Guiding HIV-1 Antibody Regimen Down-Selection and Prevention Efficacy Trial Design Using Machine Learning

Brian D. Williamson[1,*], David C. Benkeser[2], Craig A. Magaret[1],
Lindsay N. Carpp[1], Bhavesh Borate[1], and Peter B. Gilbert[1,3]

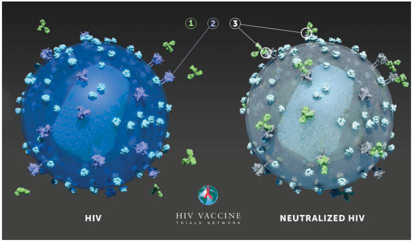
[1]Biostatistics, Bioinformatics, and Epidemiology Program, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center
[2]Department of Biostatistics, Rollins School of Public Health, Emory University
[3]Department of Biostatistics, School of Public Health, University of Washington
[*]bwillia2@fredhutch.org

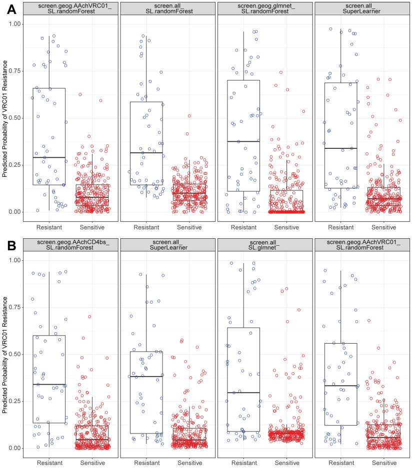
Dynamics & Evolution of HIV and Other Human Viruses
13 May 2020

Motivation

AMP
ANTIBODY · MEDIATED · PREVENTION
STUDY

NIH NIAID-sponsored HVTN + HPTN phase 2b HIV prevention efficacy trial; statistical design described in Gilbert et al. (2017) *Stat Commun Infect Dis*





Magaret, Benkeser, Williamson et al. (2019) *PLoS Comput Biol*

Snapshot: HVTN + HPTN Planned bnAb Clinical Testing*

bnAb regimen	Clinical Trial(s)	Number of Env pseudoviruses with IC_{50} data in CATNAP
VRC01	HVTN 703,704	828
VRC07-523-LS	HVTN 127,128	402
PGT121	HVTN	656
VRC07-523-LS + PGDM1400	HVTN 130	402
VRC07-523-LS + PGT121	HVTN 130	402
VRC07-523-LS + 10-1074	HVTN 130	402
VRC07-523-LS + PGT121 + PGDM1400	HVTN 130	402
VRC01/PGDM1400-10E8v4 (trispecific)	HVTN 129	205

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*as of January 2020

Critical Issues in bnAb HIV Prevention Research

For a given bnAb regimen (e.g., 1-, 2-, 3-bnAb, multispecific):

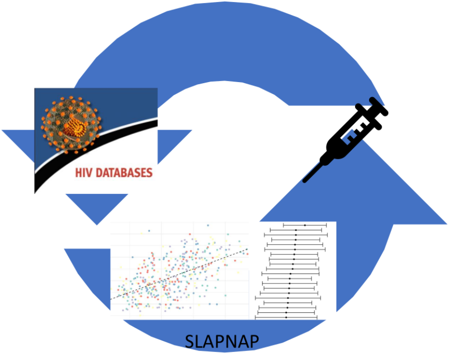
- what is the regimen's neutralization breadth*?
- what is the regimen's neutralization potency*?

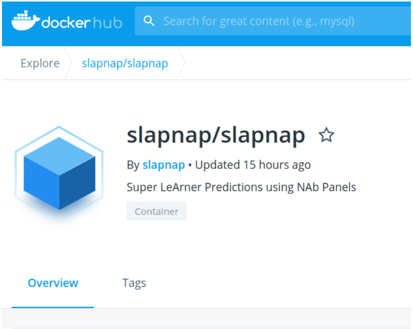
*against HIV-1 viruses circulating in the relevant population

We can address these questions with available data and machine learning.

