

Disclosure Slide

Financial Disclosure for:

Christian Fuchsberger

Sebastian Schönherr

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Cassie Spracklen

Albert Smith

Sarah Hanks

We have nothing to disclose

Section 6

The TOPMed Imputation Server



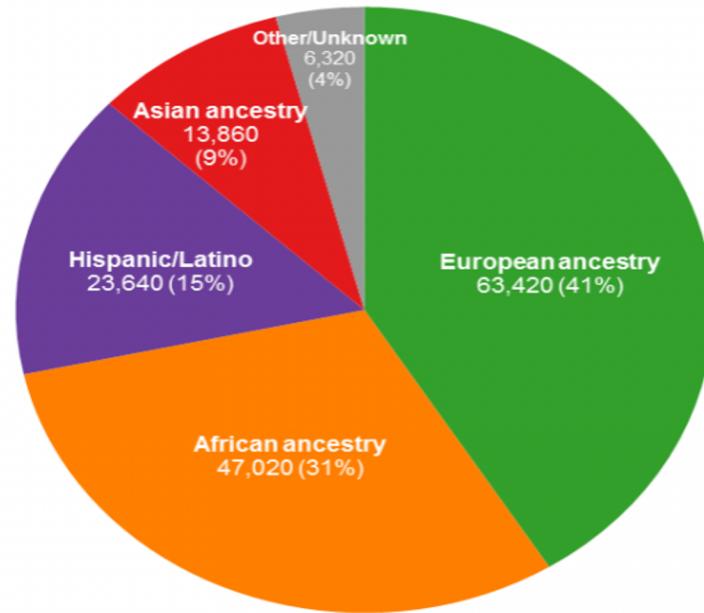
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TOPMed Program

Ancestry & Ethnicity

Phases 1-6 (~155K Participants)

- Trans-Omics for Precision Medicine (TOPMed) Program
- A Precision Medicine Initiative sponsored by National Heart, Lung and Blood Institute
- Integrating whole-genome sequencing and other omics data
- >155k participants from >80 studies



TOPMed Variant Call Set

Type	Category	PASS Variants	Singletons	Doubletons	AF > .0001	AF > .001	AF > .005	AF > .05
SNP	All	781M	46.4%	15.7%	4.50%	1.27%	1.06%	0.87%
	Synonymous	2.77M	42.2%	15.2%	5.23%	1.37%	1.06%	0.76%
	Missense	6.00M	46.4%	15.7%	3.96%	0.87%	0.56%	0.33%
	Stop Gain	197K	53.3%	16.0%	2.39%	0.44%	0.24%	0.12%
Indels	All	62.4M	49.7%	15.3%	4.22%	1.13%	0.90%	0.63%
	Inframe	112K	50.8%	15.5%	3.69%	0.70%	0.35%	0.16%
	Frameshift	271K	60.0%	15.5%	1.78%	0.31%	0.17%	0.09%

Stop-gain and frameshift variants progressively depleted among common variants

1/830 stop gain variants reaches MAF>5% vs. **1/115** among all SNPs, **1/303** among missense SNPs
1/1100 frameshift variants reaches MAF>5% vs. **1/159** among all Indels, **1/625** among inframe indels.

TOPMed Imputation

- Reference panel based on TOPMed Freeze 8 Calls
- Michigan Imputation Server ported to AWS
- Released April 2020
- <https://imputation.biodatacatalyst.nhlbi.nih.gov>
- Registration as before, open access to TOPMed panel
 - (Michigan Imputation Server accounts *not* transferred)

