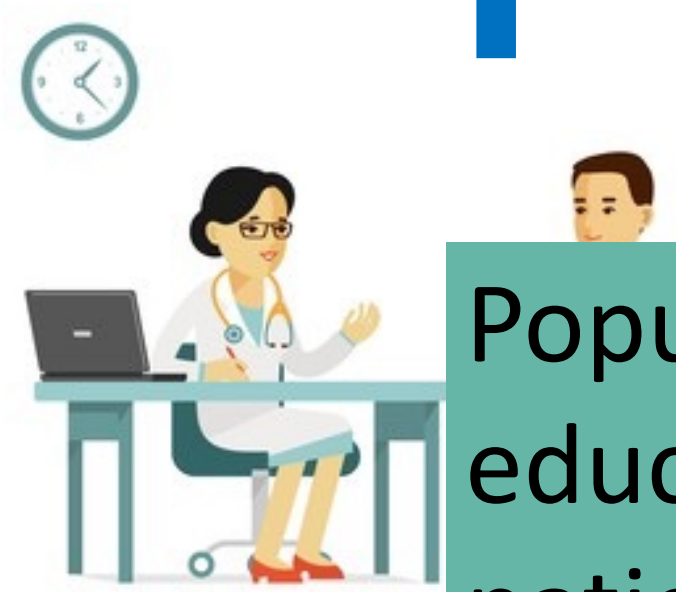
Provider Training and Patient Education: *needs and opportunities*

Kelly East, MS, CGC
Vice President for Educational Outreach
HudsonAlpha Institute for Biotechnology

Population screening can lower some educational barriers to testing access

Genetic testing & analysis



Population screening involves educational barriers to maximize patient benefits and minimize risk

INFORMATION IS POWER

free genetic testing for cancer risk

Cancer risk gene panel for adults in Alabama

Consumer-directed, physician-ordered clinical test

>6,500 and counting

Alabama Genomic HEALTH INITIATIVE

Array-based test for actionable disease risk and PGx for adults in Alabama

Clinical test through research study

Population cohort (2017-2020): 6,420

Primary care cohort (2021+: 1,207 and counting

SouthSeq

ALABAMA KENTUCKY LOUISIANA MISSISSIPPI

Whole genome sequencing (WGS) for affected infants in NICUs at 5 sites

Clinical test through research study

638 probands (2017-2021)

Lessons Learned

Population screening identifies (a lot of) people with an unmet need for diagnostic testing

Family history questionnaires are part of intake AGHI and Information is Power

46% of AGHI participants had a family history with "red flags"*

46% of Information is Power participants had a family history with "red flags"**

*Based on the first 5,369 population cohort participants

**Based on the first 3,514 participants

Personal and/or family history often does not corroborate positive genetic screening results

Table 2. Population cohort variants and rate of corroborating personal or family history.

Disease	Gene[a]	Number of variants identified	Corroborated history # (%)[b]
Hereditary breast and ovarian cancer	*BRCA1*	9	7 (78%)
	BRCA2	11	6 (55%)
Lynch syndrome	*MLH1*	3	1 (33%)
	MSH2	1	1 (100%)
	MSH6	3	0 (0%)
	PMS2	2	2 (100%)
MYH-associated polyposis	*MUTYH*	5 (4 heterozygous, 1 homozygous)	0 (%)
Multiple endocrine neoplasia type 2, familial medullary thyroid cancer	*RET*	2	1 (50%)
Hereditary paraganglioma–pheochromocytoma syndrome	*SDHB*	1	0 (0%)
Hypertrophic cardiomyopathy, dilated cardiomyopathy	*MYBPC3*	9	2 (22%)
	MYH7	5	1 (20%)
	GLA	2	0 (0%)
Arrhythmogenic right ventricular cardiomyopathy	*PKP2*	3	0 (0%)
Romano–Ward long-QT syndrome types 1, 2, and 3, Brugada syndrome	*KCNQ1*	1	0 (0%)
	KCNH2	2	0 (0%)
	SCN5A	2	1 (50%)
Familial hypercholesterolemia	*LDLR*	3	2 (67%)
	APOB	6	5 (85%)
Malignant hyperthermia	*RYR1*	9	1 (11%)

