Alabama Genomic HEALTH INITIATIVE

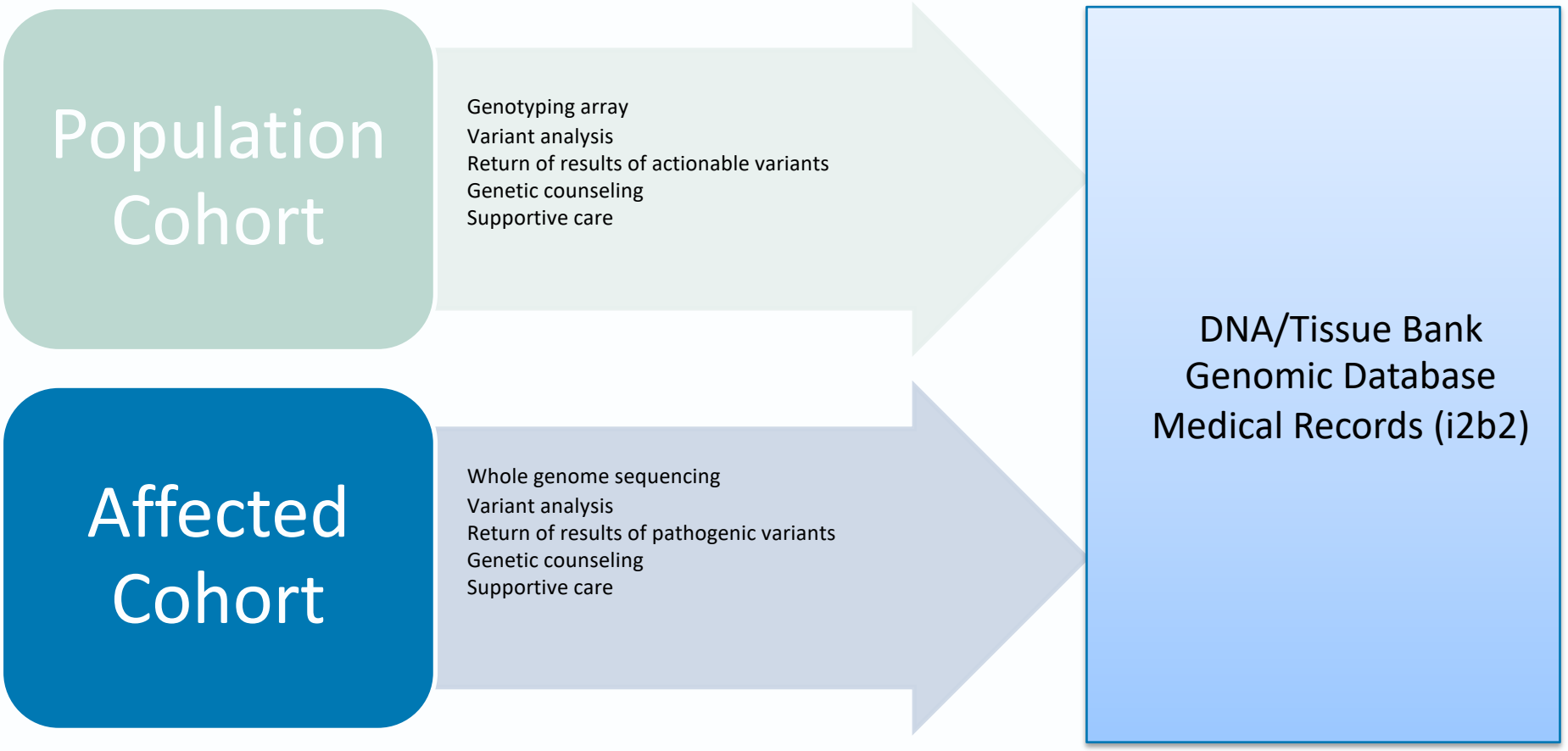
UAB Medicine/HudsonAlpha Institute for Biotechnology

