4th Annual CCTS Bioethics Forum

Bioethical Issues around Return of Results

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The AGHI Bioethics: 4 Core Values

What we return

What we may be able to return

Why some participants may want to know more than what we currently return

Possible problems of granting full access to raw data

Ethical issues of ROR — the AGHI approach

Ethics of the AGHI:

4 Core Values to Regain & Retain Trust

Transparency/Honesty

- Be honest about research benefits and risks
- Do not deceive or mislead

Respect

- Honor a patient's choice to participate or not to participate
- Avoid exploitation or stigmatization
- Respect privacy

Confidentiality

- Keep sensitive personal information confidential

Fairness

- Reach out to diverse population
- Do not exclude or exploit any specific group of people

What we return to "genotyping cohort" participants

The AGHI's current ***negative*** result letter

Dear _____,

This page reviews your research-based genetic test results from the Alabama Genomic Health Initiative. Below you will find a summary of your findings.

In the set of genes tested we did not find any gene differences, or changes, that have been linked to a high risk to develop a disease. However, this does not mean that you will not develop any disease in the future. It also does not rule out having a genetic risk factor for disease, even in the genes we tested.

What we return

The AGHI's current ***positive*** result letter: an example

We found a gene difference in your BRCA2 gene that may cause a higher risk for cancer. See attached detailed report from the lab for more information about your finding. This result should be looked at in light of your personal and family medical history.

People with differences in the BRCA2 gene have a higher risk for breast, ovarian and other cancers. Steps can be taken to lower this risk and detect cancer at an earlier, more treatable stage. These steps include more screenings at younger ages and, in some cases, surgery to lower cancer risk. A more detailed description of these risk-lowering measures is available online through the National Comprehensive Cancer Network (www.NCCN.org).

What we return

The AGHI's current ***positive*** result letter: an example

Differences in the BRCA2 gene are inherited in a dominant pattern. This means each child of a person with one of these differences has a 50% chance of inheriting the difference and having an increased cancer risk. You and your doctor should discuss this finding and what it means for your cancer risk, medical care, and family members. You may also wish to speak with a genetic counselor. To find a nearby genetics specialist, visit www.nsgc.org and use the "find a genetic counselor" resource. You can contact us at the number listed below for any questions or concerns.

Our knowledge of genetics and disease will continue to change and get better over time. Please continue regular care with your doctor and other healthcare providers to learn the latest information about this result.

What we return

The AGHI

Medically Actionable Results - 34 Reports on 59 Genes

Arrhythmogenic right ventricular cardiomyopathy: DSC2, DSG2, DSP, PKP2, TMEM43
Brugada syndrome, Long QT (Romano-Ward) syndrome: SCN5A
Dilated cardiomyopathy: LMNA
Ehlers-Danlos syndrome, vascular type: COL3A1
Fabry disease:GLA
Familial adenomatous polyposis: APC
Familial hypercholesterolemia: APOB, LDLR
Familial hypertrophic cardiomyopathy: ACTC1, MYBPC3, MYH7, MYL2, MYL3, PRKAG2, TNNI3, TPM1
Familial thoracic aortic aneurysm: ACTA2, MYH11
Hereditary breast-ovarian cancer: BRCA1, BRCA2
Hereditary paraganglioma-pheochromocytoma syndrome: SDHAF2, SDHB, SDHC, SDHD
MYH-associated polyposis: MUTYH
Hypercholesterolemia: PCSK9
Hypertrophic cardiomyopathy: TNNT2
Juvenile polyposis: BMPR1A, SMAD4
Li-Fraumeni syndrome: TP53
Loeys-Dietz syndrome, type 3: SMAD3
Loeys-Dietz syndrome, type 1 and 2; Familial Thoracic Aneurysms and Dissections: TGFBR1, TGFBR2
Long QT (Romano Ward) syndrome, type 1: KCNQ1
Long QT (Romano Ward) syndrome, type 2: KCNH2
Lynch syndrome: MLH1, MSH2, MSH6, PMS2
Malignant hyperthermia: CACNA1S , RYR1, RYR2
Marfan syndrome: FBN1
Multiple endocrine neoplasia, type 1: MEN1
Multiple endocrine neoplasia, type 2a: RET
Neurofibromatosis, type 2: NF2
Ornithine carbamoyltransferase deficiency: OTC
Peutz-Jeghers syndrome: STK11
PTEN hamartoma tumor syndrome: PTEN
Retinoblastoma: RB1
Tuberous sclerosis complex: TSC1, TSC2
Von-Hippel-Lindau syndrome: VHL
Wilms' tumor: WT1
Wilson Disease: ATP7B

23andMe

Health Predisposition – 11 reports on 16+ genes

Age-Related Macular Degeneration: CFH, ARMS2
Celiac Disease: variants near HLA-DQA1 and HLA-DQB1
Familial Hypercholesterolemia: APOB, LDLR
Type 2 Diabetes: "Based on data from 23andMe research participants"
Alpha-1 Antitrypsin Deficiency: SERPINA1 gene
Hereditary breast-ovarian cancer: BRCA1, BRCA2
G6PD Deficiency: G6PD
Hereditary Hemochromatosis: HFE
Hereditary Thrombophilia: F5, F2
Late-Onset Alzheimer's Disease: APOE
Parkinson's Disease: LRRK2, GBA