TOPMed Panel

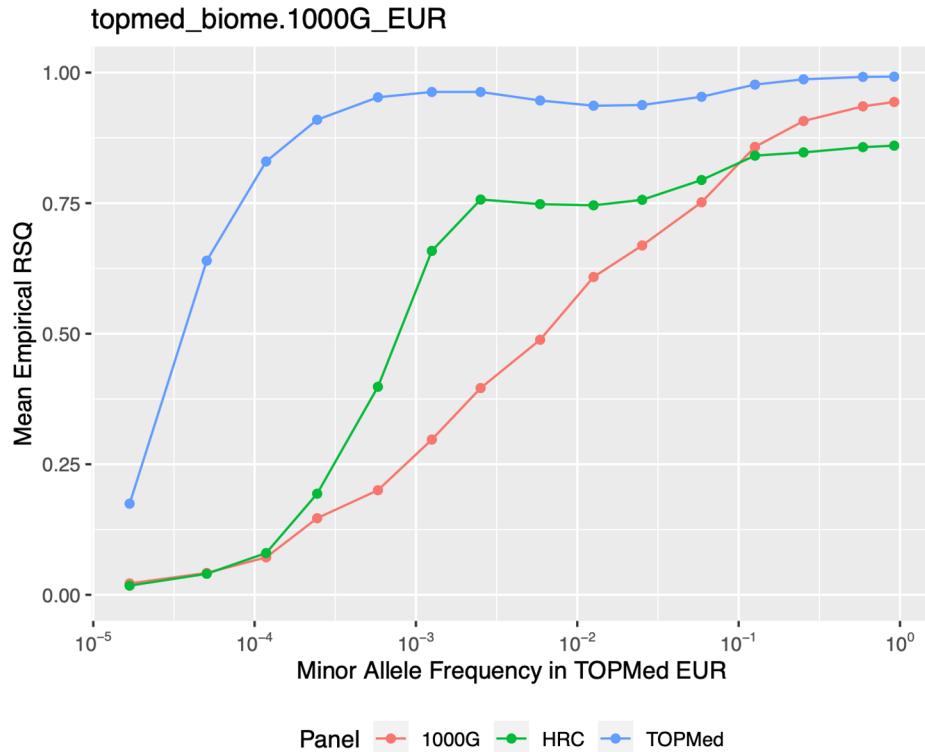
Variation type	Non-reference allele frequency bins				Totals
	(0, 0.005]	(0.005, 0.01]	(0.01, 0.05]	(0.05, 1)	
SNVs	270,352,495	3,365,284	5,330,340	7,020,861	286,068,980
Insertions	5,462,262	74,150	130,506	148,595	5,815,513
Deletions	15,406,052	185,606	297,186	333,748	16,222,592
Totals	291,220,809	3,625,040	5,758,032	7,503,204	308,107,085