[a]Reportable variation in the following genes have not yet been identified in any Alabama Genomic Health Initiative (AGHI) population cohort participants to date: *TP53*, *STK11*, *APC*, *BMPR1A*, *SMAD4*, *VHL*, *MEN1*, *PTEN*, *RB1*, *SDHD*, *SDHAF2*, *SDHC*, *TSC1*, *TSC2*, *WT1*, *NF2*, *COL3A1*, *FBN1*, *TGFBR1*, *TGFBR2*, *SMAD3*, *ACTA2*, *MYH11*, *TNNT2*, *TNNI3*, *TPM1*, *MYL3*, *ACTC1*, *PRKAG2*, *MYL2*, *LMNA*, *RYR2*, *DSP*, *DSC2*, *TMEM43*, *DSG2*, *PCSK9*, *ATP7B*, *OTC*, *CACNA1S*.
[b]Corroborated history defined as having a relevant reported personal or family history that was flagged by AGHI criteria.

Only 36% of patients with a positive AGHI disease risk finding had a corroborating phx/fhx

Reference: doi: https://doi.org/10.1038/s41436-020-01034-4

Personal and/or family history often does not corroborate positive genetic screening results

These surprising findings can be distressing for patients, and providers to accept and use in decision making

Most management guidelines were based on penetrance/risk levels observed in affected patients/families.

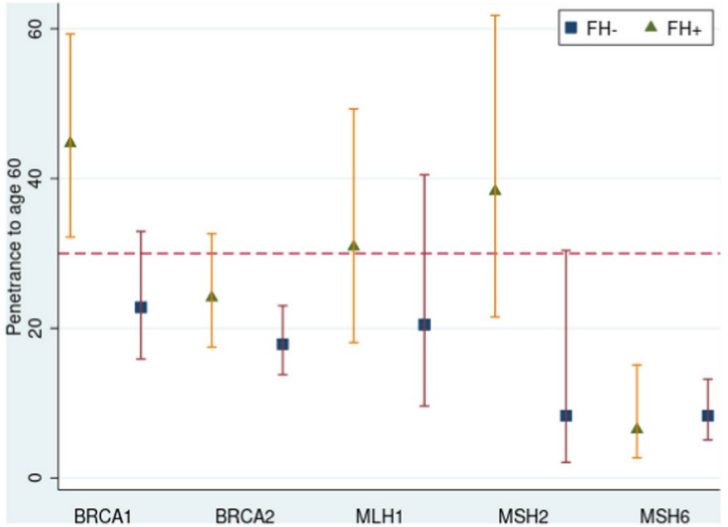
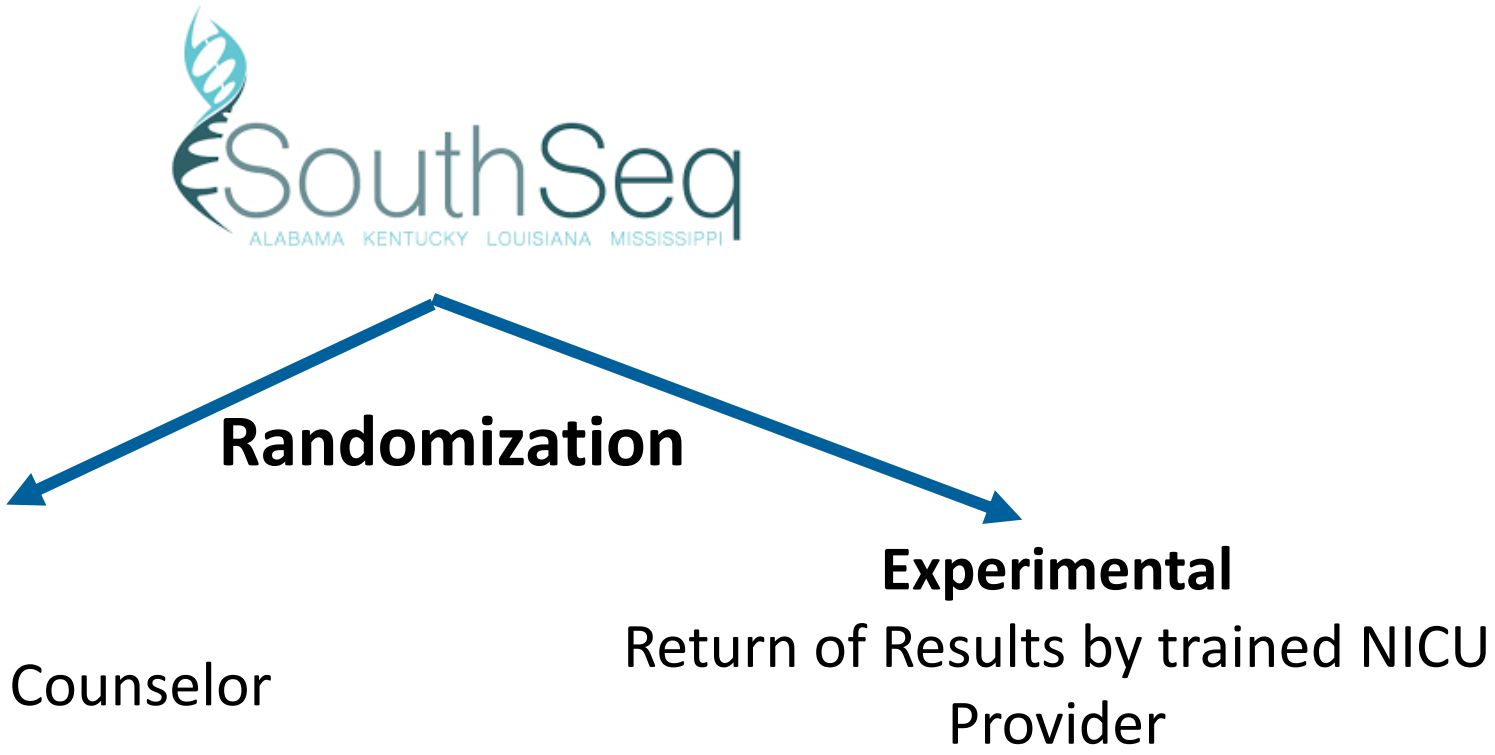


