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About TOPMed

Updated 10/24/2023

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Overview

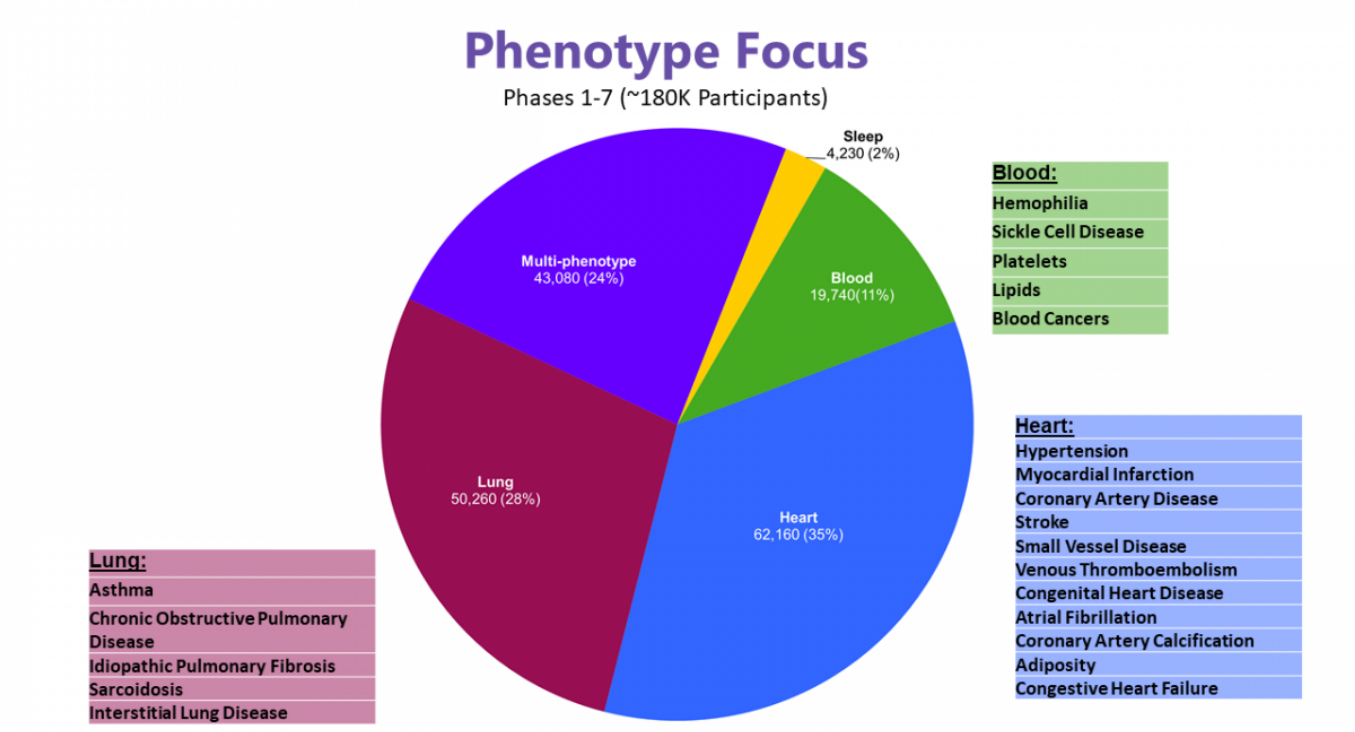
The Trans-Omics for Precision Medicine [8] (TOPMed) program, sponsored by the National Institutes of Health [9] (NIH) National Heart, Lung and Blood Institute [10] (NHLBI), is part of a broader Precision Medicine Initiative [11], which aims to provide disease treatments tailored to an individual's unique genes and environment. TOPMed contributes to this Initiative through the integration of whole-genome sequencing (WGS) and other omics (e.g., metabolic profiles, epigenomics, protein and RNA expression patterns) data with molecular, behavioral, imaging, environmental, and clinical data.

Study Characteristics

A primary goal of the TOPMed program is to improve scientific understanding of the fundamental biological processes that underlie heart, lung, blood, and sleep (HLBS) disorders. TOPMed is providing deep WGS and other omics data to pre-existing 'parent' studies [12] having large samples of human subjects with rich phenotypic characterization and environmental exposure data.

