WHITE PAPER

LIQUID BIOPSIES
The Key to Transforming Cancer Care

Current Market Analysis, Potential Opportunities, and Future Growth
Liquid biopsies have the potential to transform cancer care given they could address key unmet needs by enabling:

1. Early detection of cancer
2. Tumor characterization when a tissue biopsy is not feasible / available
3. Comprehensive assessment of tumor changes over time
4. Real-time monitoring during and post treatment

Liquid biopsies could do so without the need for surgical intervention. We estimate current utilization of liquid biopsies in cancer care is in the single digit percentage range, with most of the activity in translational research and clinical trials. Current drivers and moderators of adoption include:

- Lack of large studies demonstrating clinical utility
- Variability in concordance between circulating analytes and tumor biopsy
- Limited / low frequency events of circulating analytes
- Variability in the level of circulating analytes by cancer type and stage
- Limited standardization of workflows
- Limited reimbursement

+ Availability of high sensitivity technologies (e.g., digital PCR [dPCR], next-generation sequencing [NGS])
+ Addition in NCCN guidelines for metastatic NSCLC if repeat biopsy is not feasible
+ Increasing number of targeted therapies
+ Shift towards personalized medicine
+ Increasing CDx deals with liquid biopsy component
+ Emergence of tumor agnostic testing (e.g., microsatellite instability, tumor mutational burden, NTRK genes)

We expect liquid biopsies to initially provide utility in treatment selection where they can identify well-characterized mutations (e.g., EGFR; exon 19 deletions, T790M, L858R) associated with targeted therapies (e.g., Tarceva, Tagrisso) in well-defined patient populations and disease states. Disease monitoring, and more specifically a subset of monitoring, drug resistance, may present the next addressable opportunity given the ability to track longitudinally, although the frequency of monitoring that would provide clinical utility is yet to be established. Diagnosis, while feasible, is unlikely in the short-term; liquid biopsies may be used as a complement, given the continued importance of histopathology. Early detection is the ultimate goal but demonstration of technical feasibility is 2+ years and >$1B away from being determined. GRAIL, an Illumina spinout focused on early detection, has raised $1B in funding, and initiated a massive clinical trial planning to enroll 120,000 to train and validate an early detection cancer test.
The current market landscape is convoluted with >50 companies in the space targeting the full spectrum of blood-based analytes (e.g., ctDNA, CTCs, exosomes, miRNA, protein), technologies (e.g., dPCR, NGS), and settings (e.g., early detection, diagnosis, treatment selection and disease monitoring), where liquid biopsies could have utility. The market is dominated by service providers with LDTs (e.g., Guardant Health, Foundation Medicine, Biocept,) using NGS-based pan-cancer approaches. There is only one FDA approved liquid biopsy kit on the market, Roche’s companion diagnostic test, cobas EGFR v2 kit approved June 1st, 2016. While LDTs currently appear to be sufficient, IVD designation may facilitate reimbursement, which is currently a significant market moderator.

We anticipate service providers will face pressure from two fronts:

1. Top tier AMCs and cancer centers with capabilities and expertise to develop their own LDTs based on an incentive to customize the assay, control the process and own the data

2. Kit manufacturers facilitating incorporation of in-house testing in molecular diagnostic labs and large reference labs at a lower price point and with a potentially faster turnaround time.
According to the World Health Organization, cancer is one of the leading causes of death worldwide, with approximately 14 million new cases reported in 2012, which resulted in 8.2 million deaths. With cancer remaining one of the greatest disease burdens worldwide, researchers and clinicians alike are striving to mitigate cancer morbidity and mortality by giving patients personalized, targeted therapies and devising techniques for earlier detection of cancer. Within the past decade, improvements and investments in genomic and molecular techniques as well as bioinformatics has driven disease treatment and management toward more data-driven medicine. Within oncology, advances in sequencing technologies has expanded molecular profiling of tumor tissue beyond the capabilities of immunohistochemistry and imaging, allowing for identification of specific genetic abnormalities within a tumor to match patients to the most suitable therapies and clinical trials.

Cancer diagnosis remains difficult considering patients can be asymptomatic or the cancer symptoms present as non-specific. Early signs and symptoms are often ignored by patients, allowing the cancer to grow and metastasize, so that by the time the patient seeks medical attention, survival prospects are poor. For example, SEER data indicates between 2007 and 2013, 57% of lung cancer cases assessed were diagnosed when the tumor had metastasized, compared to 16% of cases diagnosed when the tumor is confined to the primary site. This difference equates to “50% drop in survival rate from 56% to 5%.”