SLAPNAP:

Super LeArner Predictions using NAb Panels



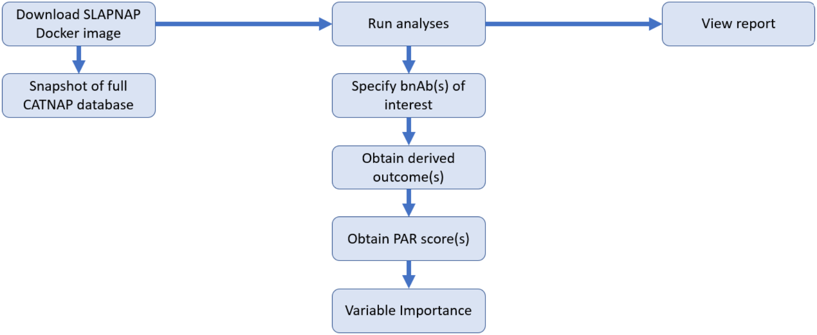


slapnap/slapnap ☆

By slapnap • Updated 15 hours ago

Super LeArner Predictions using NAb Panels

SLAPNAP Pipeline



Download SLAPNAP Docker image

Snapshot of full CATNAP database

Run analyses

Specify bnAb(s) of interest

Obtain derived outcome(s)

Obtain PAR score(s)

Variable Importance

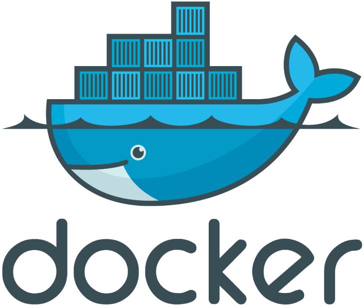
View report

Key Components of SLAPNAP: Containerization

Download SLAPNAP Docker image

Run analyses

View report



Lightweight | Fully reproducible

Key Components of SLAPNAP: CATNAP database

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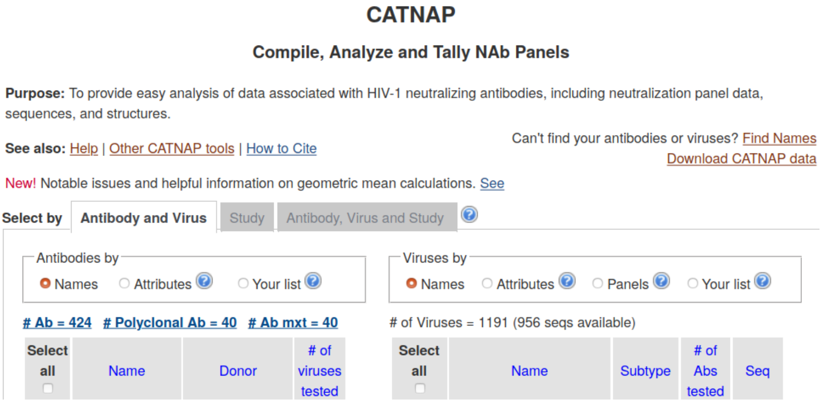
CATNAP: publicly-available database [Yoon et al. (2015) *Nuclic Acids Res*]



CATNAP

Compile, Analyze and Tally NAb Panels

Purpose: To provide easy analysis of data associated with HIV-1 neutralizing antibodies, including neutralization panel data, sequences, and structures.

See also: Help | Other CATNAP tools | How to Cite

Can't find your antibodies or viruses? Find Names
Download CATNAP data

New! Notable issues and helpful information on geometric mean calculations. See

Select by **Antibody and Virus** | Study | Antibody, Virus and Study

Antibodies by
● Names ○ Attributes ○ Your list

Viruses by
● Names ○ Attributes ○ Panels ○ Your list

\# Ab = 424 # Polyclonal Ab = 40 # Ab mxt = 40

Select all ☐	Name	Donor	# of viruses tested

\# of Viruses = 1191 (956 seqs available)

Select all ☐	Name	Subtype	# of Abs tested	Seq

Key Components of SLAPNAP: CATNAP database

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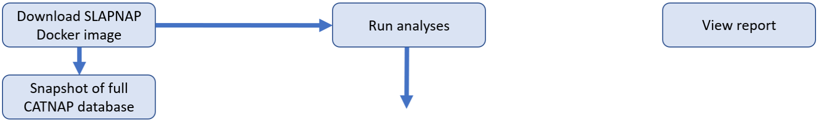
CATNAP: publicly-available database [Yoon et al. (2015) *Nuclic Acids Res*]