***Fig. 2:* Effect of family history on penetrance to age 60.** Penetrance to age 60 was calculated using the survival model and shown per gene, split by positive or negative family history. Error bars show the 95% confidence intervals. A red dotted line has been added at 30% to indicate the lifetime risk level (note: not risk to age 60) used by NICE to guide enhanced surveillance in women at risk of breast cancer in the UK.[30] These guidelines consider all *BRCA1* and *BRCA2* carriers to be high risk. The latest Mallorca guidelines for Lynch syndrome also suggest enhanced surveillance for all *MLH1*, *MSH2* and *MSH6* carriers.[31] This consists of 2 yearly colonoscopy from age 25 for *MLH1*/*MSH2* carriers and age 35 for *MSH6* carriers.

Reference: doi: https://doi.org/10.1016/j.eclinm.2023.102159

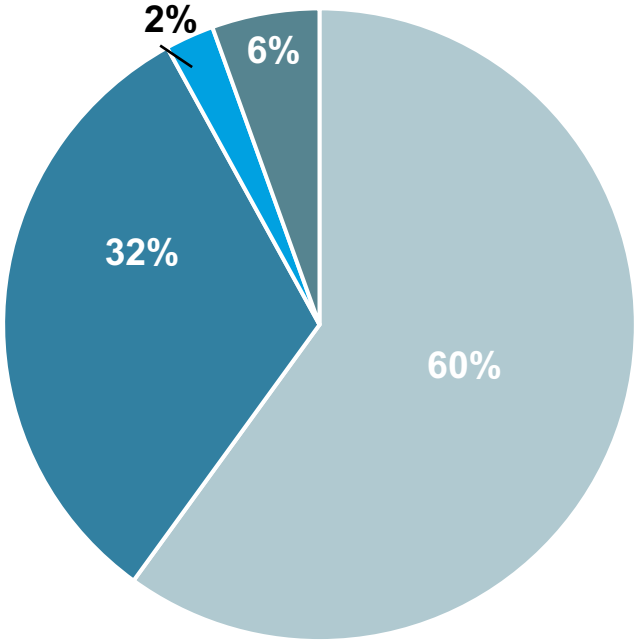
Patients and providers often overinterpret the meaning of negative/uninformative genetic testing results