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1 World Health Organization
2 National Center for Biotechnology Information
3 Surveillance, Epidemiology, and End Results Program
Once diagnosed and optimal treatment administered, monitoring of patients is typically done via imaging, and although non-invasive, can only detect significant changes in tumor size and has a lower limit of detection (e.g., millions of cells). This lag in detection can prevent timely responses to changes in an often fast-evolving tumor, such as switching treatment due to development of resistance.

Monitoring during remission, also known as surveillance, is also primarily conducted using imaging at intervals that can range from months to years. Unfortunately, many cancer patients relapse. NCI investigators assessed the recurrence rates in ~2,000 lung cancer patients who were diagnosed at different stages. They found that ~30% of patients who were diagnosed at early stages (I A, IB) recurred and ~65% of patients who were diagnosed at later stages (II A, IIB, III A) recurred. Recurrence is attributed to micrometastasis – small amounts of cancer, even single cells, that persist post-treatment but remain undetectable with current methods. With the emergence of highly sensitive technologies (e.g., digital PCR, NGS) it has now become feasible for liquid biopsies address many of these challenges.

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4 American Cancer Society  
5 National Cancer Institute
What is a Liquid Biopsy?

What is a Liquid Biopsy – and how could it address unmet needs in cancer treatment?

Background

A liquid biopsy is a testing approach that samples bodily fluids such as blood, urine, cerebrospinal fluid, or saliva to identify specific biomarkers (e.g. DNA, RNA, proteins, exosomes) as part of disease diagnosis, treatment, and management. A biomarker, as defined by the NIH Biomarkers Definitions Working Group, is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Increasing research in oncology biomarkers circulating the blood, and recent increased sensitivity of technologies (e.g., NGS, dPCR) to detect these low-frequency markers, is driving excitement for cancer applications of liquid biopsies. The key biomarkers currently being pursued are circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and exosomes.

Key Advantages of a Liquid Biopsy

Liquid biopsies offer potential key advantages over current cancer workflows.

NON-INVASIVE

In most instances, a liquid biopsy requires a blood draw, which is a direct benefit in cases where tissue may be inaccessible (e.g., cancers that originate in the lung or pancreas). In addition, repeat liquid biopsies could be conducted throughout treatment and or during remission without surgical intervention.

REAL-TIME

One of the most exciting advantages of a liquid biopsy, is real-time tracking of tumor genetics through serial blood draws over time. This would potentially allow physicians to gather molecular information about the tumor before, during, and after treatment, and to change treatment regimens sooner, if resistance mutations develop over the course of drug administration.

COMPREHENSIVE

Tissue-based tumor profiling may only capture a snapshot of the molecular mechanisms of the solid tumor, whereas liquid biopsies can potentially characterize a tumor’s heterogeneity. This includes intratumor heterogeneity, which exists between different regions of the same tumor, and temporal heterogeneity, which exists between primary and local or distant recurrences.⁶

⁶ National Center for Biotechnology Information
Current Utilization of Liquid Biopsies

Current Utilization of Liquid Biopsies in Cancer Treatment

**SCREENING**

IMAGING
- CT Scan
- MRI
- Mammogram
- Ultrasound
- X-ray

**DIAGNOSIS**

TUMOR BIOPSY OR SURGICAL RESSECTION

If not enough tissue sample is available

MOLECULAR PROFILING

LIQUID BIOPSY

Liquid biopsy is particularly useful
- Instead of tumor biopsy
- For difficult to biopsy tumors
- Not enough tissue sample

STAGING

**TREATMENT**

TREATMENT SELECTION

IMAGING

LIQUID BIOPSY SERIAL MONITORING
- Monitoring during & after therapies
- Resistance mutations identified quickly

COMPLETE REMISSION

REAPPEARANCE OF CANCER AFTER DISEASE-FREE PERIOD

Sensitivity of technologies makes screening for detection of minimal residual disease feasible

RECURRENT
Currently, utilization of liquid biopsies in traditional clinical settings (outside of clinical trials) remains low – single digit percentage according to primary interviews. However, excitement around its potential for cancer screening and particularly treatment selection and monitoring has driven researchers and physicians to begin adopting liquid biopsy as part of their workflows. Oncologists at key AMCs, including the University of Washington, University of Pittsburgh, University of Michigan, Abramson Cancer Center of the University of Pennsylvania, and Massachusetts General Hospital, shared with us that liquid biopsy tests are currently mostly utilized in translational research / clinical trial settings and reported to order only 300 or fewer tests each year, usually from service providers such as Guardant Health, or Foundation Medicine. In most cases, clinicians collect a liquid biopsy sample alongside the routine tissue biopsy samples to compare results for validation purposes. Only in specific instances, when a patient’s tumor was not accessible via biopsy or the biopsied sample was not sufficient for sequencing, or repeat biopsy was not possible, would physicians order a liquid biopsy test as a standalone diagnostic. This falls in line with the latest update (2017) to the NCCN guidelines for non-small cell lung cancer, which recommends considering plasma biopsy for metastatic disease if a repeat biopsy is not feasible.7