Study Designs

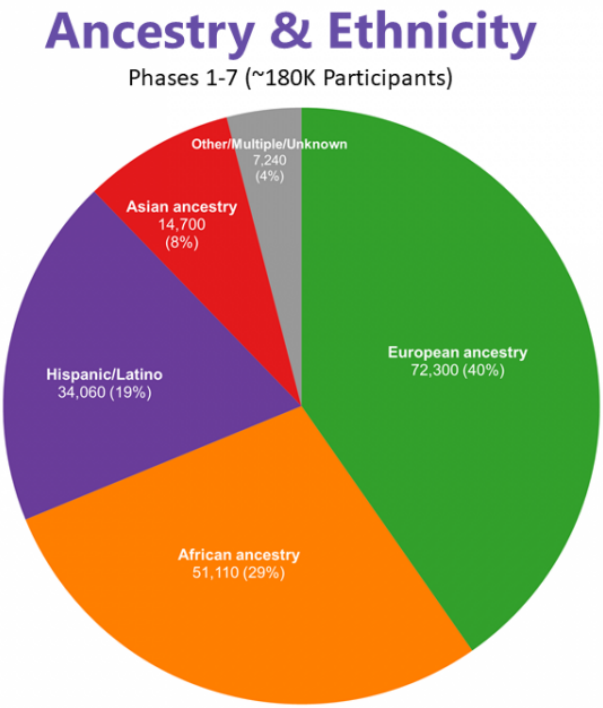
As of September 2021, TOPMed consists of ~180k participants from >85 different studies with varying designs. Prospective cohorts provide large numbers of disease risk factors, subclinical disease measures, and incident disease cases; case-control studies provide large numbers of prevalent disease cases; extended family structures and population isolates provide improved power to detect rare variant effects. The phenotype pie chart below shows the numbers and percentages of participants in studies with a focus on HLBS, as well as the percentage belonging to cohort studies that have collected many different phenotypes. It also shows areas of focus within each of the major HLBS categories.



Participant Diversity

Achieving ancestral and ethnic diversity is a priority in selecting contributing studies. Currently, 60% of the 180k sequenced participants are of predominantly non-European ancestry. Discovery of genotype-phenotype associations frequently includes pooled analysis across ancestry groups and studies, using statistical models that account for population structure and relatedness.

The pie chart below summarizes TOPMed participant diversity using a combination of self-identified or ascriptive race/ethnicity categories, study inclusion criteria, or other demographic information provided by study investigators. Please note that while groupings may correlate to some extent with genetic ancestry, TOPMed recommends distinguishing between genetically and non-genetically inferred descriptions in analyses and publications, as described in these Guidelines on the use and reporting of race, ethnicity, and ancestry in TOPMed [13].



Whole Genome Sequencing

WGS was performed by several sequencing centers [14] to a median depth of 30X using DNA from blood, PCR-free library construction and Illumina HiSeq X technology. A Support Vector Machine quality filter was trained with known variants and Mendelian-inconsistent variants. The Informatics Research Center [15] conducts joint genotype calling across all samples available to produce genotype data "freezes."

In TOPMed data freeze 8, with variant discovery on ~186k samples, 811 million single nucleotide variants and 66 million short insertion/deletion variants were identified and passed variant QC.

In TOPMed data freeze 9, variant discovery was initially made on ~206k samples including CCDG, but subset to 158,470 TOPMed samples plus 2,504 1000 Genomes samples. 781 million single nucleotide variants and 62 million short insertion/deletion variants were identified and passed variant QC. These variant counts are slightly smaller than the corresponding numbers in data freeze 8 due to omitting sites which show no variation in TOPMed samples. More information about WGS methods can be found under Sequencing and Data Processing Methods [16].

Omics

TOPMed Omics data processing is being performed by several sequencing centers [14]. The program requires that omics data be submitted to dbGaP, along with thorough documentation of biosampling and laboratory methods, as well as sample provenance. Visit the Standards webpage [17] to find available documented omics pipelines specific to omics type and phase. Below is a summary of the approved data sources for each study/cohort name categorized by data type.

