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HEALTHCARE INNOVATION IS REVOLUTIONIZING CANCER DETECTION

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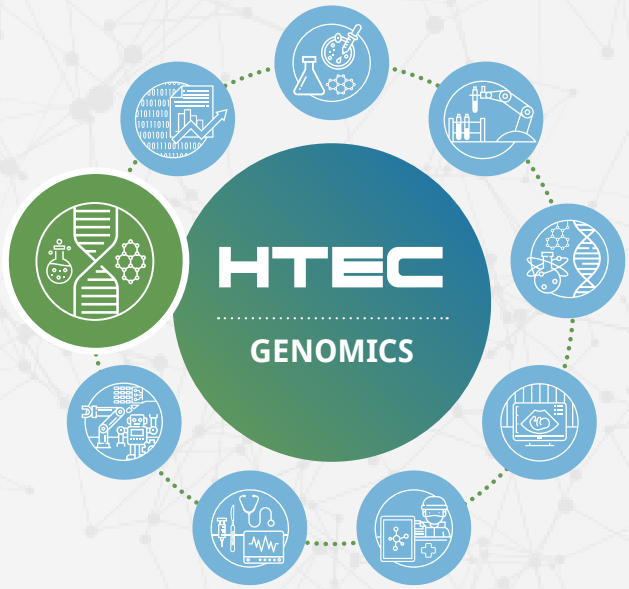
Raise your hand if you or a loved one would like to know eight months ahead of time whether a treated cancer has returned. Keep it raised if you or a loved one would rather have an oncologist test a tumor for all possible cancer genes rather than just one. Raise your hand again if you would rather collect a stool sample at home than undergo a colonoscopy to detect colorectal cancer. Whether you raised your hand or not, keep reading to find out how to invest in these revolutionary technological advances. **The ROBO Global Healthcare Technology and Innovation Index (ticker: HTEC)** offers broad exposure to the most disruptive areas in healthcare. In this white paper, we take a deeper look at one subset of these areas within genomics: the genetic oncology testing market.



THE HOT DEBATE BETWEEN LIQUID BIOPSY AND ITS ALTERNATIVES

The fastest growing cancer test today is the liquid biopsy, which is simply a routine blood draw. The more traditional test uses a tissue biopsy sample. There are numerous debates among the investor community as to whether liquid will eventually replace tissue. Liquid samples are much easier to obtain. However, non-liquid samples are arguably higher quality. We believe both liquid and non-liquid are essential, and both offer significant revenue growth and value creation opportunities. For example, if you put a 4x multiple on the $30B liquid comprehensive genetic profiling market, this adds over $100B in new market cap. And this is only one area of genomics innovation. HTEC brings exposure to both these markets through several innovative companies, including Natera, Roche, and Illumina.

THE LIQUID BIOPSY MARKET IS TWICE THE SIZE OF TISSUE

Liquid biopsy can detect circulating tumor cells (CTC) or DNA in the blood (a.k.a ctDNA), enabling the detection of cancer cells without conducting an invasive tumor biopsy. The process involves drawing the patient's blood and sending it to the lab. The lab instruments look for cancer cells and count them or amplify the DNA for analysis. This testing modality offers the promise to expand access to testing to people in remote areas around the world who may not otherwise be able to travel to see an oncologist. Blood can be drawn in lower cost settings, including the patient's own home by lower-cost clinicians using lower-cost devices. As with many things that can be done remotely, the pandemic has further strengthened the value proposition for liquid sampling.

Another compelling benefit for liquid biopsy is its broad array of use cases, such as early stage screening and post-treatment monitoring. These indications have compounded the market for genetic cancer testing. In fact, liquid biopsy's addressable market of $30B[1] is more than double the size of the tissue market. It's effective for early stage cancer, because liquid biopsy tests can detect cancer cells before the presence of a tumor is known. It can also be used during cancer treatment to see whether the treatment is working, or after treatment, to monitor the patient and see whether the cancer has stayed away. For example, breast cancer survivors spend five years post-treatment in a watch-and-wait pattern, with only an annual mammogram to indicate whether they remain cancer free. With blood testing, they can get screened every three months, which would enable a sooner intervention if needed, and greater peace of mind. Liquid biopsy can also be used to identify patients for clinical trials and the use of targeted therapeutics.