Supported by State of Alabama

Genomic analysis of 10,000 citizens over five years

Return of clinical data

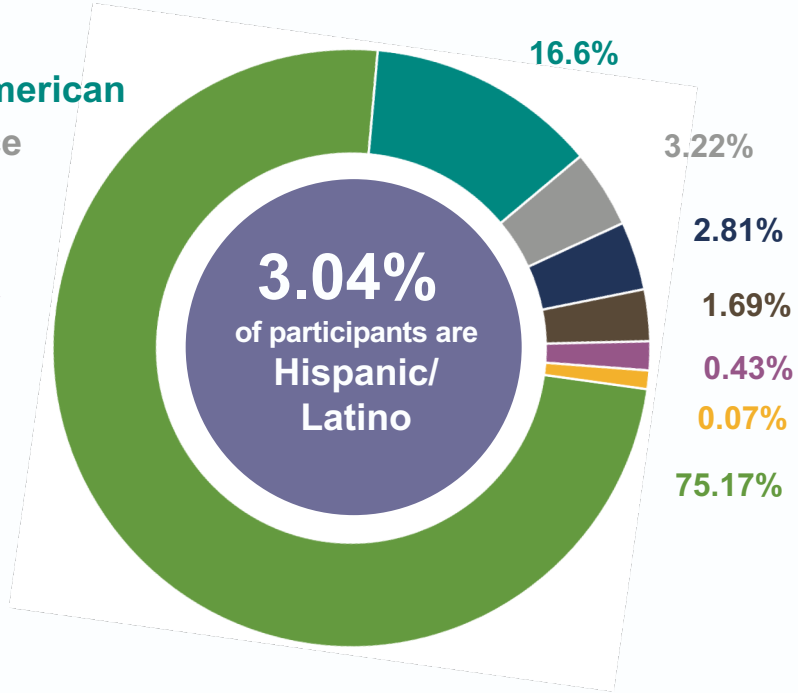
Research database and biobank


Population Cohort
Genotyping array
Variant analysis
Return of results of actionable variants
Genetic counseling
Supportive care
Affected Cohort
Whole genome sequencing
Variant analysis
Return of results of pathogenic variants
Genetic counseling
Supportive care
DNA/Tissue Bank
Genomic Database
Medical Records (i2b2)

Population Cohort Enrollment Demographics (as of 3.12.19)

ENROLLMENT BY RACE:

- White
- Black or African American
- More than One Race
- Asian
- Unknown
- American Indian or Alaska Native
- Native Hawaiian Or Other Pacific Islander



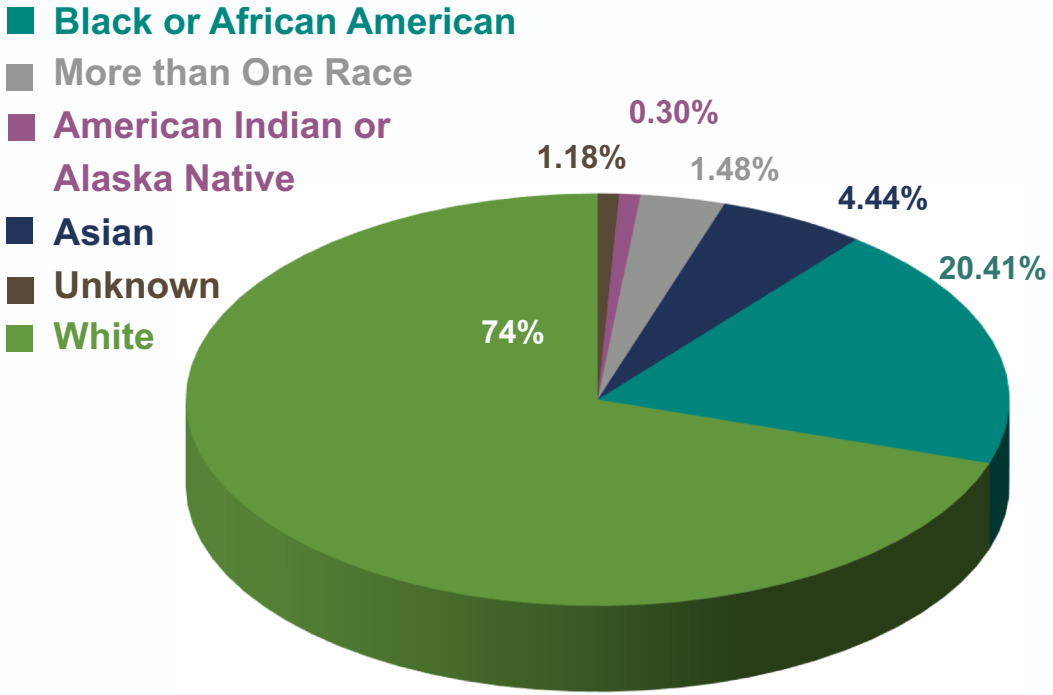
ENROLLMENT BY GENDER:

74%

26%

Whole Genome Sequence Cohort Enrollment Demographics (as of 3.12.19)

ENROLLMENT BY RACE:



ENROLLMENT BY GENDER:

52%

48%

8.88% of Participants are **Hispanic/Latino**

Alabama Genomic HEALTH INITIATIVE

Cumulative Population Cohort Enrollment

- 4374 participants
- 66 of 67 counties
- 60 actionable results returned to participants = 1.4% of general population

Updated 3/12/19

ACMG Secondary Findings in Population Cohort

Type	Genes
Tumor Predisposition Breast/ovarian, Li-Fraumeni, Peutz-Jeghers, Lynch, Polyposis, Von Hippel-Lindau, MEN1/2, Medullary thyroid cancer, PTEN hamartoma syndrome, Retinoblastoma, Paraganglioma/pheochromocytoma, Tuberous sclerosis complex, WT1-related Wilms' tumor, NF2	BRCA1/2, TP53, STK11, MLH1, MSH2, MSH6, PMS2, APC, MUTYH, BMPR1A, SMAD4, VHL, MEN1 RET, PTEN, RB1, SDHD, SDHAF2, SDHC, SDHB, TSC1, TSC2, WT1, NF2
Connective Tissue Dysplasia Ehlers-Danlos vascular type, Marfan, Loeys-Dietz, Familial aortic aneurysms and dissections	COL3A1, FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYH11
Cardiac Hypertrophic cardiomyopathy, dilated cardiomyopathy, Arrhythmia	MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA, RYR2, PKP2, DSP, DSC2, TMEM43, DSG2, KCNQ1, KCNH2, SCN5A
Metabolic Hypercholesterolemia, Wilson disease, Ornithine transcarbamylase deficiency	LDLR, APOB, PCSK9, ATP7B, OTC
Pharmacogenetic Malignant Hyperthermia	RYR1, CACNA1S

Updated 3/12/19

Family History Review

- Forms focus on ACMG SFv2.0 conditions
- Reviewed by Genetic Counselors
- Triaged into 3 categories using published testing criteria guidelines