**Clinical Utility Challenges**

Ultimately, demonstration of clinical utility (i.e., whether the test can provide information about diagnosis, treatment, management, or prevention of a disease that will be beneficial to the consumer), will be the primary driver for adoption of liquid biopsies in cancer care. Given that tissue biopsy is the gold standard in cancer diagnosis and treatment, liquid biopsies will be compared and validated against it. While liquid biopsies could provide similar, different or additional information relative to the tumor depending on context, information gathered from a liquid biopsy will likely need to be concordant with molecular information from a tissue biopsy to demonstrate validity. High concordance may not be achievable in several situations, including when the liquid biopsy analytes (e.g., ctDNA, CTCs, exosomes):

1. Represent a different region of the tumor than the one biopsied
2. Represent an additional lesion(s) not biopsied
3. Are not shed into circulation or only a subset of tumor-derived analytes are shed into circulation

All the above could conceivably result in vastly different mutation profiles and thus be considered discordant with the tissue biopsy. The extent to which liquid biopsy profiles represent the tumor is under investigation and will need to be determined in several specific circumstances, such as cancer type and stage. To demonstrate clinical utility, liquid biopsy approaches will require expensive, large-scale longitudinal studies. While challenges exist, exciting evidence for the approach validity and clinical utility continues to emerge.

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7 National Comprehensive Cancer Network
Clinical Utility Studies

Given the potential for the liquid biopsies to transform cancer care, there is significant clinical trial activity. A comprehensive search of oncology clinical trials that include a liquid biopsy component returns ~3,500 trials (~7% of all oncology trials). Emerging studies continue to demonstrate that liquid biopsies can accurately identify genomic mutations in circulating tumor DNA (ctDNA) with high concordance with tissue. At the 2016 ASCO Annual Meeting, Dr. Philip Mack, Director of Molecular Pharmacology at the University of California Davis Comprehensive Cancer Center, reported results from the largest study on ctDNA of NSCLC patients, with 15,191 individuals included and a total of 17,628 blood samples collected. The researchers reported that Guardant360, which could detect ctDNA concentrations below 0.4% of total DNA in blood, accurately identified 94 to 100 percent of mutations when compared to mutation profiles of actual tissue samples available in The Cancer Genome Atlas (TCGA) database. The liquid biopsy test was also able to uncover additional resistance mutations not found in clinical samples assessed by TCGA. Findings from Mack’s group demonstrated both the accuracy of and additional clinical insights derived from blood-based ctDNA tests.

A recent prospective colorectal cancer study was also published in the journal Oncotarget and led by Manuel Hidalgo, previously the Director of the Spanish National Cancer Research Centre that has since become Chief of Hematology/Oncology at Beth Israel Deaconness Medical Center. Hidalgo tracked 25 patients receiving standard FOLFIRI-cetuximab regimen over a two-year period. A total of 2,178 ctDNA mutational analyses were conducted using Sysmex Inostics’ BEAMing, one of the most promising digital PCR tumor analysis technology at the initiation of the study in 2013. Overall, the group witnessed that patients with ctDNA that reflected KRAS mutation had the most prolonged response from anti-EGFR therapy and those who developed rapid mutations often resulted in quick deterioration. Furthermore, the researchers’ BEAMing results aligned with results from tumor tissue mutation kits from Life Technologies and Roche. As the first prospective liquid biopsy study in colorectal cancer, Hidalgo’s group demonstrated that ctDNA mutation levels could accurately serve as a prognostic tool and potentially expand to screening and diagnostics in the future.

Recent data presented by Roche at ASCO 2017, demonstrated their ctDNA surveillance kit, AVENIO, could effectively detect minimal residual disease (MRD) in stage II and III colorectal cancer patients. At the same meeting, Grail, a company focused on early detection applications, showed their sequencing-based liquid biopsy assay could capture 73% of mutations found in tissue samples from 124 metastatic breast, lung and prostate patients. Undoubtedly, demonstration of approach validity and clinical utility will be necessary in several settings and the outcome and breadth of these studies will determine the extent to which liquid biopsies penetrate the standard of care workflow. Numerous companies have entered the space and are tackling the spectrum of analytes (e.g., ctDNA, CTCs, exosomes, miRNA, protein) and settings (e.g., early detection, diagnosis, treatment selection and disease monitoring) where liquid biopsies could have utility. These companies are also tackling the spectrum of business models (e.g., service provider, kit manufacturer) and regulatory strategies (e.g., LDT, IVD).