Carrier Status - 44 reports

ARSACS	Agenesis of the Corpus Callosum with Peripheral Neuropathy	
Autosomal Recessive Polycystic Kidney Disease		Beta Thalassemia and Related
Hemoglobinopathies	Bloom Syndrome	Canavan Disease
Congenital Disorder of Glycosylation Type 1a		Cystic Fibrosis
D-Bifunctional Protein Deficiency		Dihydrolipoamide Dehydrogenase Deficiency
Familial Dysautonomia	Familial Hyperinsulinism	Familial Mediterranean Fever
Fanconi Anemia Group C	GRACILE Syndrome	Gaucher Disease Type 1
Glycogen Storage Disease Type Ia, Ib		Hereditary Fructose Intolerance
Herlitz Junctional Epidermolysis Bullosa		Leigh Syndrome, French Canadian Type
Limb-Girdle Muscular Dystrophy Type 2D, 2E, 2I		MCAD Deficiency
Maple Syrup Urine Disease Type 1B		Mucolipidosis Type IV
Neuronal Ceroid Lipofuscinosis		Niemann-Pick Disease Type A
Nijmegen Breakage Syndrome		Nonsyndromic Hearing Loss and Deafness, DFNB1
Pendred Syndrome and DFNB4 Hearing Loss		Phenylketonuria and Related Disorders
Primary Hyperoxaluria Type 2	Rhizomelic Chondrodysplasia Punctata Type 1	Salla Disease
Sickle Cell Anemia	Sjögren-Larsson Syndrome	Tay-Sachs Disease
Tyrosinemia Type I	Usher Syndrome Type 1F, 3A	Zellweger Syndrome Spectrum

Wellness - 8 reports

Alcohol Flush Reaction, Caffeine Consumption, Deep Sleep, Genetic Weight, Lacose Intolerance, Muscle Composition, Saturated Fat and Weight, Sleep Movement

Traits (appearance and senses) -24 reports

Ability to match musical pitch, Asparagus Odor Detection, Bitter Taste, Cheek Dimples, Cilantro Taste Aversion, Cleft chin, earlobe type, earwax type, eye color, fear of heights, finger length ratio, freckles, hair photobleaching, hair texture, hair thickness, long or dark hair, misophonia, mosquito bite frequency, motion sickness, newborn hair, photic sneeze reflex, red hair, skin pigmentation, sweet vs. salty, toe length ratio, unibrow, wake-up time (mine said "people with your genetics in their 40s wake up on average around 7:53 am on their days off." 23andMe looked at 450 places in my DNA that are associated with being either a morning person or a night person), widow's peak

What we may be able to return

The AGHI	23andMe
Infinium Global Screening Array Kit	Infinium OmniExpress Kit
An economical next-generation genotyping array that enables population-scale genetics, translational research, variant screening studies, and precision medicine research by combining highly optimized multiethnic genome-wide content, curated clinical research variants, and QC markers.	A powerful option for genome-wide association studies that provides high sample throughput with comprehensive genomic content and the flexibility to include up to 30,000 semi-custom markers.
Fixed markers: ~ 640,000 Custom marker add-on capacity: Up to 50,000	Fixed Markers: ~710,000 Custom marker add-on capacity: Up to 30,000
~2304 samples per week	~2304 samples per week
Species: Human	Species: Human

This table is based on a comparison table found on: Illumina.com

What we may be able to return

- *Medically non-actionable* results
- Carrier status
- Non-medical biological traits
- Ancestry-related information
- Full raw data found on the genotyping chip

Limitations:

- Budget
- Scientific accuracy, clinical certainty
- Ethical implications

Why some participants may want to know more than what we currently return

REVEAL study participants at risk for Alzheimer's talk about their genetic test results (7:04) University of Michigan School of Public Health, Dec. 9, 2011
https://youtu.be/SMQB1A3IArU

Why some participants may want to know more than what we currently return

- With careful follow-up, some people, even when informed of increased genetic risk for a medically non-actionable condition, adjust well to the information - they may not develop depression or anxiety after receiving the information

- Such people may even perceive the information as useful - even when it doesn't inform clinical intervention, people may still use the information to take certain action, such as purchasing long-term care insurance or being more conscious of a healthy lifestyle

Possible problems of granting full access to raw data

“DNA Test Results Wrongly Tell Dallas Man He Has Genetic Condition,”
NBCDFW, Dec 4, 2018 (2:20)
https://www.nbcdfw.com/news/health/DNA-Test-Results-Wrongly-Tell-Dallas-Man-He-Has-Genetic-Condition-501927981.html

See also: "The Online Gene Test Finds a Dangerous Mutation. It May Well Be Wrong.”
NY Times, 2 July 2018.
https://www.nytimes.com/2018/07/02/health/gene-testing-disease-nyt.html

So, what should we do?

Should researchers return the following?

- *Medically non-actionable* results
- Carrier status
- Non-medical biological traits
- Ancestry-related information
- Full raw data found on the genotyping chip

Consider the limitations:

- Budget
- Scientific accuracy, clinical certainty
- Ethical implications

Ethical Issues of ROR – the AGHI's approach

In the genotyping informed consent form:

- Clearly state that we plan to return a limited number of ***medically actionable results*** to all participants (currently ACMG59)

When an AGHI participant requests access to raw data:

- Provide ***a separate informed consent process*** to let him or her consider scientific limitations and ethical implications of receiving and using raw data

Ethics of the AGHI:

4 Core Values, again

Transparency/Honesty

- Be honest about limitations to the technology we utilize
- Do not deceive or mislead

Respect

- Avoid exploitation or stigmatization
- Respect privacy
- Avoid causing unnecessary anxiety or confusions

Confidentiality

- Keep sensitive personal information confidential

Fairness

- Reach out to diverse population
- Do not exclude or exploit any specific group of people