HTEC member Natera offers a liquid biopsy test for post-treatment monitoring for colorectal cancer recurrence. Natara is known as the global leader in prenatal genetic screening because of its Panorama cfDNA blood test. It leveraged this technology to expand beyond prenatal testing and is changing the game for cancer and post-treatment monitoring. For example, colorectal cancer recurs in 7–42% of cases among those who have undergone treatment, depending on the stage of the cancer[2], and 80% of the time the recurrence is detected, it's too late. Natera's Signatera test can detect recurrence nearly nine months sooner than traditional monitoring methods, which will enable earlier intervention and save more lives. Natera has also made headway in breast, lung, and bladder cancers.

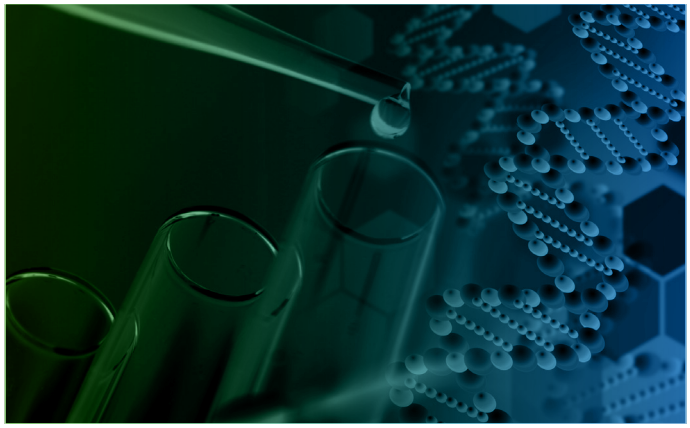
Liquid biopsy can also potentially be a proxy for its tissue counterpart, especially for patients who are elderly or too frail to undergo surgery for a traditional tissue biopsy. This is often the situation with prostate cancer patients. It may also be the preferred method for patients whose tumor may be in areas that are difficult to access, such as the lung.

BUT DON'T DISCOUNT THE VALUE OF TISSUE

While liquid offers numerous benefits, the market for more traditional types of samples in cancer testing is not going away any time soon. Non-blood samples offer unique advantages, as they offer a more comprehensive representation of the cancer tumor than liquid samples. Tissue samples are collected directly from the primary tumor for analysis, which provides a richer view of the DNA and RNA for analysis. The disadvantage is that these samples are less convenient to obtain than blood. Tissue sampling of the tumor involves a surgical procedure which brings the risks and complications inherent whenever surgery is involved, particularly in immunocompromised patients. That said, as testing evolves from single gene to comprehensive genetic profiling, the $10–15B tissue market opportunity creates compelling investment opportunities.

[1] Foundation Medicine, Company Presentations
[2] Mayo Clinic

COMPANIES ARE GEARING UP TO OFFER BOTH LIQUID AND TISSUE FOR COMPREHENSIVE TESTING



Foundation Medicine, Inc. (FMI) is a wholly-owned subsidiary of Roche (HTEC member), the US market leader in tissue testing for comprehensive genetic profiling (CGP), which tests for a panel of genes as opposed to a single gene. Cindy Perettie, the CEO of FMI, believes we are seeing the tipping point of adoption, and sees the complementary value of liquid biopsy testing to help take more share. In fact, if one company offers both types of tests, it can provide whichever is appropriate throughout the patient's cancer journey. This benefits the patient and oncologist in that all of the patient's genetic health data will be neatly stored in one place. FMI has a liquid CGP lab-developed test on the market, as well as being in the late stages of FDA approval for wider distribution.