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8 ClinicalTrials.gov
9 Excludes trials that were terminated, withdrawn or the status is unknown
10 GenomeWeb.com
**Liquid Biopsy Competitors**

*Select Liquid Biopsy Competitors by Application*

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- *Other sample types include exosomes, mtDNA, DNAme, combination, proprietary biomarkers*
The current market landscape is convoluted with >50 companies in the space targeting the full spectrum of blood-based analytes (e.g., ctDNA, CTCs, exosomes, miRNA, protein), technologies (e.g., dPCR, NGS), and settings (e.g., early detection, diagnosis, treatment selection and disease monitoring), where liquid biopsies could have utility. Based on the size of the opportunity and scale required to operate profitably (hundreds of thousands of samples), we expect that a shake-out will happen in the long term, with consolidation of around 15-20 players. We have developed a competitive intelligence tool to track companies in the space across key metrics such as product activity, research activity, funding or financial activity, leadership hiring activity, and external engagement. Below are some of companies being tracked.

Select Liquid Biopsy Companies

**BIOCARTIS**

Biocartis, a molecular diagnostics company based in Belgium, launched a liquid biopsy test on its Idylla platform at the end of 2015, providing the first fully automated liquid biopsy assay. Both the Idylla ctBRAF Mutation Assay (RUO) and the Idylla ctKRAS Mutation Assay (RUO) have a turnaround time of approximately 100 minutes with less than 1 minute of hands-on time. Blood volumes of ~1mL are added directly to the system, which then provides quantitative assessment and detection of ctBRAF or ctKRAS mutations in ctDNA. Now, Biocartis is focused on demonstrating clinical utility of their liquid biopsy tests, having already released study results in March 2017 about how the ctBRAF Mutation Assay effectively monitored patients during treatment and confirmed resistance mutations.

**BIODESIX**

Focusing primarily on NSCLC through their respective genomic and proteomic molecular assays, GeneStrat and VERISTRAT, Biodesix hopes to inform treatment selection of targeted therapies. According to Biodesix, both assays have a turnaround-time of 72 hours, currently making these tests one of the fastest commercially-available liquid biopsy assays. Both assays are coverage by Medicare and several private payers, and through a recent partnership with Indian firm Positive Bioscience, Biodesix continues to push to market and increase adoption of its liquid biopsies.

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11 [Cap Today](#)
12 [BioCartis](#)
13 [NASDAQ GlobeNewswire](#)
14 [GenomeWeb.com](#)
15 [Biodesix](#)
CYNVENIO BIOSYSTEMS
Cynvenio, based in Westlake Village, California, offers a proprietary fully-automated LiquidBiopsy platform while also a panel of ClearID liquid biopsy tests, identifying active cancer genes in breast\(^\text{16}\) (release January 2017)\(^\text{17}\) and lung (released May 2017)\(^\text{18}\) through analyzing a combination of CTC, cfDNA, and germline DNA. Moreover, Cynvenio provides ClearID Solid Tumor Panel\(^\text{19}\) is a comprehensive test that matches patients to ongoing clinical trials and PD-L1 Expression Assay\(^\text{20}\) that identifies active cancer genes to help inform treatment. Meanwhile, Cynvenio is pushing toward additional coverage for its liquid biopsy assays, announcing its most recent expansion to include Blue Cross Blue Shield of Illinois.\(^\text{21}\)

EPIC SCIENCES
Currently in limited release, Epic Sciences’ Epic AR-V7 Test detects CTC or rare immune cell populations to identify prostate cancer patients with truncated AR protein and inform treatment for targeted therapies, such as Zytiga or Xtandi. Approximately 20-25% of men with metastatic castration-resistance prostate cancer (mCRPC) fail to respond to first line treatment, and this percentage increases to 60-70% in the second-line setting. Epic AR-V7 identifies AR-positive patients to treat them with taxane chemotherapies rather than standard drugs. Epic Sciences has \(^\text{~}42\) industry partnerships and is involved in over 200 clinical trials;\(^\text{22}\) more recently, however, the company secured $40 million in Series D financing round as it ramps up for development of commercial assays for new indications (e.g. lung).\(^\text{23}\)