- IC_{50} and IC_{80} neutralization values
- Derived outcomes:
  - for J nAbs, predicted $\text{IC}_k = \left(\sum_{j=1}^{J} \text{IC}_{k,j}^{-1}\right)^{-1}$ [Wagh et al. (2016) *PLoS Pathogens*]
  - $\text{IIP} = \frac{10^m}{\text{predicted IC}_{50}^m + 10^m}$; $m = \log_{10}(4)/\{\log_{10}(\text{predicted IC}_{80}) - \log_{10}(\text{predicted IC}_{50})\}$
  - Estimated sensitivity $=$ predicted $\text{IC}_{50} < 1$
  - Multiple sensitivity $= \sum_{j=1}^{J}(\text{IC}_{50,j} > 1) \leq 2$
- Input feature groups:
  - Amino acid sequence sites: gp120 CD4 binding sites, gp120 V2, gp120 V3, gp41 MPER
  - Other groups: Region-specific counts of PNG sites, viral geometry, cysteine counts

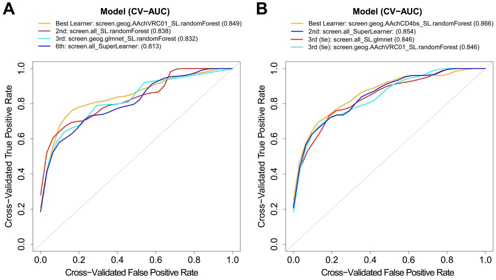
Key Components of SLAPNAP: PAR Scores



Proteomic Antibody Resistance (PAR) score

[Magaret, Benkeser, Williamson et al. (2019) *PLoS Comput Biol*]

- Predicted probability of resistance of Env pseudovirus to bnAb
- Uses Super Learning [van der Laan et al. (2007) *Stat Appl Gen Mol Bio*]



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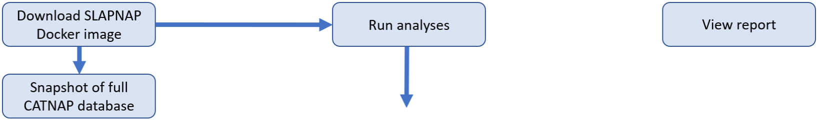

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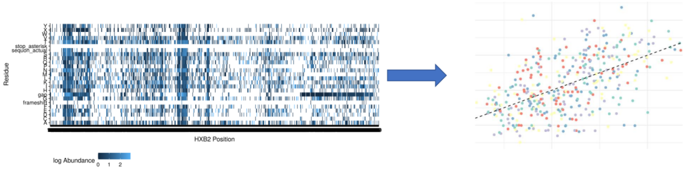
Super Learning:



Goal: learn best possible outcome predictor

Ensembling + cross-validation

Key Components of SLAPNAP: Variable Importance

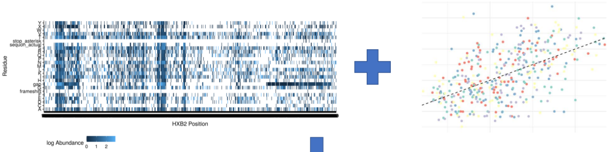
Download SLAPNAP Docker image

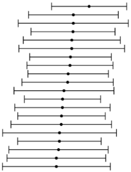
Snapshot of full CATNAP database

Run analyses

View report

Biological variable importance [Williamson et al. (2020) *arXiv*]



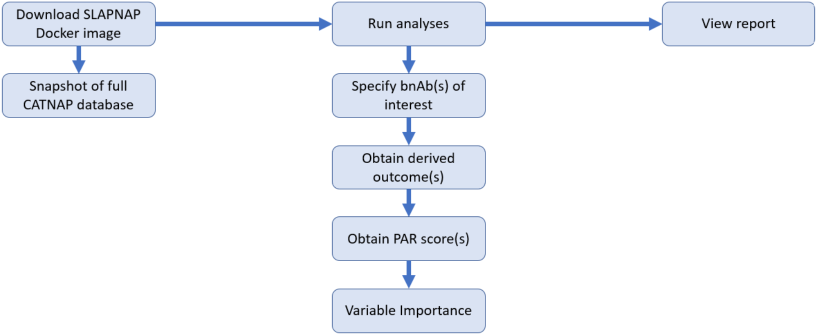


Goal 1: biological importance

- Population R^2
- Population AUC

Goal 2: learner importance

Key Components of SLAPNAP: Report



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Run analyses

Specify bnAb(s) of interest

Obtain derived outcome(s)

Obtain PAR score(s)