Leading to false reassurance, particularly in those with personal/family history.



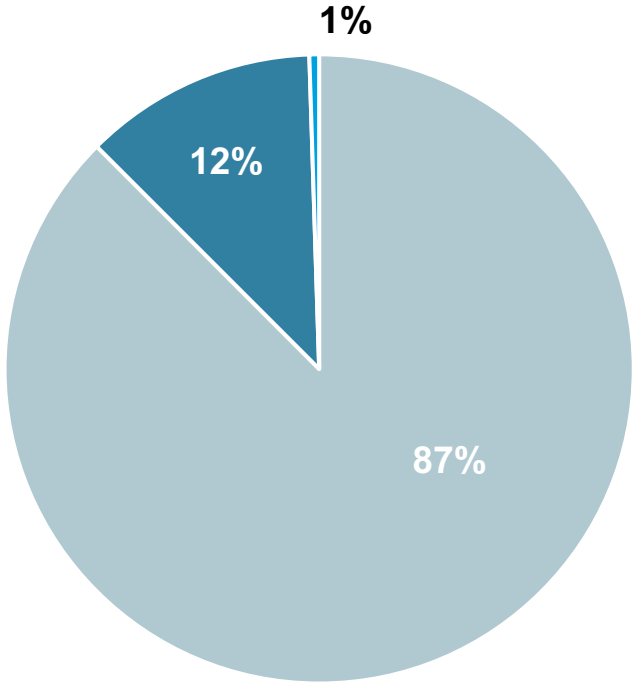
SouthSeq Provider Error Rates

Non-Genetic Providers (n=199 cases)



NGPs were significantly more likely to make both minor ($p=1.6 \times 10^{-5}$) and major ($p=8.3 \times 10^{-4}$)

Genetic Counselors (n=217 cases)



Reference: manuscript in preparation

SouthSeq Provider Errors

Thematic analysis of 20 major errors from 15 different cases

Major Error Theme	Frequency	Illustrative Quote
Overinterpretation of negative results	5	“This means it's not genetic so that's good news because [patients] future children aren't at risk for similar health concerns “ “We’re so glad that it was a negative result. It doesn’t give you any answers but it does show that what happened was not caused by her genes"
Omission of critical details	5	Ex. Provider did not discuss the recurrence risk for a pathogenic result inherited from dad.
Misquoting recurrence risk	4	“This is an autosomal dominant condition so there’s a 25% chance future pregnancies may be affected.”

Reference: manuscript in preparation

Patients and providers often overinterpret the meaning of negative/uninformative genetic testing results

What does it mean for a person's cancer risk if a genetic risk factor *is found* in his or her DNA through Information is Power?		
The person will definitely develop cancer during his or her lifetime.	1	0.5
The person has an increased risk for cancer during his or her lifetime, but may or may not ultimately develop it.*	191	99.5
The person currently has cancer.	0	0.0
The person is not at increased risk for cancer, but his or her children are.	0	0.0
What does it mean for a person's cancer risk if a genetic risk factor is *not found* in his or her DNA through Information is Power?		
The person will definitely not develop cancer during his or her lifetime.	1	0.5
The person has a decreased risk for cancer during his or her lifetime compared to the general population.	52	27.1
The person has the same risk as the general population, unless there are other risk factors known.*	139	72.4
The person does not currently have cancer.	0	0.0

Always some level of residual risk, but the risk level depends on the patient and test ordered. This makes broad education messaging a challenge.