\(^{16}\) ClearID Breast Cancer Blood Test Brochure
\(^{17}\) Cynvenio
\(^{18}\) ClearID Monitoring
\(^{19}\) ClearID Solid Tumor Cancer Panel
\(^{20}\) ClearID PD-L1 Expression Assay
\(^{21}\) Cynvenio
\(^{22}\) MedCity News
\(^{23}\) 360Dx
**EPIGENOMICS**

Epigenomics’ lead product Epi proColon, received FDA approval in April 2016\(^{24}\) and was subsequently launched at LabCorp testing sites the following month.\(^{25}\) Epigenomics assays use a proprietary biomarker, DNA methylation of a DNA called Septin9, which is altered in colorectal cancer tumor cells. The test was approved for use in average-risk patients who choose not to undergo guideline-recommended colonoscopy or stool-based fecal tests. Meanwhile, Epigenomics’ second product, Epi proLung, is a lung cancer detection test and is not yet commercially available.

**EXACT SCIENCES**

In a bold attempt to reduce time between FDA approval and Medicare coverage, Exact Sciences’ pursued a parallel-review of Cologuard, a non-invasive colorectal cancer stool-screening test, and received FDA and CMS approval on the same day in August 2014. Since that day, Exact Sciences has completed 202,000\(^{26}\) Cologuard tests through the second quarter of 2016. As Cologuard volume continues to increase, Exact Sciences’ are also focused in other areas of research, releasing study results in March 2017 with Mayo Clinic that identified lung biomarkers and showed promise for development of a lung cancer test.\(^{27}\)

**EXOSOME DIAGNOSTICS**

Exosome Diagnostics launched ExoDx Lung (ALK) in January 2016,\(^{28}\) becoming the first exosomal RNA-based liquid biopsy test. Additional tests for lung cancer, including ExoDx Lung (EGFR) and ExoDx Lung (T790M), are set to release later this year to identify patients more likely to respond to EGFR therapies and those with T790M mutations. Exosome Diagnostics has also expanded to early cancer detection and risk assessment through the release of ExoDx Prostate (IntelliScore),\(^{29}\) which is used to assess patient’s risk of high-grade prostate cancer and whether they should undergo invasive tumor biopsy.

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\(^{24}\) GenomeWeb.com  
\(^{25}\) BusinessWire  
\(^{26}\) Exact Sciences  
\(^{27}\) Exact Sciences  
\(^{28}\) ExosomeDx  
\(^{29}\) ExosomeDx
FREENOME

Freenome, a liquid biopsy company founded in 2014, has the vision to “reinvent disease management through early detection and intervention.” The two-year-old company has been focused on detecting material shed by tumor cells, including DNA, immune cells, and metabolic elements, and using machine learning to find novel patterns to detect cancer at very early stages. In March 2017, Freenome raised $65 million in a round of Series A funding with plans to conduct clinical validation studies of their cancer screening technology, Adaptive Genomics Engine, which is computational system that can be trained to recognize complex patterns from materials found in the blood. Freenome has partnered with 25 academic institutions to launch this clinical study while also engaging the FDA to receive feedback about the types of studies it would need to demonstrate clinical utility and ultimately receive FDA approval, which they believe is key to commercial success further down the life. Currently, Freenome is working on evaluating the platform mainly for four cancer types: lung, breast, prostate, and colon.

FOUNDATION MEDICINE

Foundation Medicine, a key service—provide in genomics and molecular medicine, released a comprehensive liquid biopsy test FoundationACT in May 2016. This blood-based ctDNA assay interrogates 62 genes and fusions across six genes, providing molecular profiling for patients who cannot receive a tissue biopsy or do not have tissue samples available to perform the company FoundationOne tissue biopsy molecular test. Foundation Medicine, after launching their liquid biopsy assay, also announced a partnership with AstraZeneca to develop liquid biopsy companion diagnostic assays to identify patients who will benefit from AstraZeneca’s cancer drugs.

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30 Medium: Freenome Raises $65M in Series A from Andreessen Horowitz, GV and others
31 BusinessWire
32 GenomeWeb.com
33 GenomeWeb.com
34 BusinessWire
35 GenomeWeb.com
**GENOMIC HEALTH**

Genomic Health, having grown a strong business from detecting cancer in tissue biopsies, launched their Oncotype SEQ Liquid Select in June 2016 to identify genomic alternations across 17 genes to provide actionable information about treatment of stage IV solid tumors.\(^\text{36}\) Validation study results were released later last year in October, demonstrating a sensitivity ~95% and specificity >99%. Through a collaboration with Epic Sciences in July 2016 to develop an AR-V7 liquid biopsy test for metastatic prostate cancer, Genomic Health is also striving toward development of additional liquid biopsy tests.

