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Early Cancer Detection: Will New Screening Technology Disrupt Cancer Care?

by Ben Comer

The emergence of multi-cancer blood tests for early detection is captivating investors and driving multi-billion-dollar acquisitions. Companies such as GRAIL, Thrive Earlier Detection and Guardant are predicting revolutionary change in the way cancer is diagnosed and treated. The biggest hurdle, however, may be coaxing health care systems and health insurers to join the revolution.

Early cancer detection diagnostics, along with the success of anti-smoking campaigns, are the two biggest reasons for declining mortality rates in cancer over the last several decades, even as immunotherapies, precision oncology treatments and other innovations targeting late stage cancers are improving outcomes – to an extent. To truly bend the mortality curve in oncology, early cancer detection is needed beyond the five cancer types for which routine screening products and national guidelines already exist: breast cancer, cervical cancer, prostate cancer, colon cancer and lung cancer in high-risk individuals, according to a growing number of clinicians and cancer researchers, and early detection diagnostics product developers.

In late October 2020, *In Vivo* and *MedTech Insight* convened a virtual panel to better understand the potential impact of early, multi-cancer detection diagnostics, as well as the significant challenges to broad adoption and commercialization. Panelists included Sam Asgarian, chief medical officer, Thrive Earlier Detection; Helmy Eltoukhy, CEO, Guardant Health; Harris Kaplan, managing partner, Red Team Associates and CEO of Healogix; and Azra Raza, Chan Soon-Shiong professor of medicine and director of the MDS Center at Columbia University in New York City. Raza, an oncologist and researcher who has treated cancer patients for over 20 years, lost her husband, Dr. Harvey Preisler, director of the Rush Cancer Institute in Chicago, to lymphoma in 2002. He was 61 years old.

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Raza, author of *The First Cell: And the human costs of pursuing cancer's last*, published in October 2019, is an outspoken advocate for early cancer detection. "Early detection can be curative for a lot of patients," said Raza. Currently in the US, "we are spending something like $27bn in screening measures, and we detect 9 million positive cases," said Raza. "But of those 9 million, only 200,000 are real cancers, and 8.8 million are false positives. We need sophisticated molecular and genetic markers for screening healthy individuals, to find illness before it has become a bona fide clinical disease, and to prevent it. We are still using the old techniques of slash, poison and burn [to treat cancer] and that has got to stop."

High false positive rates in single cancer detection may contribute to adoption and reimbursement barriers for emerging multi-cancer early detection diagnostics, a situation similar to the way that adverse immune responses to early cell therapies in the 1990s created a higher burden of proof for the next generation of cell and gene therapies. Single cancer screening tests save lives, but they "focus on sensitivity, and give up on specificity, which leads to a lot of false positives," Josh Ofman, chief medical officer and external affairs at GRAIL, an early cancer detection diagnostics company, told *In Vivo*. "The efficiency to find cancer today is pretty poor. You're spending most of your money on false positives; it can cost on average up to around $90,000 to $100,000 to diagnose a case of cancer today."

Early Multi-Cancer Detection

Early studies point toward wider detection and lower false positive rates with multi-cancer screening technology, or 'liquid biopsy,' which requires only a blood draw, instead of the standard tissue biopsy for making a cancer diagnosis. And the market for molecular diagnostics in cancer is expected to grow substantially in the next five years, according to Meddevicetracker *(see Exhibit 1)*.

Exhibit 1.

Country/region	2019	2020	2021	2022	2023	2024	CAGR (%) 2019-24
US	245	251	259	268	279	292	3.6
5 Euro*	119	125	133	143	156	173	7.7
Japan	34	36	38	41	44	49	7.2
RoW	295	328	479	537	593	646	16.9
Total	**694**	**741**	**909**	**989**	**1,073**	**1,159**	**10.8**

*Source: *5 Euro = five major European markets of France, Germany, Italy, Spain and the UK*
Source: Meddevicetracker, 'Molecular Diagnostics' September 2020

Thrive Earlier Detection, which launched just over a year ago with $110m in series A financing, is developing the CancerSEEK liquid biopsy, a technology licensed in from Bert Vogelstein's lab at Johns Hopkins University. In October, Thrive was acquired for $2.15bn by Exact Sciences Corp., a cancer screening and diagnostics company marketing the Cologuard screening test for colon cancer, as well as Oncotype tumor profiling tests that help guide treatment decisions for cancer patients.