TOPMed WGS and Omics Summary of Approved Projects

Short Name	Study/Cohort name	PI	Populations	dbGaP ID	WGS	RNA-seq	Methylation	Metabolomics	Proteomics
ATGC	Asthma Translational Genomics Collaborative	Burchard Esteban; Williams, L. Keoki;		ATGC dbGaP IDs [18]	16,494	9,290			
MESA	Multi-Ethnic Study of Atherosclerosis	Rotter, Jerome; Rich, Stephen	Multi-ethnic populations	phs001416 [19]	7,107	8,903	13,286	12,800	14,200
HCHS_SOL	Hispanic Community Health Study - Study of Latinos	Kaplan, Robert; North, Kari		phs001395 [20]	7,834	7,733	13,000	12,226	
ARIC+VTE	Venous Thromboembolism project	Boerwinkle, Eric	20% African American	phs001211 [21] phs001402 [22] phs000993 [23]	10,531	6,111	16,524	16,524	
CARDIA	Cell Disease Whole Genome Sequence Analysis in Early Cerebal Small Vessel Disease	Fomage, Myriam; Hou Lifang		phs001612 [24]	3,472	6,000	9,480	12,000	12,000
MLOF	My Life, Our Future: Genotyping for Progress in Hemophilia	Konkle, Barbara; Johnsen, Jill		phs001515 [25]	5,670	4,500			
PVDOMICS	Pulmonary Vascular Disease Omics Analyses	Erzurum, Serpil; Barnard, John; Geraci, Mark; Beck, Gerald; Comhair, Suzy		phs002358 [26]	1,137	4,388	1,800		
SPIROMICS	SubPopulations and InteRmediate Outcome Measures In COPD Study	Meyers, Deborah A		phs001927 [27]	2,711	3,980		3,417	
FHS	Framingham Heart Study	Ramachandran, Vasan S.; Levy, Dan; Heard-Costa, Nancy	3 generation EA pedigrees	phs000974 [28]	7,077	5,071	4,012	6,742	5,802
Africa6K	Integrative Genomic Studies of Heart and Blood Related Traits in Africans	Tishkoff, Sarah; Williams, Scott		phs002194 [29]	6,392	2,934			
HIPS	Hemophilia Inhibitor PUPs study	Brown, Deborah		phs002302 [30]	25	2,596			
WHI	Women's Health Initiative	Kooperberg, Charles; Reiner, Alex		phs001237 [31]	11,310	2,365	4,400	4,400	1,000
LTRC	Lung TIssue Research Consortium	Silverman, Edwin		phs001662 [32]	1,541	1,548	3,041	1,548	1,548
IPF	Whole Genome Sequencing in Familial and Sporadic Idiopathic Pulmonary Fibrosis	Schwartz David; Fingerlin, Tasha		phs001607 [33]	2,883	835			
PharmHU	The Pharmacogenomics of Hydroxyurea in Sickle Cell Disease	Boerwinkle, Eric; Sheehan, Vivien; Pace, Betty Sue		phs001466 [34]	862	826			
COPDGene	Genetic Epidemiology of COPD	Silverman, Edwin	30% African American	phs000951 [35] phs000946 [36]	10,829	800	11,843	8,353	
TOPCHeF	Trans-Omics for Precision Medicine for Congestive Heart Failure	Taylor, Matthew; Mestroni, Luisa; Graw, Sharon		phs002038 [37]	839	776	1,174		
nuMoM2b-HHS	nuMoM2b-Heart Health Study	Blue, Nathan; McNeil, Becky			4,341	600			
MDS	Genomics of Myelodysplastic Syndromes	Walter, Matthew; Goll, Johannes; Lindsley, R. Coleman; Saber, Wael; Padron, Eric; Miller, Christopher		phs002360 [38]	473	145			

