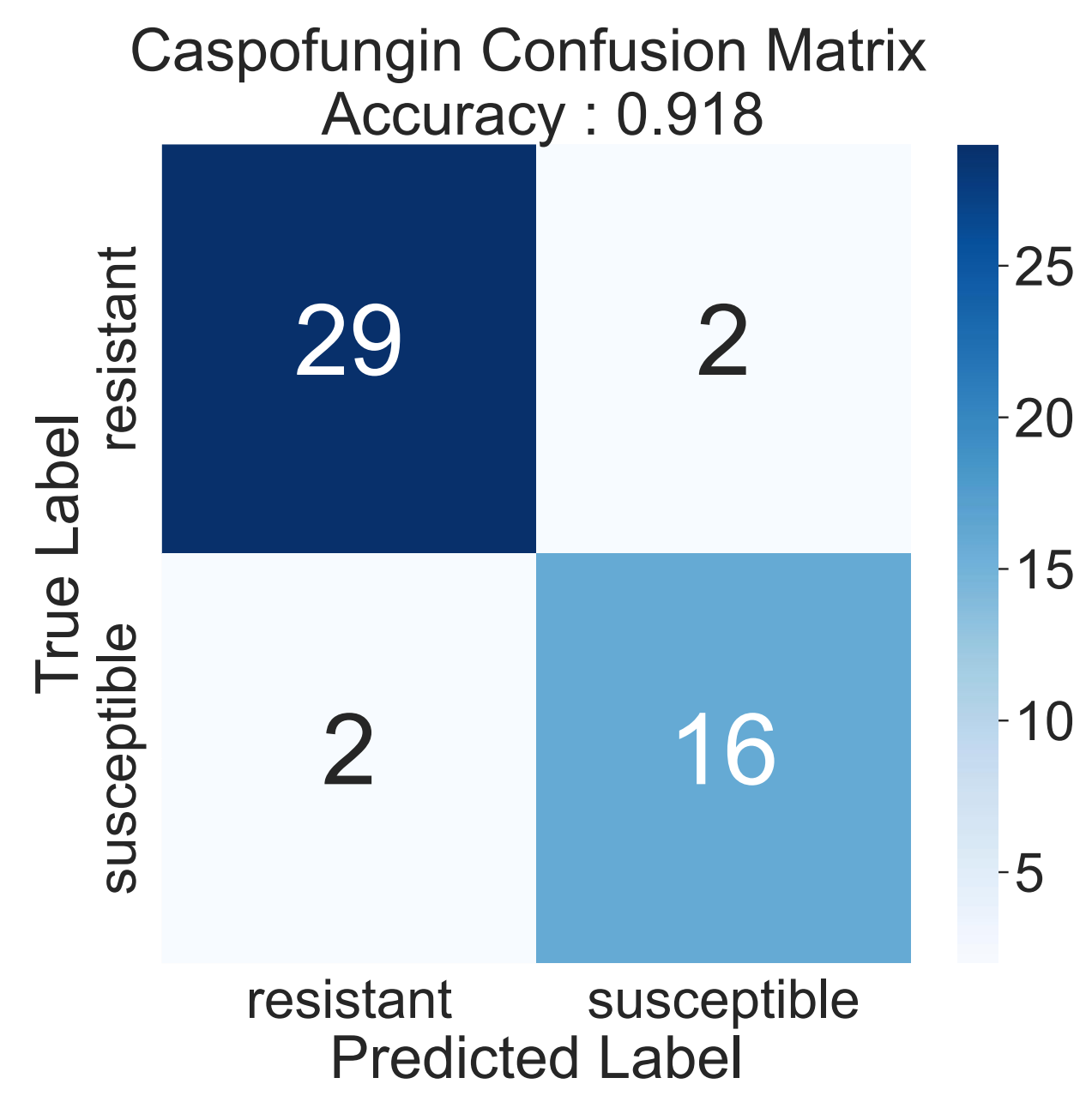


## Analysing Data

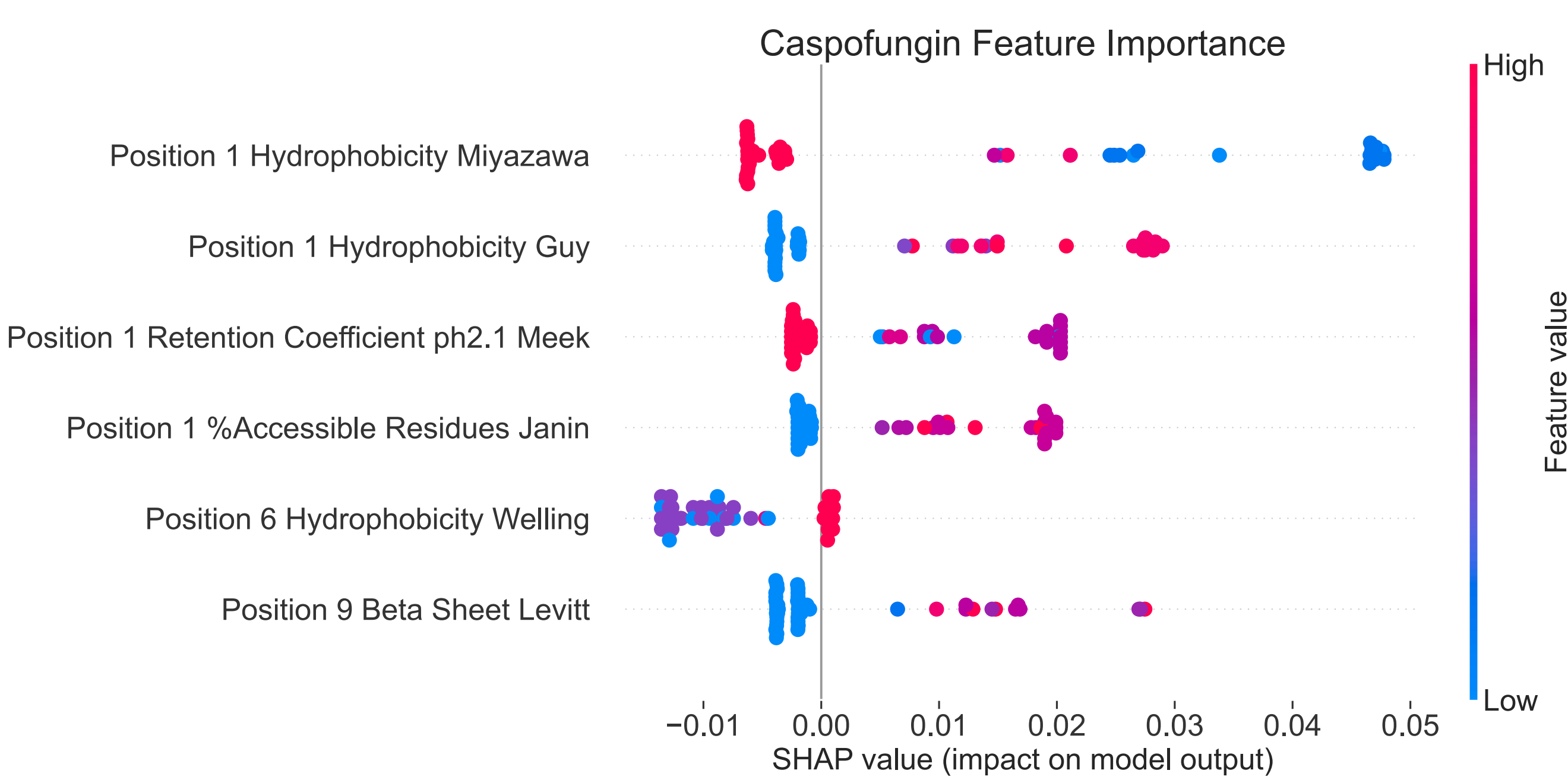
- Insertion of single-mutation hotspot sequences and multiple-mutations hotspot sequences in *S. cerevisiae*.
- Variants conferring resistance to caspofungin are selected.
- A resistance score is calculated for each variant by comparing sequencing read frequencies before and after applying selective pressure.
- Resistance score distributions are bimodal, meaning most mutations either confer resistance or not.



## Machine Learning



A random forest classifier was trained on the resistance scores and amino acid properties of single-mutation hotspot sequences. When shown multiple-mutations hotspot sequences, it can classify them in the correct category with 92% accuracy.



SHAP values highlight which amino acid properties at specific positions are determinant to confer caspofungin resistance, for example having a residue at position 1 with a low value for the feature “hydrophobicity Miyazawa” is associated with resistance.

# Yes

Our random forest classifier accurately classifies never-before-seen hotspot sequences for the target of the antifungal caspofungin as conferring resistance (or not). Combinations of specific amino acid properties and the position of the mutation contribute the most to the model.

<sup>1</sup>Perlin DS. Mechanisms of echinocandin antifungal drug resistance. Ann N Y Acad Sci. 2015 Sep;1354(1):1-11. doi: 10.1111/nyas.12831. Epub 2015 Jul 17. PMID: 26190298; PMCID: PMC4626328.