

It's now been three years since our genomics project, GeneScreen, began. We would like to **thank you** for your participation. We couldn't have done this project without you. We'd also like to share with you what we've learned in the process of carrying out this exciting project!

But first, a refresher . . .

Genetic or genomic screening in the general population has not been widely studied. GeneScreen was a research study conducted in 2016 by a team from University of North Carolina (UNC) and Kaiser Permanente Northwest (KPNW). It was paid for by the National Institutes of Health (NIH).

Most health conditions are caused by a combination of things, including diet, exercise, environment, and genes. For example, colon cancer is usually caused by many factors acting together.

Each factor may only have a small impact on the total chance for a person to develop colon cancer. But in a few families, the biggest reason someone has a health condition like colon cancer is because of a specific change (called a "gene variant") in the DNA in one single gene.



Everyone in the family who inherits that variation has a high genetic risk for developing the disease. In these families, the genetic risk is the most important factor.

The GeneScreen test looked for specific variations in genes that can cause one of 11 health conditions. Most of these were related to either cancer or heart disease. These conditions are serious but can be prevented or treated effectively.



Only 2 in every 100 people will have one of these gene variants.

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The goal of GeneScreen was to learn how to test or screen adults for 11 preventable or treatable genetic health conditions. We also wanted to learn what people think about this kind of genetic screening.

We studied possible harms and benefits by surveying and interviewing people who participated in the screening and those who chose not to. We asked about their motives to join or decline, what they hoped for, who they talked with about GeneScreen, including family members, and after the results were returned, what they thought of them.

Study Questions

1

Which genes should be included in the screening test?

2

Who should participate?

3

What is the best way to carry out this screening project?

4

Should we continue and expand?

Who Joined?

Recruitment began on 2/17/2016 and ended on 5/13/2016.

UNC: 71 / 436 = 16% of those recruited joined.

KPNW: 196 / 650 = 30% of those recruited joined.

The majority of GeneScreen participants (n = 262) were:

- Female (69%), white (79%), older than 61 years (50%), and non-Hispanic (90%)
- Well educated; 76% had at least 4 years of college or a graduate or professional degree
- In receipt of an income of \$75,000 per year or more (54%)

African Americans were least likely to respond to the GeneScreen recruitment letter.

- 93% of African American males did not log in
- 83% of African American females did not log in
- 64-71% of whites and others did not log in



GeneScreen Conditions

LYNCH SYNDROME increases a person's chance to develop several types of cancer, most commonly colon cancer, but women are also at a significantly higher risk for uterine and ovarian cancers.

FAMILIAL ADENOMATOUS POLYPOSIS (FAP) increases the risk for colon cancer and some other types of cancer.

MUTYH-ASSOCIATED POLYPOSIS (MAP) increases the risk for colon cancer and some other types of cancer.

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME (HBOC) increases a person's chance of developing several types of cancer.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN2) increases a person's chance to develop growths (neoplasms) in the endocrine system, the glands that make the body's hormones.

MARFAN SYNDROME causes the connective tissues in the body to be weaker than they should be.

LONG QT SYNDROME is a heart rhythm problem.

FAMILIAL HYPERCHOLESTEROLEMIA (FH) puts people at high risk of early-onset cardiovascular disease.

ALPHA-1 ANTITRYPSIN DEFICIENCY (AAT DEFICIENCY) makes a person much more likely to get certain lung problems and, in some cases, liver disease.

HEREDITARY HEMOCHROMATOSIS is a condition in which people store too much iron in the body. The extra iron builds up in the organs of the body, especially the liver, and can cause problems like cirrhosis, diabetes, and cardiomyopathy.

MALIGNANT HYPERTHERMIA causes a serious reaction to certain medicines used for general anesthesia.

Why Join?

"To learn about my potential risks in life..." "...so I know how to prevent them in the future."

"The desire to share any important info with my children and other family members."

"I have cardiovascular disease, diabetes, hypertension and I would like to know if I have the genes for these."

Why Not Join?

"I am not interested in knowing my risk for future health problems from my genes. At my age (77) I know my current problems and I am aware of future complications . . . I don't have a great deal of confidence that the gene test is accurate and feel it may raise more concerns than cures, especially for family members."

"You can't un-know something once you know it. But the main reason, for me was that the results end up in my medical records. I think I would've been MUCH more willing to participate if the results were kept anonymous, de-identified, or just given to me."

What Happened?

The GeneScreen test identified 15 positive screening results; 14 were confirmed in a clinical laboratory.