**GRAIL**

GRAIL, an Illumina spinoff that raised $100 million in Series A funding, was founded in January 2016 and has a mission of detecting cancer from a blood test. Utilizing Illumina’s sequencing technology, GRAIL plans to develop a pan-cancer screening test by measuring levels of circulating nucleic acids in the blood. In its first multi-center clinical study,\(^\text{37}\) the Circulating Cell-free Genome Atlas (CCGA),\(^\text{38}\) GRAIL plans to recruit 10,000 healthy and disease individuals to profile cell-free DNA across different cancer types. With multiple community and academic collaborators, the study will include four dozen clinical trial sites where blood and tissue samples will be collected from healthy patients and those diagnosed with cancer. In January of this year, GRAIL announced plans to raise more than $1 billion in Series B financing\(^\text{39}\) and reached $900 million by March 2017. With this funding, GRAIL initiated its second multi-center clinical study in February 2017, the STRIVE study,\(^\text{40}\) a longitudinal, prospective study that will enroll up to 120,000 women at the time of their screening mammogram to train and validate a blood tests for breast cancer detection.

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36 Genomic Health  
37 NASDAQ GlobeNewswire  
38 ClinicalTrials.gov  
39 BusinessWire  
40 ClinicalTrials.gov
GUARDANT HEALTH
Guardant Health, headquartered in Redwood City, California, raised $100 million in funding from leading venture capital firms for development of its first product, Guardant360, which came to market in 2014. The 73-cancer gene panel has now been ordered over 35,000 times, making it the most widely used comprehensive liquid biopsy test. In January 2016, Guardant raised $100 million in Series D funding and announced plans to expand and develop blood tests for cancer detection. A year later, in January 2017, Guardant announced its separate partnership with pharmaceutical players AstraZeneca, Merck, and Pfizer, to develop GuardantOmni, a 500 plus gene panel, allowing physicians to screen patients for multiple clinical trials and enabling drug companies to accelerate clinical trials and development of target therapies. More recently, in May 2017, Guardant announced its ambitious goal of moving toward early cancer detection, securing another $360 million in funding to sequence tumor DNA of 1 million cancer patients in five years. Helmy Etoukhy, Guardant CEO and Co-founder, stated that “conquering cancer is at its core a big-data problem,” emphasizing that this goal of sequencing 1 million patients in a short amount of time will greatly accelerate progress toward understanding this complex disease.

INIVATA
In January 2016, Inivata, a global clinical cancer genomics company, raised $45 million Series A funding to validate InVision, the company’s proprietary ctDNA analysis platform. One year later, at the 2017 ASCO Meeting, Inivata highlighted new clinical data in a study on patients with NSCLC, demonstrating that InVision liquid biopsy analysis was more sensitive than digital droplet PCR. In addition, InVisionFirst assays, that target specific cancer mutations are also under development and not yet commercially available.

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41 Tucson News Now
42 PR Newswire
43 BCC Research
44 Inivata
MYRIAD GENETICS
Myriad Genetics, a leading personalized medicine company based in Salt Lake City, Utah, first released myRisk in September 2013, a 28-gene panel that identifies risk of up to 8 cancers. Since then, Myriad has launched a suite of liquid biopsy tests, which have been ordered by over 90,000 physicians with an upwards of 2 million tests. Most of these assays are focused on risk assessment, including BRACAnalysis, COLARIS, COLARIS AP, and MELARIS. Alternatively, BRACAnalysisCDx was FDA-approved in December 2014 for BRCA1 and BRCA2 as a companion diagnostic for AstraZeneca’s Lynparza through identification of ovarian cancer patients with deleterious germline BRCA variants. Approval for this test was later expanded in March 2017 to include treatment with another PARP inhibitor, Tesaro’s Zejula.

ONCOCYTE
Oncocyte’s Lung Cancer Confirmatory Test is designed to be used after radiologic imaging results when diagnosis of a lung nodule is unconfirmed. Oncocyte’s assay and optimized predictive algorithm evaluates a panel of genes and even considers lung nodule size, reaching 95% sensitivity and 74% specificity.