51%

4%

45%

Updated 3/12/19

Biobank

- 14,512 plasma aliquots
- 4048 DNAS
- 3955 buffy coats
- 3886 whole blood

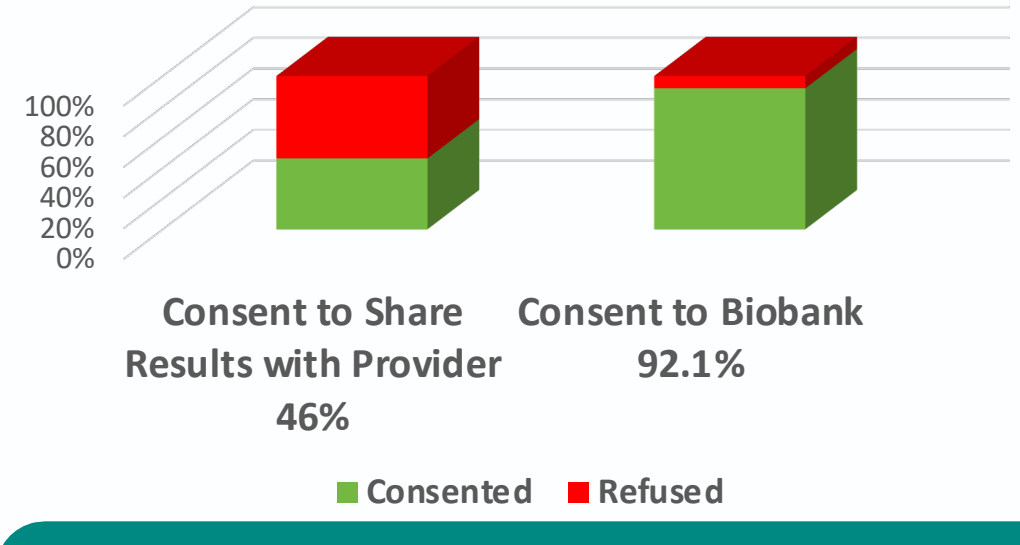
Bioinformatics

- 3779 annotated chips from population cohort
- 104 annotations containing 243 participants from the WGS cohort