SCVI	Stanford Cardiovascular Institute iPSC Biobank Study	Wu, Joseph; Bustamante, Carlos		phs002338 [39]	1,163	82			
AA_CAC	African American Coronary Artery Calcification project	Taylor, Kent D.; Rotter Jerome	African American Families	phs002194 [40]	1,159				
AFGen	Identification of Common Genetic Variants for Atrial Fibrillation and PR Interval - Atrial Fibrilation Genetics Consortium	Ellinor, Patrick		AFGen dbGaP IDs [18]	12,742				
Amish	Genetics of Cardiometabolic Health in the Amish	Mitchell, Braxton D.	Old Order Amish large extended pedigrees	phs000956 [41]	1,120				
PGX_Asthma	Pharmacogenomics of Bronchodilator Response in Minority Children with Asthma [42]	Burchard, Esteban; Hernandez, Ryan	500AA, 500 Puerto Rican, and 500 Mexican of extremely non-responding asthma patients.	Please see this TOPMed Project's Parent Studies	1,500				
BAGS	Barbados Asthma Genetics Study	Barnes, Kathleen	African descent Barbados families with >40% of asthmatic members	phs001143 [43]	1,085				
BCC-PREG	The Boston-Colombia Collaborative for Adverse Pregnancy Outcomes	Gray, Kathryn J.; Casa Romero, Juan P		Please see this TOPMed Project's Parent Studies.	14,615				
BioMe	Mount Sinai BioMe Biobank	Loos, Ruth J.F.; Kenny, Eimear		phs001644 [44]	11,626				
Boston-Brazil_SCD	Boston-Brazil Collaborative Study of Sickle Cell Disease	Sankaran, Vijay G.		phs001599 [45]	415				
CFS	Cleveland Family Study	Redline, Susan	African American	phs000954 [46]	1,300				
CHS	Cardiovascular Health Study	Psaty, Bruce; Tracy, Russell		phs001368 [47]	4,780		8,041	8,619	8,619
COPDMet	Plasma and BALF Metabolomics in COPDGene and SPIROMICS	Bowler, Russell		Please see this TOPMed Project's Parent Studies	0				
CRA_CAMP	The Genetic Epidemiology of Asthma in Costa Rica and the Childhood Asthma Management Program	Weiss, Scott T	Costa Rica is a special Hispanic population with asthma prevalence at 24%	phs001726, [48] phs000988 [49]	6,647		3,000	3,000	
DS_CHD	Down Syndrome Associated Atrioventricular Septal Defects: New Omic Resources	Sherman, Stephanie L.		Please see this TOPMed Project's Parent Studies.	469				
ECLIPSE	Evaluation of COPD Longitudinally to Idenity Predictive Surrogate Endpoints	Silverman, Edwin		phs001472 [50]	2,355				
GEM-OSA	Genetics, Epigenetics and Metabolomics of OSA subtypes	Pack, Allan; Carrier, Julie; Magalan, Ulysses; Mignot, Emmanuel; Ayas Najib		Please see this TOPMed Project's Parent Studies.	3,000		3,000	3,000	
GeneSTAR	Genetic Studies of Atherosclerosis Risk	Mathias, Rasika	African American families, European families	phs001218 [51]	1,780				

GenSalt	Genetic Epidemiology Network of Salt Sensitivity	He, Jiang		phs001217 [52]	1,858				
GOLDN	Genetics of Lipid Lowering Drug and Diet Network	Amett, Donna K	European families	phs001359 [53]	965				
HLKSCD	Genetic Variation of Heart, Lung, and Kidney Disease in Sickle Cell Disease: Pre- and Post-Curative Therapies	DeBaun, Michael; Eapen, Mary; Kang, Guolian; Edwards, Todd; Weiss, Mitch; Estepp, Jeremie; Gordeuk, Victor; Li, Bingshan; Saraf, Santosh			1,780				
HyperGEN_GENOA	Hypertension Genetic Epidemiology Network and Genetic Epidemiology Network of Arteriopathy	Amett, Donna K	African American families	phs001345 [54] phs001293 [55]	3,153				
JHS	Jackson Heart Study	Carson, April; Raffield, Laura	African American mixed family and population based	phs000964 [56]	3,418		1,659	5,266	5,266
OMG_SCD	Outcome Modifying Genes in Sickle Cell Disease	Ashley-Koch, Allison; Telen, Marilyn		phs001608 [57]	653				
PCGC_CHD	Pediatric Cardiac Genomics Consortium's Congenital Heart Disease	Gelb, Bruce; Seidman, Christine		phs001735 [58]	3,888				
PROMIS	Pakistan Risk of Myocardial Infarction Study	Saleheen, Danish	South Asian ancestry from Pakistan	phs001569 [59]	9,204				
PUSH_SCD	Pulmonary Hypertension and the Hypoxic Response in Sickle Cell Disease	Nekhai, Sergei		phs001682 [60]	423				
REDS-III_Brazil	Recipient Epidemiology and Donor Evaluation Study-III	Custer, Brian; Kelly, Shannon	Brazilian	phs001468 [61]	2,746				
SAFS	San Antonio Family Studies	Blangero, John; Curran, Joanne	Mexican American in SAFHS extended pedigrees	phs001215 [62]	1,819				
Samoan	Samoan Adiposity Study	McGarvey, Stephen	Samoan	phs000972 [63]	1,295				
Sarcoidosis	Genetics of Sarcoidosis in African Americans	Montgomery, Courtney	African American families	phs001207 [64]	1,330				
SARP	Severe Asthma Research Program	Meyers, Deborah A		phs001446 [65]	1,890				
THRV	Taiwan Study of Hypertension using Rare Variants	Rotter, Jerome; Chen, Yii-Der Ida	Taiwan Chinese families	phs001387 [66]	2,170				
UNID_CM	The Genetic Causes of Unexplained Cardiomyopathies	Seidman, Jonathan; Seidman, Christine			779				
Walk-PHaSST	Treatment of Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy	Gladwin, Mark; Zhang, Yingze		phs001514 [67]	437				
TOTAL					**205,092**	**69,483**	**94,260**	**97,895**	**48,435**