The CGP market is growing rapidly, as it offers more information with the same amount of sample as needed for a single gene test. With more education of the oncology community that this option exists, this market has a lot of upsides. In 2018, only 16% of all cancer patients received a CGP test. That grew to 18% in 2019 and is tracking toward 25% of the market today. Considering that more than a third of all cancer patients don't receive a genetic test at all, there remains a high degree of upside. Increasing insurance coverage and a broad distribution strategy will be the key to driving further adoption. In January, FMI announced a 15-year partnership with HTEC member Illumina, which will position FMI well for further global reach. Illumina is the world market leader in next-generation sequencing systems, which are used across the genomic spectrum of disease research, drug development, and clinical molecular testing. Through this collaboration, FMI will develop tests that can be used on Illumina's NextSeq 550Dx system and that can be done outside of FMI's central lab, and closer to where the patient lives.

FMI has also partnered with Natera to offer a liquid-based personalized cancer assay. This is based on FMI's existing panel, but also incorporates the top 6–12 drivers of an individual's cancer. Each test is used exclusively on a single patient and can monitor their cancer throughout the different stages.

INVITAE PLANS TO EXPAND REACH TO OVER ONE-FIFTH OF THE WORLD'S POPULATION

HTEC member Invitae, another leading medical genetics company, has been positioning itself for wide-scale genetic testing for years, with the long-term goal of reaching 1–2 billion humans, including the sequencing of over one billion infants at birth. Invitae also has a partnership with Illumina to work on early stage development and alpha and beta testing.

In June, Invitea announced the proposed acquisition of ArcherDx to round out its portfolio to include tissue testing, expand reach to more patients, and expand its personalized cancer monitoring capabilities. The advent of genetic testing introduced the world of genetic precision medicine, which is the development of treatments specifically tailored toward the genetic composition of the patient or disease. For this to work, researchers must first identify the gene, and then life science companies must develop the companion treatment for that gene. In order for that specific

treatment to be used again for new patients, they must be tested to see if they possess the specific gene. These tests are known as companion diagnostics, and they are essential for the use of precision medicine.

Today, many cancer patients for whom a companion diagnostic test would be appropriate don't have access to one. For example, 92% of lung cancer patients are not tested for all recommended mutations, and 60% of colorectal cancer patients are not tested within biomarker guidelines.[3] Interestingly, a large barrier to access is the patient's geographic location. An estimated 15% of genetic testing is conducted at academic medical centers, whereas 85% of cancer patients receive care in the regional or community medical setting. ArcherDx utilizes a decentralized testing model that brings universal companion diagnostics to the community setting. The merger with Invitae is expected to close by the end of 2020.

STOOL SAMPLING ISN'T FUN, BUT IT'S BETTER THAN CANCER

Another hot debate is liquid biopsy versus stool sampling. Exact Sciences (HTEC member) offers the Cologuard test that analyzes stool samples to screen and detect colorectal cancer. Because the patient collects the specimen at home, this sampling method also offers wide accessibility and is more convenient than a colonoscopy. Thus, testing can be done more frequently at a lower cost. The market is sizeable, as Exact recommends that all adults over 45 years of age conduct a Cologuard test every three years following a negative result. While Cologuard is more convenient than colonoscopy, the liquid biopsy bulls would argue that getting blood drawn would be even more convenient than handling one's own stool. However, Cologuard's defensibility lies in the fact that stool samples are more likely to detect cancer sooner, because cancer cells appear in stool at an earlier stage than they appear in blood. Finding ctDNA in the blood for colorectal cancer at an early stage is like looking for a needle in a haystack and could result in missing the cancer altogether. Exact's ability to detect sooner gives the patient a better chance of survival. Therefore, we expect they'll continue to own this market for the foreseeable future. The company is also working on its own liquid version of the screen, which will provide further defensibility should liquid evolve to be as effective as stool.