Panel based on TOPMed Freeze 8

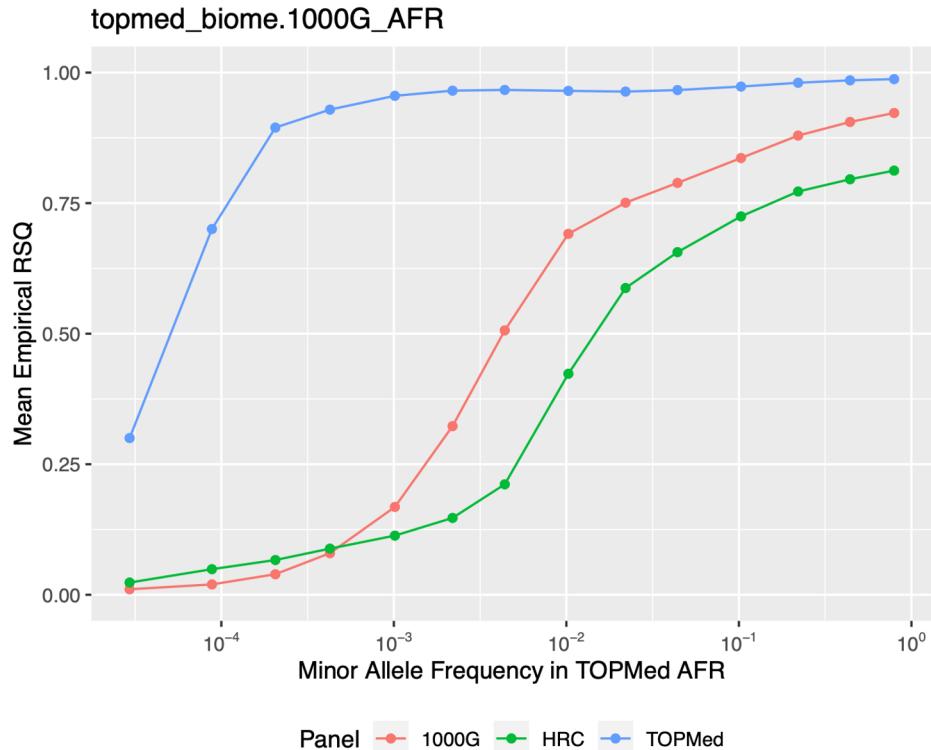
TOPMed Panel Compared

	TOPMed_r2	HRC	1000G Genomes
N samples	97K	39K	2,500
Ancestry	Multiethnic	European	Multiethnic
N variants	308M	39M	88M
Avg. depth	38X	8X	4X
Genome build Position	b38	b37	b37

