Grail to pour $1 billion into blood test to detect early cancer

Illumina spin-out Grail plans to invest over $1 billion in early-stage cancer detection using liquid biopsy approaches. The unprecedented private equity investment, which is due to close in the current quarter, will enable Grail to pursue its lofty aims of revolutionizing cancer diagnostics and ultimately transforming patient outcomes. Recruitment has already begun for a pilot trial called the Circulating Cell-Free Genome Atlas (CCGA) study, which will compare the cell-free nucleic acid profiles of 7,000 newly diagnosed cancer patients with those of 3,000 healthy volunteers, to build a genomic picture of early-stage cancer. This is a prelude to a series of much larger studies that will recruit hundreds of thousands of participants, who will be followed longitudinally in an effort to pinpoint the onset of cancer much earlier than is the case today.

Few would argue with the basic premise that early cancer detection is a good idea—it is generally the best prognostic indicator. Whether circulating tumor DNA (ctDNA) analysis, a potentially powerful but still emerging technology, is sufficient for that task is an open question for now—but one that Menlo Park, California–based Grail will be able to interrogate from multiple angles. Its ambitions extend beyond that goal, however. It aims eventually to lower the cancer burden by fostering new treatment paradigms that offer substantial improvements over current standards of care. "Otherwise you don't have utility, you just have detection," says Mark Lee, Grail's head of clinical development and medical affairs.

That circulating DNA from cancer cells is present in blood has been recognized for decades, but the recent emergence of ultrasensitive DNA sequencing methods has transformed its status from biological curiosity to invaluable analyte (*J. Clin. Med.* **6**, E3, 2017). "From a technology standpoint, it's early days," says Alex Aravanis, head of R&D at Grail. ctDNA-based testing is already used to guide therapy selection and to monitor treatment responses in patients with advanced cancer (*Nat. Biotechnol.* **34**, 1090–1094, 2016). But early detection in otherwise asymptomatic individuals requires far greater levels of sensitivity, as the levels of ctDNA in circulation correlate with tumor burden. "The field has some anecdotal data—it's starting to become more than that," he says. Grail expects to generate data for internal company use this year but will keep the CCGA study open until 2022 in order to follow participants' outcomes. It is by no means clear at this point, however, that ctDNA analysis will work for all cancers—levels of detectable ctDNA vary considerably across different indications (*Sci. Transl. Med.* **6**, 224ra24, 2014).

Kiyoshi Takahase Segundo / Alamy Stock Photo

Grail will characterize circulating cell-free DNA profiles using ultra-broad and ultra-deep sequencing to develop a blood test for early cancer.

The big attraction of ctDNA analysis—and other liquid biopsy approaches, such as exosome analysis—stems from their low cost and ease of use. Although tissue biopsy remains the gold standard for confirming a cancer diagnosis at present, a single sample may not necessarily give a complete molecular picture of a particular cancer. Inconsistent or confounding results often arise due to genomic heterogeneity either within an individual tumor or between a primary tumor and distal metastases (*N. Engl. J. Med.* **366**, 883–892, 2012). Moreover, obtaining a biopsy is costly, invasive and, for some patients, potentially risky. Liquid biopsies, which require only a blood or urine sample, enable surveillance of diagnosed cancers to be conducted with far greater frequency than current methods allow. Aravanis notes that current screening approaches, such as prostate-specific antigen test, mammography and, in the case of lung cancer, low-dose computed tomography, are indirect measures of cancer and can give rise to large numbers of false positives. "Because circulating tumor DNA is a more direct measure of cancer and represents the genomic diversity of cancer throughout the body," he adds, these tests can deliver improved sensitivity and specificity for early cancer detection.

Grail's ultimate goal, to develop a ctDNA-based pan-cancer test for early detection of multiple cancer indications, will require very large-scale longitudinal studies. In the meantime, the company plans to introduce tumor-specific individual screening tests first, although it is keeping its plans under wraps for now. For ctDNA analysis to become clinically useful in cancer detection—at whatever stage—the usual rules apply: its sensitivity, specificity and predictive value need to be firmly established in defined populations. "The question is whether your technology is sensitive enough," says Laura van't Veer, professor of laboratory medicine at the School of Medicine of the University of California, San Francisco, and the inventor of MammaPrint, a genomic test that predicts the risk of post-surgical recurrence of breast cancer based on the expression profiles within tissue biopsies of a 70-gene panel. The confirmatory study, MINDACT, enrolled 6,693 breast cancer patients (*N. Engl. J. Med.* **375**, 717–729, 2016). Although applauding the Grail initiative, van't Veer retains an open mind on its feasibility. "I would wonder whether a one million [individual] cohort of the general population would be large enough to prove that this approach would be more effective than screening," she says. She favors starting with high-risk groups and working back to the broader population.