THERE'S CANCER INFORMATION RIGHT INSIDE YOUR NOSE

HTEC member Veracyte seeks to tackle the $30B lung cancer diagnostic market with next-generation sequencing tests that can help oncologists determine whether a patient is at risk of lung cancer without having to perform an invasive biopsy, using information collected from a bronchoscopy. The company is currently working on an even less invasive nasal swab test to further stratify patient risk. Veracyte expects to launch this product next year and estimates the global market opportunity to be $6B.

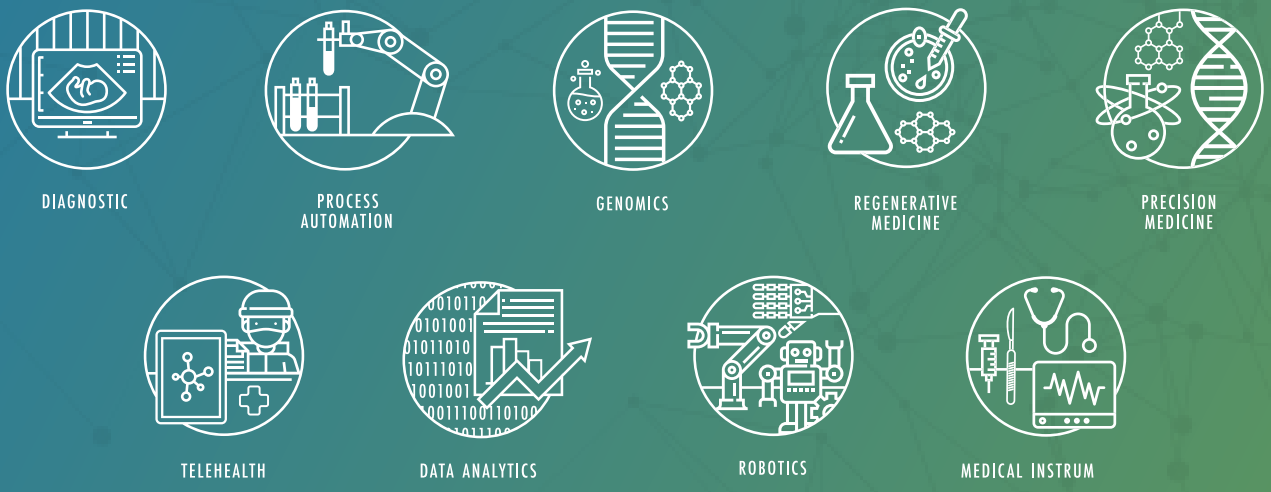
In summary, each sample type has unique benefits that make them essential in cancer diagnostics. Both traditional and new tests are essential, have a place in an oncology practice, and can be used throughout each patient's cancer journey. Companies that offer a wide range of capabilities are well positioned to reap the benefits of being a one-stop-shop as the market continues to grow and adoption accelerates.

[3] ArcherDx, Company Presentations

GENOMICS IS ONLY ONE PIECE OF THE TRANSFORMATIVE PIE

While genomics is causing wide-scale disruption, it's important to note that adjacent areas are also seeing an influx of investment due to their broad market opportunities. Genomics companies need to partner with life sciences companies to develop precision medicine. The healthcare system needs very advanced data and AI capabilities to analyze the vast amount of data exploding out of genomic science, in order to make it actionable. Medical instruments and diagnostics are also needed to perform surgeries and maintain overall health and wellness, and all of these areas are going to transform healthcare in the next decade. Thus, investors who are only looking at one or two innovative areas in healthcare may be missing out on some great investment opportunities. HTEC offers exposure to only the best-in-class companies from genomics, as well as eight other subsectors.

HTEC SUBSECTORS



Our team of research analysts continually updates the portfolio to include companies that meet our criteria. The resulting list of holdings is typically comprised of companies that aren't owned in most portfolios. For more information on how to invest in HTEC, **click here.**

Nina Deka brings nearly two decades of healthcare industry and investment research experience to the ROBO Global research team.