In its interventional DETECT-A study, published in April 2020, Thrive screened 10,000 healthy women aged 65 to 75 for multiple cancers, and detected 26 previously unknown tumors among the participants, or twice the number found with conventional screening. The two key outcomes of the study, said Asgarian, were to "detect cancer early enough so that the treatment is curative, and to find of it we can do it in a safe way." Notably, cancer types with no currently approved screening test, such as ovarian cancer, were detected in the study. There were 101 false positives. The study was a success, and Thrive now plans to "work very closely with the FDA" to design a pivotal registration trial across multiple cancers.

Primary Care Coordination

GRAIL is also developing a liquid biopsy test for multiple cancers, called the Galleri test, capable of detecting over 50 cancer types at early stages. Originally spun out of Illumina, a genomic sequencing company, in 2016, GRAIL attracting high profile investors including Jeff Bezos and Bill Gates, as well as pharma companies including Johnson & Johnson, Bristol-Myers Squibb and Merck & Co. In September 2020, Illumina announced that it would acquire the company back for $8bn. Of the 50 cancers the Galleri test can detect, 45 have no recommended screening, Ofman notes, adding that "70% to 79% of all cancer deaths in the US occur in cancers that don't have a recommended screening test at all." The FDA granted a breakthrough device designation to the Galleri test in May 2019, but the company plans to launch the product as a lab-developed test in 2021. Potential FDA clearance for the test is still "a couple of years out," said Ofman.

Studies conducted by GRAIL, including the STRIVE prospective study of 100,000 women receiving mammograms, the SUMMIT study of 25,000 men and women ages 50 to 77 with a high risk of lung cancer, and most recently, the investigational PATHFINDER study enrolling 6,200 patients and evaluating the impact of the Galleri test in clinical practice, aim to demonstrate the utility of multi-cancer early detection. The PATHFINDER study is important in that it addresses a needed shift to primary care for early detection, and treatment guidance, something GRAIL and Thrive see as the future.

Since the multi-cancer tests also predict a tissue of origin, such as ovarian or head and neck, for

example, physicians can evaluate those signals in specific locations or regions, or refer the patient to the appropriate specialist to the do the work-up. “Right now, we practice sick care, secondary and tertiary care beyond the reach of primary care providers,” said Asgarian. With a simple blood draw, a primary care doctor can “work with the patients and population that he or she knows so well. They are diagnosing diabetes, allergies, all these other diseases and illnesses, and now they will have the tool and can do the same thing but apply it to cancer. Not to treat it, but to coordinate the care and allow a specialist to see it at an earlier stage where the treatment can be curative.”

Guardant Health was founded in 2012 and taken public in 2018. The company’s Guardant360 liquid biopsy test has been validated by more than 150 peer-reviewed publications, and more than 150,000 tests have been used to date. However, the Guardant360 test is used for genomic profiling in advanced cancer patients, to guide drug therapy decision-making. For example, it serves as a companion diagnostic for AstraZeneca’s non-small cell lung cancer drug Tagrisso (osimertinib). Guardant360 is “able to detect very low concentrations of cell-free DNA and reconstruct the genomics of the tumor in those patients. Then we can match the mutations in the genome with the best possible therapies,” said Eltoukhy, Guardant’s CEO. Guardant is currently testing its LUNAR-2 assay in the 10,000-volunteer ECLIPSE trial for the early detection of colorectal cancer. “When we started the company eight years ago, there was $90m total of NIH funding for early detection, out of 10s of billions of dollars. Now you see the funding rounds, with Thrive, with other companies, with Guardant. It has been gratifying to see that investors really do appreciate the impact that early detection can have on this space.”

Reimbursement Challenges

Despite the dazzle of early study results for multi-cancer screening, real challenges exist in driving adoption and product reimbursement. Part of the reason that Guardant is going after early detection of colorectal cancer in its ECLIPSE study, is because the pathway to commercialization has already been forged by companies like Exact Sciences and Cologuard. “The technology is moving against reimbursement headwinds,” said Kaplan at Red Team Associates. “When it comes to screening, I think payers are very sensitive to paying twice.” For example, if a patient gets a positive result from an Exact Sciences Cologuard test, which costs $600, the next step is a colonoscopy to confirm the result. Even so, revenues for Exact Sciences’s cancer screening tests tripled between 2017 and 2019, according to Meddevicetracker. And more than 335,000 Cologuard tests were covered by Medicare in 2018, with payments of over $170m *(see Exhibit 2*).