Notes:

AFGen dbGaP IDs: phs001435 [68], phs001543 [69], phs001624 [70], phs001732 [71], phs001600 [72], phs001189 [73], phs001546 [74], phs001606 [75], phs001547 [76], phs001725 [77], phs001545 [78],

phs000993 [79], phs001598 [80], phs001062 [81], phs001434 [82], phs001544 [83], phs001024 [84], phs001601 [85], phs001933 [86], phs000997 [87], phs001032 [88], phs001040 [89]

ATGC dbGaP IDs: phs001728 [90], phs001729 [91], phs001730 [92], phs001602 [93], phs001603 [94], phs001604 [95], phs001605 [96], phs000920, phs001542 [97], phs001661 [98], phs001727 [99], phs000921 [100], phs001467 [101]

Note: You may encounter phs links that redirect to a dbGaP error page in the table above. If so, this is because the TOPMed dbGaP study webpages do not go live until the study accession is released.

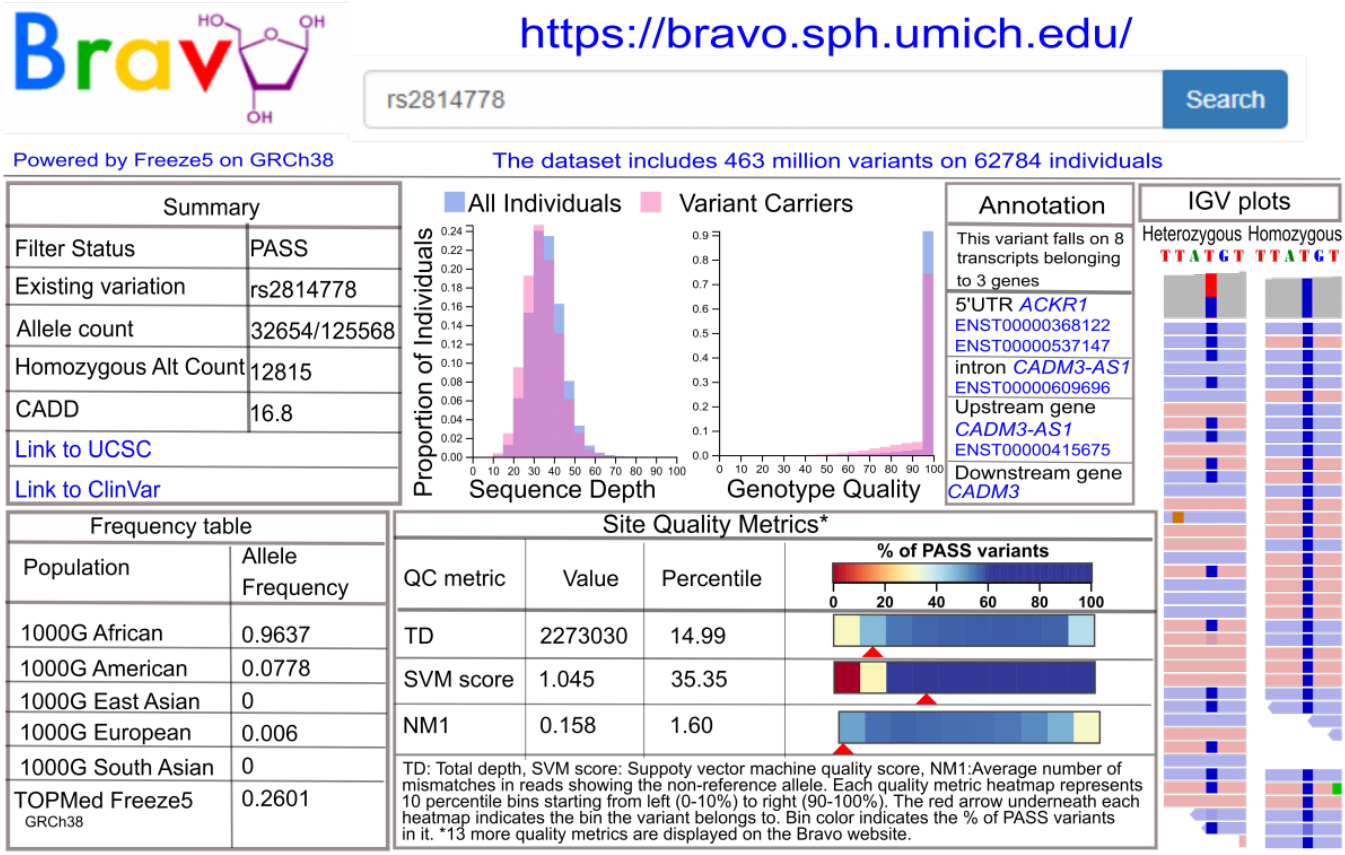
Note: TOPMed is generating a rich resource of multi-omics data that will include approximately 40K samples undergoing RNA-sequencing, 37K samples from metabolomics profiling, 57K samples from DNA methylation, and 4K samples from proteomics assaying. These projected totals include all stages of progress, from DNA/RNA that are currently being extracted, to those that are undergoing sequencing/profiling, or those that have completed the sequencing/profiling pipelines. Therefore, most omics data are in the process of being generated and will be released in the future.