References: doi: https://doi.org/10.1016/j.pec.2020.10.014; https://doi.org/10.1016/j.xhgg.2021.100055

The benefits of population screening extends beyond the patient being tested

Benefit to relatives is often cited as a reason for participating in genetic screening

Many screening findings are dominantly inherited, putting many relatives also at risk

Patients often discuss their results with their relatives

Provider role in facilitating cascade testing is often limited

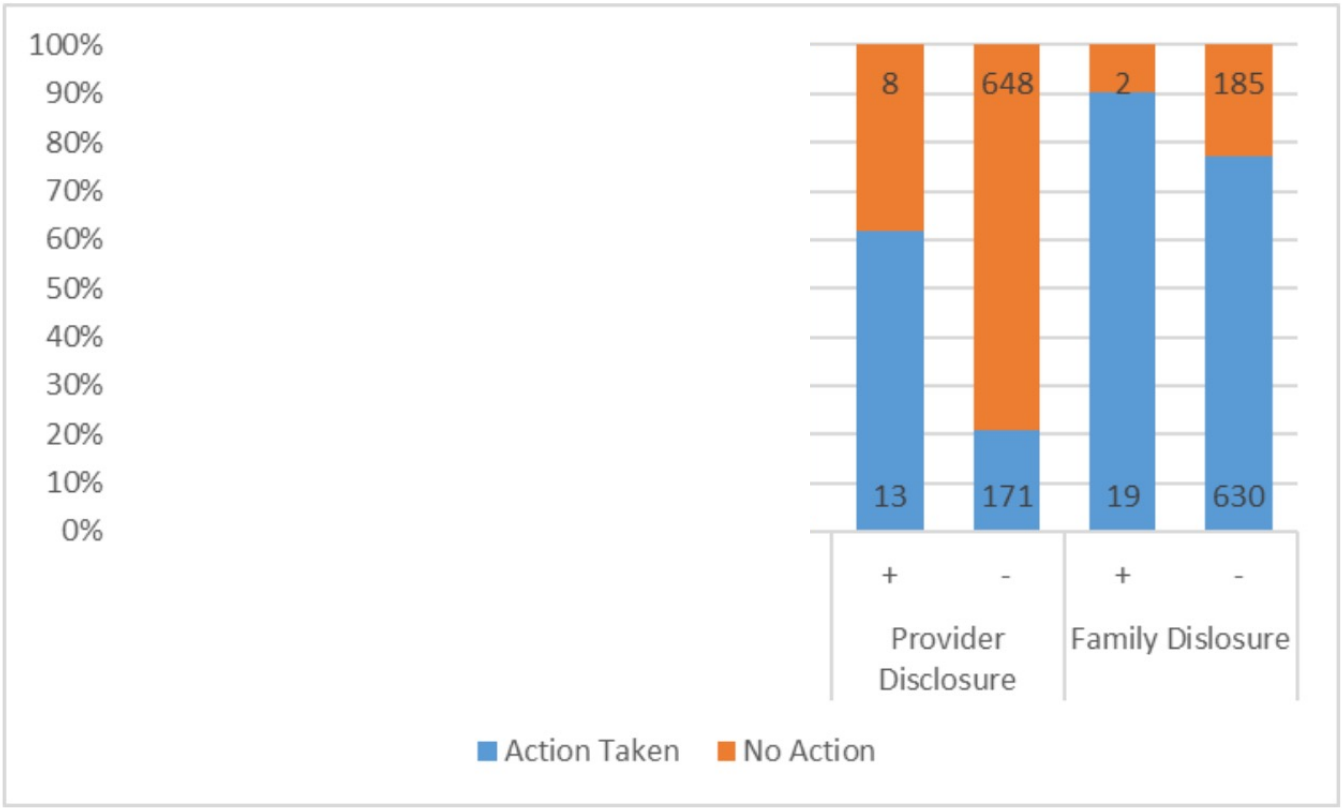
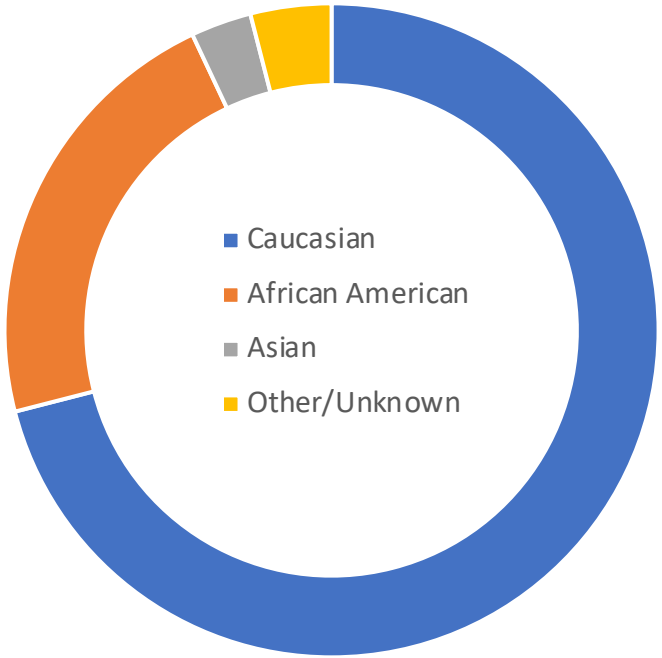