- 92% consent to biobank and share data

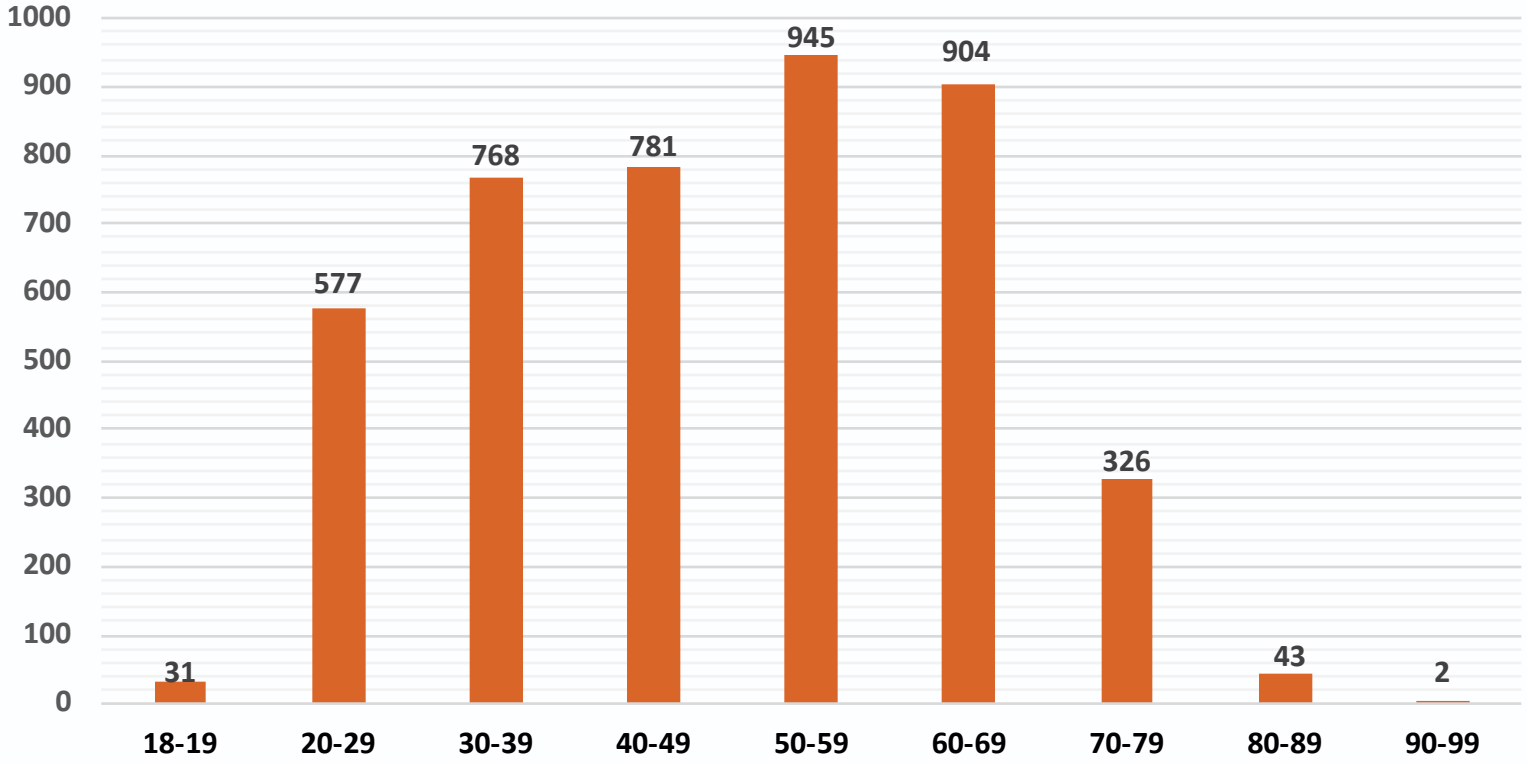
Updated 3/12/19

FY17-19 AGHI Participant Consent



Updated 3/12/19

FY17-19 AGHI Population Cohort Participants by Age



Updated 3/12/19

Alabama Genomic HEALTH INITIATIVE

Whole Genome Sequencing Results

- 319 total whole genome participants
- 142 total families enrolled (probands and parents)
- 121 total families analyzed to date
- 49 primary variants returned
  - 26 VUS
  - 12 Likely Pathogenic
  - 11 Pathogenic
- 5 secondary variants returned
- 40.5% primary result return rate

Updated 3/12/19

Genome Sequencing Primary Results

- *ACTN1* – Bleeding disorder, platelet-type 15
- *AHI1* – Joubert Syndrome 3
- *ATP7A* – Menkes disease
- *ALDH18A1* – Spastic Paraplegia 9A
- *BRAF* – Cardio-facio-cutaneous Syndrome
- *CACNA1A* – Episodic ataxia, type 2
- *CDKL5* –Epileptic Encephalopathy, early infantile, 2
- *IFIH1* – Aicadri-Goutieres Syndrome 7
- *ITPR1* – Spinocerebellar Ataxia
- *INVS* – Nephronophthisis 2, infantile
- *KDM1A* – Cleft palate, psychomotor retardation, distinctive facial features
- *MFF* – encephalopathy due to mitochondrial and peroxisomal fission
- *NAA15* – Intellectual Disability
- *PAX5* – Leukemia, acute lymphoblastic, susceptibility to, 3
- *PUF60* – Verheij syndrome
- *RALA* – (recently published new disease gene)
- *SCN8A* – Epileptic Encephalopathy
- *SCRAP* – Floating-Harbor Syndrome
- *SLC26A4* – Pendred Syndrome
- *SPG11* – Spastic paraplegia 11, autosomal recessive
- *TCF4* – Pitt-Hopkins syndrome
- *YWHAZ* – (collaboration in progress)

Updated 3/12/19

Some Bioethical Challenges

- Population Cohort
  - False reassurance
  - Non-penetrance
  - Unexpected medical findings
  - Sample discrepancies
  - Withdrawal of consent
  - Release of raw data
- Affected Cohort
  - Secondary findings

Alabama Genomic HEALTH INITIATIVE

Supervision of the Alabama Genomic Health Initiative to ensure maximum value to participants, the research community, and state of Alabama

Oversight Committee

Charged with overall responsibility and accountability for conducting the Alabama Genomic Health Initiative

Principal Investigators

Working groups leading defined areas of responsibility for the Alabama Genomic Heath Initiative

Bioethics	Data and Bioinformatics	**Education**	Genomics	Participant and Provider Engagement
• Ethical, legal and social implications • Informed Consent	• Data Management • DNA Preparation • Biobanking • Research Support	• Participant education • Genetic counseling • Communication of results to participants and providers	• Genotyping • Sequencing • Return of results	• Recruitment • Engagement • Outreach