Resources for the Scientific Community

TOPMed data are being made available to the scientific community as a series of “data freezes”: genotypes and phenotypes via dbGaP; read alignments via the Sequence Read Archive (SRA); and variant summary information via the Bravo variant server [102] (see figure below) and dbSNP. Genotypes for a set of 55k samples have been released on dbGaP (freeze 5) and a freeze release of >140k samples is expected by mid 2020 (freeze 8). TOPMed WGS data are contained in study-specific accessions with names containing “NHLBI TOPMed”, while most phenotypic data are in parent study accessions. The TOPMed accessions can be identified by searching the dbGaP web site for “TOPMed” [103]. More information about what data are available and how to access it can be found on the Data Access [104] page.

TOPMed is currently adding other omic assays to samples that have been whole-genome sequenced; these include RNAseq, metabolomics, proteomics and epigenomics.

Overview of Bravo variant server resources



This content was adapted from a poster [105] presented at the 2018 American Society of Human Genetics (ASHG) meeting, "Overview of the NHLBI Trans-Omics for Precision Medicine (TOPMed) program: Whole genome sequencing of >100,000 deeply phenotyped individuals" (Poster 3145/T).

Source URL (modified on 10/24/2023 - 2:05pm):https://topmed.nhlbi.nih.gov/about?mini=2018-04

Links

[1] https://topmed.nhlbi.nih.gov/about#Overview [2] https://topmed.nhlbi.nih.gov/about#Study Characteristics [3] https://topmed.nhlbi.nih.gov/about#Study Designs [4] https://topmed.nhlbi.nih.gov/about#Participant Diversity [5] https://topmed.nhlbi.nih.gov/about#Whole Genome Sequencing [6] https://topmed.nhlbi.nih.gov/about#Omics [7] https://topmed.nhlbi.nih.gov/about#Resources for the Scientific Community [8] https://www.nhlbi.nih.gov/science/trans-omics-precision-medicine-topmed-program [9] https://www.nih.gov/ [10] https://www.nhlbi.nih.gov/ [11] https://ghr.nlm.nih.gov/primer/precisionmedicine/initiative [12] https://topmed.nhlbi.nih.gov/group/project-studies?field_is_this_a_value=sub&order=field_this_study_s_short_name&sort=asc [13] https://topmed.nhlbi.nih.gov/guidelines-use-and-reporting-race-ethnicity-and-ancestry-topmed [14] https://topmed.nhlbi.nih.gov/group/sequencing-centers [15] https://topmed.nhlbi.nih.gov/group/irc [16] https://topmed.nhlbi.nih.gov/data-sets [17] https://topmed.nhlbi.nih.gov/standards [18] https://topmed.nhlbi.nih.gov/about#Notes [19] https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001416 [20] https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001395 [21] https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001211 [22] https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001402 [23] https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000993 [24] https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001612 [25] https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001515 [26] http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs002358 [27]

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