Exhibit 2.

Company	2017	2019	CAGR (%) (2017-2019)

Exact Sciences	266.0	815.1	75.1
Myriad Genetics	679.4	789.4	7.8
Genomic Health	340.5	403.5	8.9
Foundation Medicine	91.7	343.0	93.4
Guardant Health	42.1	180.5	107.1
NeoGenomics	68.2	115.6	30.2
Agendia	15.0	26.0	31.7
Biodesix	20.0	19.1	-2.3
MDxHealth	27.7	8.1	-46.1
MetaMark	4.0	2.1	-27.4
Total (excluding Others)	**1,554.6**	**2,702.3**	**31.8**

Source: Meddevicetracker, 'Molecular Diagnostics' September 2020

Many companies are now working to develop early detection diagnostic technologies. But the extent to which new screening technology will be adopted by the health care system, and how quickly, remains an open question. There is a pathway in colorectal cancer screening, paved by Exact Sciences, which "laid out the way to get into clinician workflows, into screening guidelines, and most importantly, to get reimbursement, because we're piggybacking on colonoscopy where multiple studies have shown the med-health benefit … that helps thing move much more quickly," said Eltoukhy.

"I would say that 80% of the challenge is actually getting a technology that works into the health care system, changing the standard of care, changing clinician workflows, getting reimbursement, getting into [screening] guidelines … all of those things are frankly much harder and a much bigger expense" than technology development, said Eltoukhy. "We're starting with a single cancer, but then we're going to multi-cancer quickly, with liquid biopsy for the metastatic setting starting with lung cancer and then expanding horizontally from there to over a hundred cancer types. We believe the same thing can happen in early detection, but you really have to pick your beachhead."

Companies such as GRAIL and Thrive may need more data, in the form of long-term, multi-year studies, to demonstrate overall survival, in order to get over reimbursement hurdles and accelerate adoption of early detection for multiple cancers. There is also the issue of positive early cancer results in healthy, asymptomatic patients. Raza acknowledged that widespread multi-cancer screening would be very hard to apply to the entire population right away. There is also the danger associated with a positive test screening. "If today I go and get my blood tested for circulating tumor cells and they come and tell me Dr. Raza, we are finding adenocarcinoma cells hanging around in your blood, the next thing I'll do for myself is run to get a PET scan, and see which gland in my body is producing cancer," said Raza. "Let's say the PET scan comes back negative. Now what do I do? How many times do I repeat this blood circulating tumor cell test on myself? And should I schedule another PET scan in six months? It's going to expose me to a lot of radiation. And all these months I'm going to be very anxious."

Ultimately, however, detecting a cancer early means there's more chance to manipulate it to the patient's advantage, Raza believes. Earlier cancer detection may also lead to better treatment options, if screening tools are used for clinical trial recruitment to investigate new therapies. "We think this is going to be really helpful for drug developers who are trying to test the value and effectiveness of their products in earlier stage cancers," said Ofman. "The problem we have right now is that we don't detect very many early-stage cancers, so it's really hard for [biopharmaceutical companies] to study their drugs" in those cohorts.

Screening Guidelines

Thrive and GRAIL would both like to see their multi-cancer screening tools added to cancer screening guidelines that already exist. "Once a year, if you're over the age of 50, which means you're at an elevated risk of cancer, add a multi-cancer early detection blood test, so we can look for all those other cancers," said Ofman. "We'll find some additional breast cancer, colon cancer, others … but the majority of the value will be finding cancers that we're not currently screening for."

According to Raza, the US health care system does not have a choice about moving to early cancer detection, and away from the current focus on extending life in advanced stages of cancer. She uses the acronym "CRUSH" to describe the problem: Complexity of cancer addressed by Reductionist approaches, creating Ultra hype about minor advances (in mouse models), paired with Simplistic clinical trials, and High fiscal cost. "It's unconscionable that 42% of people who are diagnosed with cancer lose every penny of their life savings in two-plus years," she said. "It's obscene, and we shouldn't be doing it."