Variable Importance

View report

Example: Predicting HIV-1 Neutralization by VRC01

Pull the latest image: `docker pull slapnap/slapnap`

Run the container:

```
sudo docker run \
  -v <path to output directory>/output:/home/output/ \
  -e nab="VRC01" \
  -e outcomes="ic50;ic80;iip;sens1;sens2" \
  -e learners="rf;lasso;xgboost" \
  -e cvtune="TRUE" \
  -e cvperf="TRUE" \
  -e importance_grp="marg" \
  -e importance_ind="marg;pred" \
  -e return="report;data" \
  slapnap
```

mount results directory

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specify bnAb(s)

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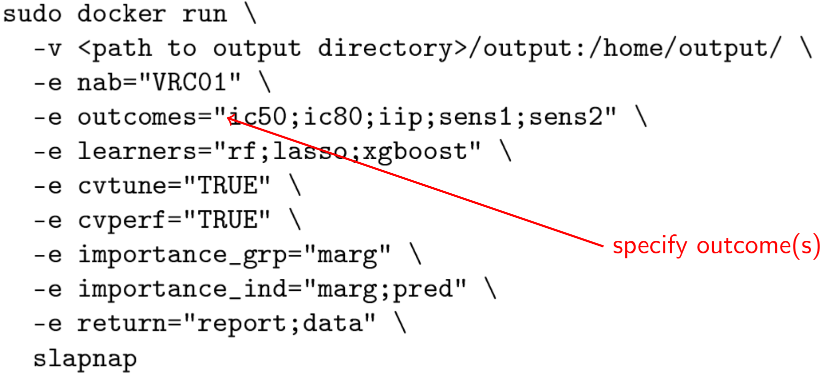

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specify outcome(s)

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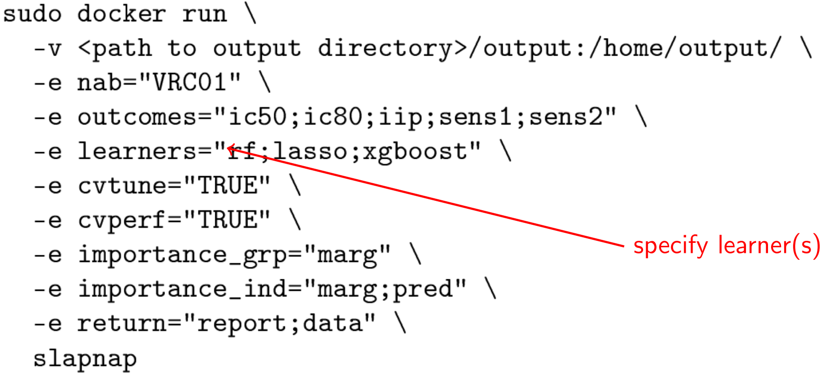

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```

specify learner(s)

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use cross-validation (recommended)

Example: Predicting HIV-1 Neutralization by VRC01

Pull the latest image: `docker pull slapnap/slapnap`

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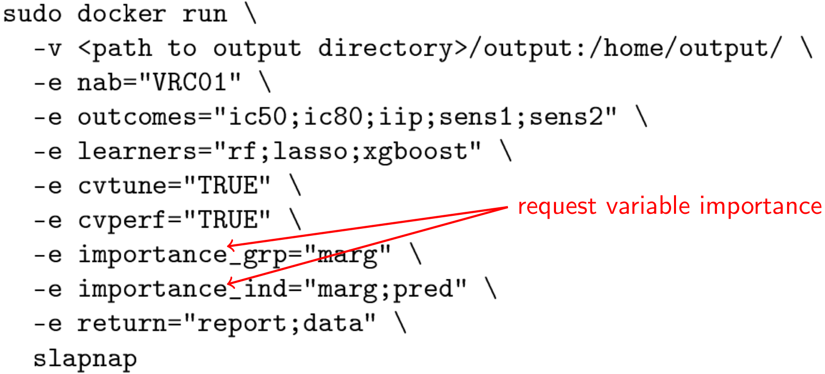