Table 1 Selected large-scale cancer screening and profiling studies

Study	Principal investigators	Goal	Indications	Analytic methods	*N*
The Circulating Cell-free Genome Atlas Study	Amy Sehnert (Grail)	Development of models for early cancer detection based on circulating tumor (ct) DNA, by comparing cell-free (cf) DNA profiles from newly diagnosed cancer patients with those of healthy controls	Solid tumors	Deep sequencing of ctDNA isolated from peripheral blood	10,000
iStopMM (Iceland Screens Treats or Prevents Multiple Myeloma)	Sigurdur Kristinsson (University of Iceland, Reykjavik), Ola Landgren (Memorial Sloan Kettering Cancer Center, New York)	Establishing whether screening individuals to identify those with the precursor syndrome monoclonal gammopathy of undetermined significance (MGUS), combined with early intervention, improves outcomes	Multiple myeloma	Serum protein electrophoresis and light-chain analysis of all subjects; immunofixation and whole-genome sequencing of those with MGUS	140,000
Utility of Plasma Circulating Tumor DNA (ctDNA) in Asymptomatic Subjects for the Detection of Neoplastic Disease	Glenn Braunstein, Judy Neidich (Pathway Genomics, San Diego)	Early detection of cancer in high-risk asymptomatic individuals using ctDNA analysis of 96 prespecified mutations in nine cancer driver genes	Any neoplasm	ctDNA analysis	1,000
Clinical Utility of Circulating Tumor DNA (ctDNA) Analysis by Digital Next-Generation Sequencing of Over 5000 Advanced NSCLC Patients	Philipp Mack (University of California, Davis, Sacramento, California)	Retrospective ctDNA profiling using the Guardant360 instrument to identify cancer-associated mutations in a panel comprising 54–70 genes	Non-small-cell lung cancer	ctDNA analysis	5,206
Concordance Between ctDNA Assay and FoundationOne	Phil Stephens (Foundation Medicine)	Testing whether Foundation Medicines ctDNA assay to detect genomic alterations is consistent with results obtained from genomic profiling of tissue biopsy	Solid tumors	ctDNA, genomic analysis of primary tissue biopsies	2,000

Sources: Clinicaltrials.gov, myeloma.org, http://wclc2016.iaslc.org

That's the approach that Guardant Health, of Redwood City, California, has adopted. The company is already marketing a ctDNA-based test, Guardant360, for patients with advanced solid tumors. It will soon introduce its first ctDNA-based test for cancer survivors, for whom there are no adequate methods of detecting early recurrence. The test, called Lunar I, will be aimed at five forms of cancer initially: lung, pancreatic, breast, ovarian and colorectal. It will have a sensitivity ten times greater than that of the Guardant360 system, at much lower ctDNA concentrations, says CEO Helmy Eltoukhy. "We're approaching the single-molecule limit in a tube of blood," he says. "We're now approaching the theoretical limit of detection." Lunar I will, however, cover just a fraction of the 73 genes included in the Guardant360 panel. "It's not used for therapy selection," he says. Its main purpose is simply to detect cancer recurrence, after which patients would then undergo further analysis and treatment. "We believe there'll be a large personal utility component with Lunar," Eltoukhy says. It will cost less than $1,000, whereas a Guardant360 test has a list price of $5,000.

Guardant is also working on a second iteration of Lunar, which it will aim at high-risk, asymptomatic individuals, such as smokers, carriers of *BRCA* mutations and those with a family history of cancer. Guardant, like Grail, will need to assemble very large cohorts in order to generate useful information. "With Lunar II we estimate we need to get into the hundred thousand or hundreds of thousands to get enough data to know what cancer looks like and, more importantly, what cancer does not look like," says Eltoukhy. The company has obtained 30,000 samples to date, but that number will rise to 100,000 within the next 24 months, he says.

Large-scale, private-sector research efforts such as these (**Table 1**) are getting under way just as a pioneering public-sector initiative, The Cancer Genome Atlas (TCGA), is drawing to a close. TCGA, led by the National Cancer Institute (NCI) and The National Human Genome Research Institute (NHGRI), has been a comprehensive effort to characterize the genomic basis of several dozen cancers. It has provided much of the baseline genomic information that is informing newer, more sensitive analyses enabled by new sequencing technologies. "These are very young technologies. There are not so many datasets being created," says TCGA director Jean Claude Zenklusen, of the NCI. That will change over time, and Zenklusen hopes that the organizations that generate the data will share them with the wider scientific community. "One of the for-profit entities that is giving us data is Foundation Medicine," he says referring to an agreement the Cambridge, Massachusetts–based cancer genomics firm entered with the NCI last year to supply data to the latter's Genomic Data Commons portal. "It's important that the data are not just available but usable," adds Carolyn Hutter, program director at the NHGRI. Grail's Mark Lee indicates the company will be open with its data. "We fully expect, with a resource like CCGA, to contribute to the field," he says. "It's not like we're trying to close this off and not collaborate."

Even before ctDNA-based analyses become widely adopted, the cancer burden trend in the US, which is based on both incidence and survival, has been falling. According to a recent analysis from the American Cancer Society, the cancer death rate declined during 2005–2014 by about 1.5% annually in both men and women. By 2014, the mortality rate had dropped 25% from its 1990 peak. The disease burden remains substantial; the same study forecasts 1,688,780 new cases and 600,920 deaths from cancer in 2017 (*CA Cancer J. Clin.* doi:10.3322/caac.21387, 2017). The emergence of flexible liquid-biopsy-based technologies for interrogating the molecular drivers of cancer should in the years ahead give many patients and their physicians a better fix on the principal genomic characteristics of their cancers and a better chance at making the correct treatment decisions in a timely fashion. A significant impact would be reflected in further improvements in survival.

Cormac Sheridan *Dublin*