45 Myriad
46 Nanalyze
47 GenomeWeb.com
**PATHWAY GENOMICS**
In September 2015, Pathway Genomics, a genetic DNA testing company, launched CancerIntercept Detect and Cancer Intercept Monitor, the latter of which monitors patients who have active or previously diagnosed cancer and detects for tumor progression and evolution (e.g. resistance mutations). Meanwhile, the company claimed the CancerIntercept Detect test could be used by physicians to detect elevated levels of ctDNA and identify the presence of 96 somatic mutations in nine cancer-related genes. However, Pathway Genomics had not validated the test through a long-term study prior to product launch, sparking widespread debate in the clinical diagnostics field. Later that month, the FDA sent the company’s CEO Jim Plante a letter stating that there has been “no published evidence that a test or any similar test has been clinically validated as a screening tool for early detection of cancer in high-risk individuals.” In response, Pathway Genomics stated that they have “performed appropriate validation of the test as a LDT, and we are in the process of performing additional studies.” By May 2016, Pathway Genomics announced its ongoing three clinical studies validating CancerIntercept Detect, focusing on colorectal cancer, healthy but high-risk populations, and thyroid cancer.

**PERSONAL GENOME DIAGNOSTICS**
In April 2014, Personal Genome Diagnostics (PGDx), launched the METDetect Assay for the amplification detection of the MET gene, which has been associated with a variety of cancers, including lung, gastric, brain, colorectal, and head and neck. PGDx’s assay uses its proprietary PARE (personalized analysis of rearranged ends) technology to identify structural alterations in the MET gene. In October 2016, PlasmaSELECT was launched, which is a pan-cancer targeted panel that interrogates 64 genes to identify mutations and provide actionable information. PGDx is now aiming for FDA approval, believing that this is the strategy to commercialize their assays and make sure that as many patients can access it as possible.
**ROCHE**
Roche Molecular Diagnostics, having received FDA-approval in June 2016 for the cobas EGFR Mutation Test v2, a blood-based companion diagnostic to Genentech’s anti-EGFR drug Tarceva, has been able to identify the 10-20% of NSCLC patients who have the EGFR mutation and would respond to the drug.\(^5\) In September last year, the FDA granted a label extension and approved the test as a companion diagnostic for TAGRISSO, AstraZeneca’s targeted drug for patients with metastatic EGFR T790M mutation-positive NSCLC who have progressed after EGFR tyrosine-kinase inhibitor (TKI) treatment.\(^6\) Approval of this test as a companion diagnostic affords patients, who are not suitable for a tissue biopsy to confirm T790M mutation, the opportunity to test for the mutation and re-evaluate treatment options. Currently, the cobas EGFR Mutation Test v2 is available through Baystate Health, Carolinas HealthCare System, LabCorp, and PhenoPath, but in March 2017, Health Canada also approved the test as a companion diagnostic to help physicians identify lung cancer patients who are eligible for targeted therapies.\(^7\) Given these EGFR mutations are well-characterized, there is an EGFR-specific current procedural terminology (CPT) code (81235), which based on the 2017 clinical diagnostic laboratory fee, can command payment of $331.82.\(^8\)

**TROVAGENE**
Trovagene’s blood and urine-based liquid biopsy test Trovera detects EGFR, KRAS, and BRAF mutations. In January 2017, Trovagene publicized study results of its KRAS test, demonstrating a 89% concordance to tumor tissue for urine samples and 94% for blood samples.\(^9\) In a patient case series published in March 2017 in the journal Lung Cancer, Trovera accurately identified patients with EGFR mutations who were eligible for TKI inhibitors.\(^10\) Trovagene has also sought several partnerships, including with USC Norris Cancer Center to standardize Trovera in patient care (June 2016),\(^11\) and more recently, with AstraZeneca to provide Trovera in an initial study evaluating whether combined use of blood and urine testing is as effective in identifying T790M mutations as tissue biopsy.\(^12\)
VERACYTE

Veracyte, through its commercial launch of Afirma Thyroid FNA Analysis in 2011, is focused on reducing unnecessary surgeries or biopsies due to diagnostic uncertainty. Using its proprietary Afirma Gene Expression Classifier, Veracyte can identify 30% more benign thyroid nodules among those deemed inconclusive. Similarly, Percepta, launched in April 2015, resolves lung cancer nodules and assesses a patient’s risk of lung cancer and whether more invasive procedures should be done. More recently, Veracyte has been moving to obtain coverage for these two diagnostics, announcing coverage for Afirma by Medicare, United Healthcare, Anthem and several other private insurers. In February 2017, Palmetto GBA, a Medicare Administrative Contractor (MAC), finalized its coverage policy for Percepta and providing a framework for other MACs to follow. As Veracyte continues to announce validation studies for its tests, coverage and adoption will be sure to follow.