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request variable importance

Example: Predicting HIV-1 Neutralization by VRC01

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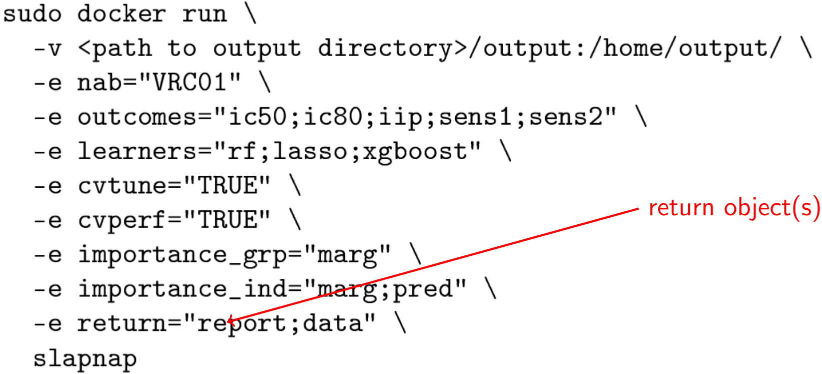

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  -e importance_ind="marg;pred" \
  -e return="report;data" \
  slapnap
```
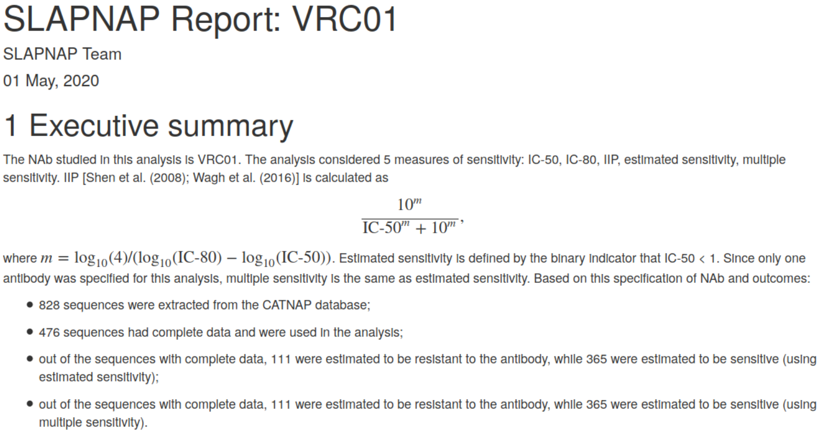

return object(s)

Example: VRC01 Report



SLAPNAP Report: VRC01

SLAPNAP Team

01 May, 2020

1 Executive summary

The NAb studied in this analysis is VRC01. The analysis considered 5 measures of sensitivity: IC-50, IC-80, IIP, estimated sensitivity, multiple sensitivity. IIP [Shen et al. (2008); Wagh et al. (2016)] is calculated as

$$\frac{10^m}{\text{IC-50}^m + 10^m},$$

where $m = \log_{10}(4)/(\log_{10}(\text{IC-80}) - \log_{10}(\text{IC-50}))$. Estimated sensitivity is defined by the binary indicator that IC-50 $<$ 1. Since only one antibody was specified for this analysis, multiple sensitivity is the same as estimated sensitivity. Based on this specification of NAb and outcomes:

- 828 sequences were extracted from the CATNAP database;
- 476 sequences had complete data and were used in the analysis;
- out of the sequences with complete data, 111 were estimated to be resistant to the antibody, while 365 were estimated to be sensitive (using estimated sensitivity);
