Development of cell-free nucleic acid-based tests for detection of invasive breast cancer: The STRIVE Study

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Rationale

Mammography (digital or tomosynthesis) is the cornerstone of screening for breast cancer, but new approaches are needed to further reduce the rate of late stage cancer diagnosed and more effectively identify women in need of additional testing and diagnostic biopsy.

Circulating cell-free nucleic acids (cfNAs) shed from tumors can be isolated from the peripheral blood (FIGURE 1) and analyzed with ultra-deep and broad sequencing of cancer-associated genes[1].

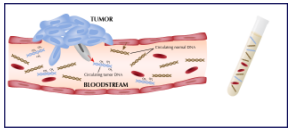

FIGURE 1: Blood test development will be based on a high-intensity sequencing approach (ultra-deep and ultra-broad). Blood components include, but are not limited to, plasma cell-free nucleic acids (cfNAs). NAs isolated from circulating cells, and exosomes.

GRAIL, Inc. (www.grail.com) aims to develop blood cfNA screening tests capable of detecting many cancer types and providing information on the tissue of origin. Such tests could be used in concert with established risk factors and/or radiographic features to improve early cancer detection. Development and validation of these tests and related algorithms will require large, well-annotated prospective cohorts of asymptomatic participants. The STRIVE Study is the first of several planned prospective cohorts to be assembled for this product development.

Study Objectives

- Determine the ability of a blood cfNA test and algorithm to identify breast cancer in a cohort of women undergoing screening mammography.
- Determine the ability of a blood cfNA test and algorithm to identify breast cancer in women with a higher likelihood of cancer missed by screening mammography.

References and Acknowledgements

1. Aravanis AM, Lee M, Klausner RD. *Next-Generation Sequencing of Circulating Tumor DNA for Early Cancer Detection*. Cell. 2017 Feb 9;168(4):571-574.

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Study Design

Overview

The STRIVE Study is a prospective cohort study of 120,000 women undergoing screening mammography that will be used to train and clinically validate a new blood test for breast cancer detection. Participants diagnosed with cancer and a random sample of participants without cancer will be included in training and validation analyses.

Participating sites

Mayo Clinic: MN, WI, FL, AZ
Sutter Health, CA;
Additional centers will activate in late 2017.

Patient eligibility

All women scheduled for routine screening mammograms are eligible. Blood must be drawn within 28 days of the mammogram and before any biopsy occurs.

Recruitment and consent

Potential participants are informed about the study in advance of their mammogram appointment. Coordinators are present in the clinic to answer questions. Efforts are made to minimize any disruption to clinic flow. At many centers, informed consent occurs electronically and can be signed remotely.

Blood draws

Participants provide 4 x 10 mL blood samples in Streck tubes within 28 days of their mammogram (FIGURE 2). Blood is shipped at ambient temperature to a central lab for processing and storage. Additional blood samples are requested from:

- Patients recalled for additional evaluation due to an abnormal screening mammogram at baseline
- Patients diagnosed with cancer 90+ days after baseline

Electronic questionnaire

Participants complete a cancer risk factor questionnaire (FIGURE 3) online using any electronic device.

Medical record data

Pertinent clinical information (including breast density and mammography results) and follow-up information will be transferred electronically to a central database.

Follow-up

Participants will be followed for all incident cancers for at least 30 months via rapid review of electronic pathology and health records information. Regular linkages with state and national cancer and vital statistics registries will be performed. Outreach will include newsletters and updates to the study website (www.joinstrive.com). Active follow-up will be used to confirm participant cancer status prior to sequencing.

Statistical methods

The study will be divided into training and validation phases. In the training phase, statistical machine learning techniques will be used to develop algorithms incorporating cfNA signals, clinical characteristics, or radiological features. In the validation phase, the prespecified locked algorithm developed from the training phase will be clinically validated in an independent group of women.

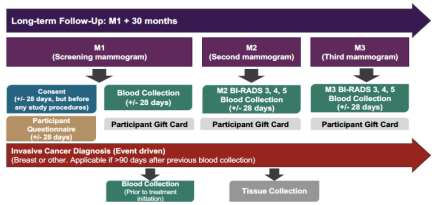

FIGURE 2. STRIVE Study schedule of events. Purple events are scheduled mammograms. Green events indicate blood collection and banking.

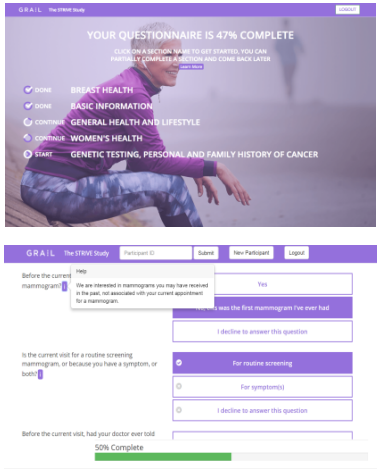

FIGURE 3: Custom participant questionnaire optimized for administration on mobile devices. 100% of questionnaires will be administered electronically.

Cohort Characteristics

Characteristics of STRIVE Study participants, December 2017

Age at enrollment (years, %)	
<40	1
40-49	20
50-59	30
60-69	29
70+	20
Race/ethnicity (%)	
White	86
Hispanic	3
Asian or Pacific Islander	5
Black/African-American	2
Multiple races or other	3
Don't know/decline to answer	1
Breast density at screening mammography (%)	
a	9
b	39
c	40
d	13
Other selected characteristics (%)	
Have a 4 year college degree or higher	65
Have had a mammogram before	97
Have had a mammogram in prior 24 months	80
Had their last mammogram at the same facility	89
Had a prior benign breast biopsy	27
Menopausal	70
Current smoker	3

TABLE 1: Characteristics of participants recruited from February to December 2017 as part of the STRIVE Study.

Implications for the Future

- The STRIVE Study will be used to train and validate new cfNA tests and related algorithms for the early detection of breast cancer and later, for multiple, other cancers.
- cfNA-based tests have the potential to improve detection in women at high risk of an occult cancer after routine breast imaging, such as women with dense breast tissue.
- A sensitive test could better identify those mammographic abnormalities that are most likely to be malignant, thereby reducing the number of unnecessary work-ups for lesions with no clinical significance.
- This effort will create a new large, prospective resource for studying the performance of contemporary screening and diagnostic mammography among population subgroups.
- The study implements a number of technologies to enable multicenter recruitment and data collection at a large scale and on a short timeline.
- In addition to remote electronic consent and online questionnaires with mobile-first design, we are developing innovative approaches for automated collection of other data, including timely follow-up for cancer diagnoses and electronic health record ingestion.
- The study is an important collaboration between academia and industry to build a prospective mammography cohort to enable a multitude of scientific inquiries.