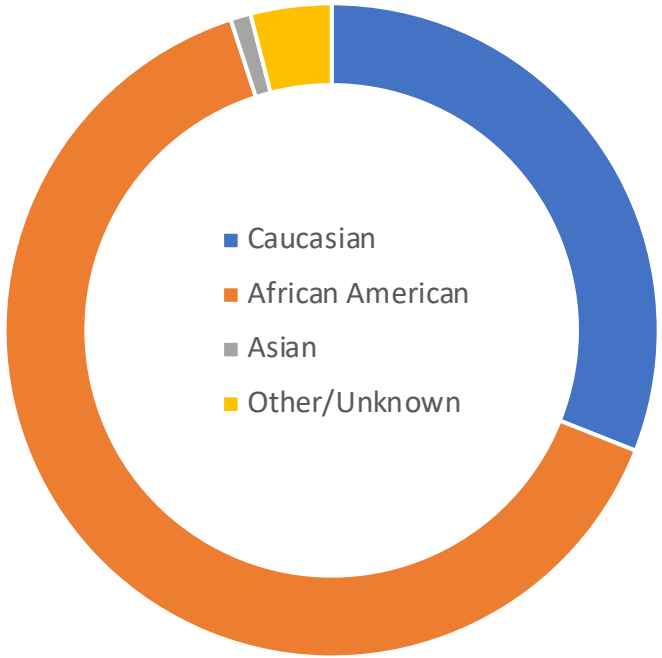
FIGURE 3. Actions taken due to AGHI results. Participants reported action taken in multiple categories, including additional tests, exams, procedures; health and wellness; insurance, result disclosure to provider; and result disclosure to family members. These categories were detailed further by participants with positive results (+) and negative results (-).

Reference: doi:10.1111/cge.14394

Integration with clinical care to improve access to screening and follow-up



AGHI population cohort



AGHI clinical cohort

Reference: doi: https://doi.org/10.1038/s41436-020-01034-4

Integration with clinical care to improve access to screening and follow-up

- Inclusion of results in medical records
- Further evaluation/testing based on phx/fhx
- Care based on genomic findings

Education/training *and* infrastructure needed to help providers know what care or referrals are needed and how to facilitate

Opportunities

- Interpreting and communicating negative results should be emphasized in provider and patient genomics education
- Program infrastructure to support family communication/cascade testing
- Program infrastructure to identify “red flags” in phx/fhx, and facilitate referrals for additional evaluation and testing
- Scalable processes for clinical genetics professionals to provide just-in-time, patient-specific support to non-genetics providers

Opportunities

- More research:
  - Documenting provider knowledge gaps and misconceptions to inform education/training interventions
  - How to identify patients, or result contexts, that are more likely to have low understanding and need more support

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keast@hudsonalpha.org