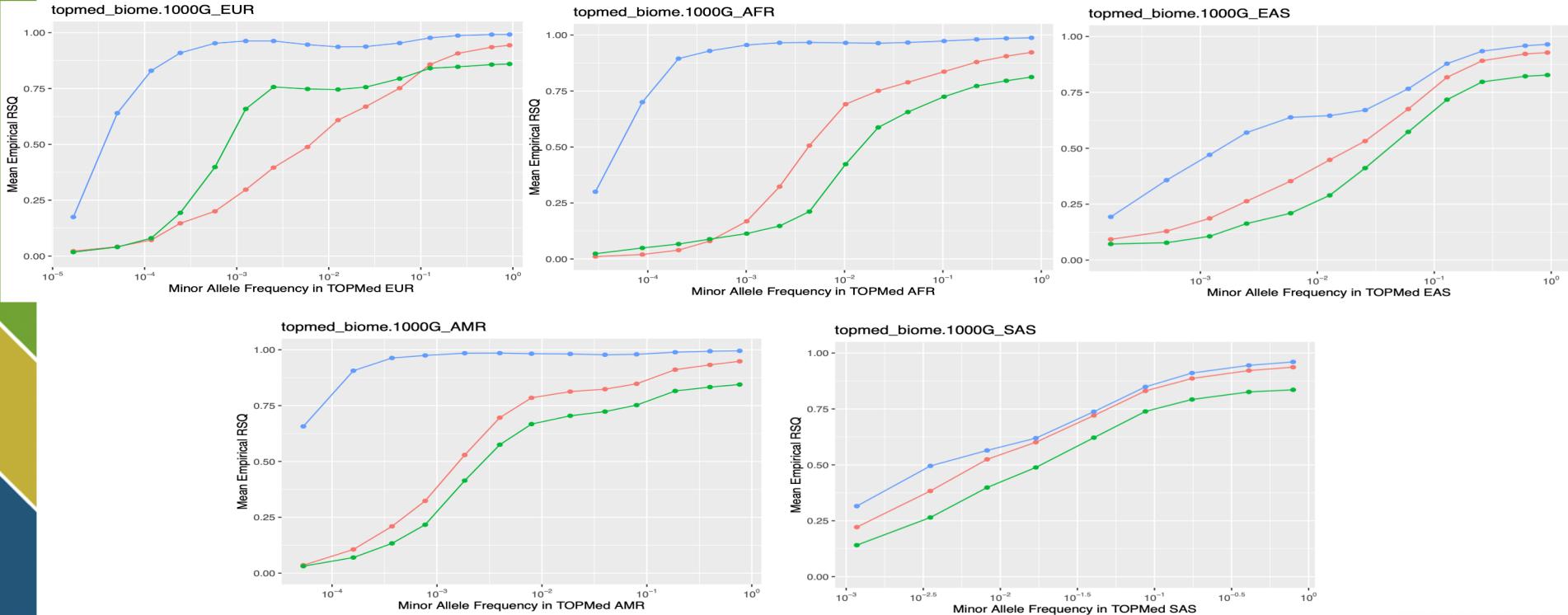
Imputation Panel Quality



Imputation Panel Quality



Imputation Panel Quality



imputation.biocatalyst.nhlbi.nih.gov

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TOPMed Imputation Server

Free Next-Generation Genotype Imputation Service

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9.2M
Imputed Genomes

888
Registered Users

8
Running Jobs

Latest News

12 August 2020
The server is online with full functionality after the latest maintenance window. We have also made improvements to efficiency and increased overall throughput. If you notice any issues, please contact us.

1 May 2020

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Genotype Imputation (Minimac4) 1.2.4

This is the new Michigan Imputation Server Pipeline using Minimac4. Documentation can be found [here](#).

If your input data is **GRCh37/hg19** please ensure chromosomes are encoded without prefix (e.g. **20**).
If your input data is **GRCh38hg38** please ensure chromosomes are encoded with prefix 'chr' (e.g. **chr20**). 

<https://imputationserver.readthedocs.io>

 Run

Name optional job name

Reference Panel TOPMed r2 

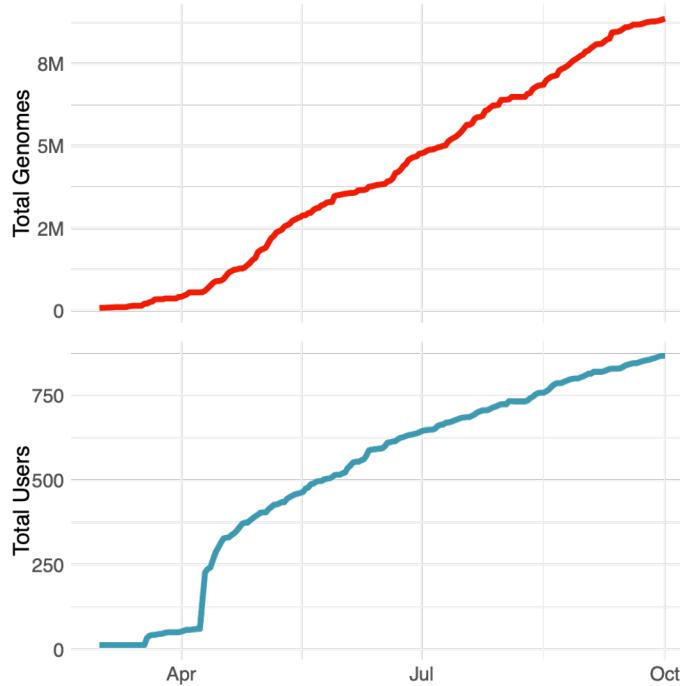
Input Files (VCF)

✓ File Upload
URLs (HTTP)
Secure File Transfer Protocol (SFTP)
S3 Bucket

Select Files

TOPMed Imputation

- Rapid uptake: 9M genomes imputed in 6 months
- Expect panel to largely supplant 1000g & HRC
- Particularly benefits ethnically diverse cohorts
- TOPMed-imputed UK BioBank to be made available (via UKBB)
- Satisfying GDPR-related concerns of European users remains a challenge



Imputation Resources

- Michigan Imputation Server
<https://imputation.sph.umich.edu/>
- TOPMed Imputation Server
<https://imputation.biodatacatalyst.nhlbi.nih.gov/>
- Documentation
<https://imputationserver.readthedocs.io/>
<https://topmedimpute.readthedocs.io/>
- TOPMed Imputation Contact
imputationserver@umich.edu