- out of the sequences with complete data, 111 were estimated to be resistant to the antibody, while 365 were estimated to be sensitive (using multiple sensitivity).

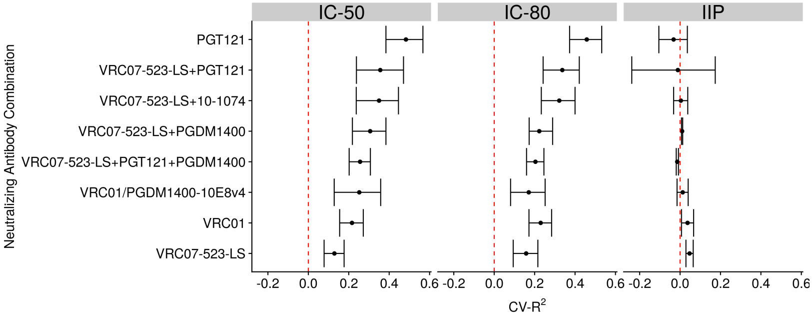
click to go to full report

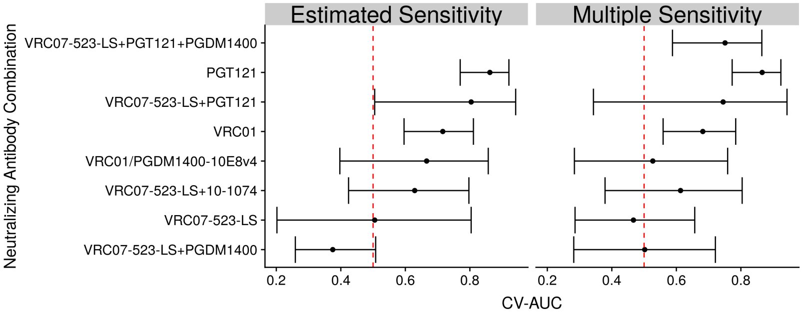
Predicting HIV-1 Neutralization for HVTN Studies

Full SLAPNAP analysis for bnAbs in HVTN + HPTN clinical testing:

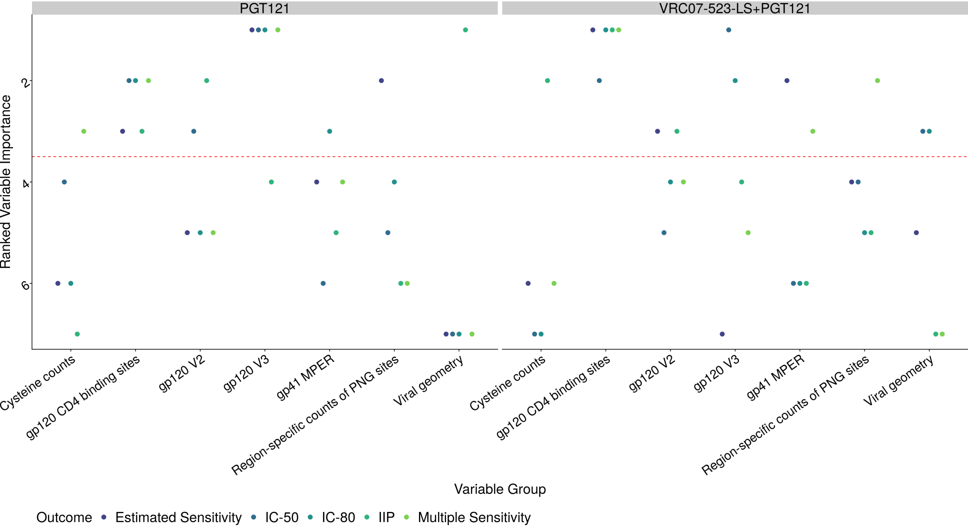
- VRC01
- VRC07-523-LS
- PGT121
- VRC07-523-LS + PGT121
- VRC07-523-LS + PGDM1400
- VRC07-523-LS + 10-1074
- VRC07-523-LS + PGT121 + PGDM1400
- VRC01/PGDM1400-10E8v4 (trispecific)

Summary of Results: Prediction Performance





Summary of Results: Variable Importance



Future Work

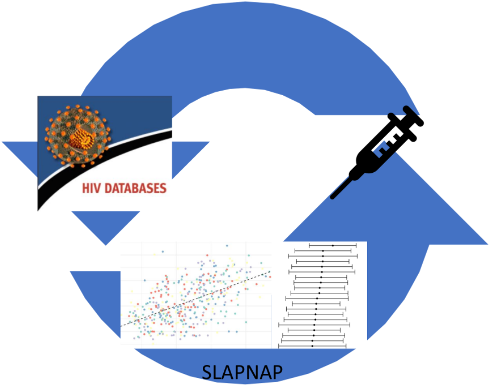
SLAPNAP performance:

- Testing on a large suite of synthetic data
- Implement new outcomes (e.g., maximum percent inhibition)

Applications:

- Help guide ranking of bnAb regimens
- Help down-selection of bnAb regimens into efficacy trials
- Augment neutralization datasets with SLAPNAP predictions based on Env sequence data sets

Conclusions



github.com/benkeser/slapnap | hub.docker.com/r/slapnap/slapnap

Acknowledgments

SLAPNAP core team

Fred Hutch: BW, Craig Magaret, Bhavesh Borate, Lindsay Carpp, Peter Gilbert

Emory: David Benkeser

Key collaborators

Adam Dingens (Fred Hutch)
Shelly Karuna (Fred Hutch)

Funding: NIAID (UM1 AI068635 [SDMC: HIV Vaccine Trials Network])