7 GeneScreen variants were found:

- ➔ **BRCA2** (n = 2) | Hereditary breast and ovarian cancer syndrome
- ➔ **HFE** (n = 7) | Hereditary Hemochromatosis
- ➔ **KCNQ1** (n = 2) | Long QT syndrome
- ➔ **LDLR** (n = 2) | Familial hypercholesterolemia
- ➔ **RET** | Multiple endocrine neoplasia, type 2
- ➔ **RYR1** | Malignant hyperthermia

What did we learn?

About the technology used for the GeneScreen panel:

- ➔ The test was valid—we compared defining a result as positive using two different technologies and found they were not different.

About the genes chosen for the GeneScreen panel:

- ➔ Social science researchers studied the gene selection process. Investigators chose to include only gene variants related to rare genetic conditions that are both serious and preventable/treatable. Criteria developed to identify these genes included: how rare is the associated medical condition, how severe is it, how effective and acceptable is the prevention/ treatment, and what is the quality of scientific evidence. However, they also relied on more personal, “subjective” opinions in making the decisions.
- ➔ One condition on the panel was Lynch Syndrome. There was considerable support for including it, and for its value to detect and prevent colon cancer. However, in a systematic review of the literature, we found little if any evidence to support its use in a broad public health genetic screening program.

About the relationship of genetic screening for rare conditions and age:

- ➔ Observations of researcher discussions revealed worry about there being less personal benefit for older participants. However, interviews revealed that people of all ages perceived similar benefits, including the benefit of testing family members, as well as similar risks, such as insurance discrimination and worry.
- ➔ Among those who received positive results, most of whom were older, there was little concern, given their age and the type of condition for which they screened positive. In fact, many already knew their risk because of personal or family history.

About joining GeneScreen:

- ➔ People found it relatively easy to make the decision to join. Many made the decision before they even went to the website.
- ➔ People reported they understood the main features of the study. However, more work is needed to make sure web-based recruitment is adequate to replace in-person informed consent.

About getting negative GeneScreen results:

- ➔ The great majority of people in the general population who undergo genetic screening will be negative—95% of GeneScreen participants received a negative results report.
- ➔ Most believed they understood the meaning of their negative result, however 44.3% indicated their results meant that they *definitely did not* have a GeneScreen variant. This is a misunderstanding given the potential for a false negative result, particularly in participants with a prior increased risk for one of the conditions.

Additional work included exploring the ethical frameworks that guided our work and the evidence needed about harms and benefits to move GeneScreen from research to a clinical offering.

A New Measure

Because of concerns about people misunderstanding the limitations of a negative screening results report, we developed a better tool to measure understanding. It includes 13 true-false statements that evaluate the effectiveness of education materials for people who receive negative results in genetic screening tests. We hope that this measure will be used with patients and research participants to help clinicians develop specific educational materials so that people understand risk appropriately.

GeneScreen 2.0

The UNC Health Care system is providing the UNC School of Medicine with \$10 million over five years to focus on delivering precision medicine to every patient. The Program for Precision Medicine in Health Care will work with programs across the School of Medicine to translate genomic technologies and data analytics into clinical care for UNC Health Care patients. One high priority area is to implement an adult genomic screening program.

The UNC PPMH plans to offer a genetic screening panel test like GeneScreen in general practices, as part of yearly wellness exams. This panel will include the Centers for Disease Control Tier 1 conditions. Nearly 2 million people in the United States are at increased risk for adverse health outcomes because they have genetic variants which predispose them to one of the following conditions*:

- ➔ Hereditary Breast and Ovarian Cancer Syndrome (HBOC) – increased risk for breast, ovarian, tubal, peritoneal, and other cancers due to mutations in BRCA1 or BRCA2 genes;
- ➔ Lynch syndrome (LS) – increased risk for colorectal, endometrial, ovarian, and other cancers associated with mutations in mismatch-repair genes; or
- ➔ Familial hypercholesterolemia (FH) – increased risk for heart disease or stroke due to mutations leading to very high cholesterol levels from an early age

**These conditions were on the original GeneScreen panel.*

Alongside this program, we will implement GeneScreen 2.0. We will: investigate factors related to accepting or not accepting this clinical offering of screening; study the response to positive and negative results; test a tool to enhance understanding of negative screening results; follow cascade (family) testing offers, and observe community responses to the offer of cascade testing. We will also explore clinician responses to the screening, and factors related to their offering it to patients.

Contact Us

If you'd like more information about the study, please contact:

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GeneScreen Publications

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