VERMILLION

ASPIRA Labs, a wholly-owned women’s health reference laboratory of Vermillion, is dedicated to diagnosis and detection of ovarian cancer at earlier stages and received FDA approval for their ovarian cancer blood test OVA1 in 2009. OVA1 considers a woman’s menopausal status and detects levels of five proteins in a blood sample that may change because of ovarian cancer. The test combines the five results into a single numerical score from 0 to 10 to suggest the likelihood that the pelvic mass is benign or malignant. Last year, in March 2016, Vermillion announced FDA approval of Overa, the second-generation version of the OVA1 test. The new test replaces two of the five OVA1 biomarkers, does not require menopausal status, and uses a single numerical digit from 0 to 5, simplifying physician work and interpretation.
With over 50 companies in the liquid biopsy space, not only do these players focus on different applications, indications, and biomarkers, but they’ve also pursued different business models and regulatory strategies.

The current landscape is dominated by service providers, such as Guardant Health, Foundation Medicine, and Personal Genome Diagnostics, who receive blood draws ordered by a physician, then analyze the molecular characteristics of the tumor-derived analytes in their CLIA certified labs and return a report of the results days to weeks later, typically including treatment and clinical trial options. Many companies have proprietary technologies and or approaches to analyze the genomic information garnered from the samples and they house their own lab infrastructure and analysis pipelines. The technological approach in many cases is NGS, which adds a level of complexity in conducting testing and analyzing the resulting data. This requires a level of expertise that has and continues to be developed internally by these companies and is not common outside of top AMCs and large reference labs. As the market is still nascent, testing approaches are still being validated and clinical utility established, thus there is incentive for companies to keep a tight reign over the entire process including owning the data, from which insights beyond those reported can be gained.

For most hospitals, molecular labs, and or reference labs, there is also limited incentive to bring testing in-house. As mentioned, liquid biopsies are being used in a limited capacity in traditional clinical settings (single digit percent), it’s unlikely individual hospitals have sufficient volume to justify bringing in testing. In addition, validating an in-house test requires resources. Given the market is still immature and standardized workflows are far from established, it’s safer to play the wait-and-see game and to test the waters with a send out, than to establish infrastructure based on the current, rapidly-evolving market. Although emerging, there are a limited number of non-service non-RUO commercial options.
However, with increased adoption of novel molecular diagnostic technologies, including NGS and digital PCR, which are commonly used to analyze liquid biopsy tests, we expect some volume to shift to in-house testing as service providers face increasing pressure from kit manufacturers and molecular labs with NGS capabilities. Hospital labs are also likely to recognize that money can be made in this endeavor. They can justify costs by highlighting studies (most notably in the rare disease space) that demonstrate that keeping ownership of samples yield improved diagnostics rates and patient clinical outcome.

The extent to which volumes shift will vary by setting. Many top AMC’s already have the capability to develop and offer blood-based LDTs. While this can take years (1-3+), additional incentives to control the process exist, including flexibility, control over the content of the assay (e.g., number of genes and or markers) and data ownership for research purposes. Also, there would likely be a benefit of faster turnaround time and potentially lower costs dependent on volumes. AMC’s might also be incentivized to adopt emerging kits with standardized workflows to drive down costs and turnaround time; both Guardant360 and FoundationACT had list prices above $5,000 and offer ~2-week TATs. Hospitals with limited lab infrastructure will likely continue using service-based approaches, either through CROs offering tests or directly through companies, whichever is most cost effective.

One of the available liquid biopsy kits is an FDA approved IVD from Roche (June 1st, 2016). The EGFR Mutation Test v.2 is a PCR-based companion diagnostic that detects specific mutations in the EGFR gene to identify metastatic NSCLC patients eligible for targeted drugs, Tarceva (OSI Pharmaceuticals) and Tagrisso (AstraZeneca). While costly, the benefit of this successful CDx approach is a well-defined patient population and clear clinically actionable information associated with a positive test. Our primary research indicates physicians want clear and clinically actionable information requiring little to no interpretation. Moreover, given the test is PCR-based, there is no requirement for expertise beyond the capabilities of a traditional molecular diagnostics lab, so this test could be validated and conducted by any CLIA certified lab without the need for significant changes in infrastructure. It’s clear however that there is increasing utilization of testing modalities such as NGS and digital PCR and more complex analysis beyond point mutations (e.g., fusions, indels, copy number variations, structural variations, tumor mutational burden, microsatellite instability). Companies are leveraging the breadth of analysis that NGS enables to create pan-cancer assays, which include clinically actionable information across multiple cancers and a number of emerging and investigational markers. Given the increasing number of available targeted therapies and options, this approach could simplify the therapy selection process significantly.

In May of 2017, Roche launched its NGS-based ctDNA analysis kits AVENIO, which include all reagents, bioinformatics, and software such that any lab with NGS capabilities can run the test. The 17 gene, 77-gene, and 197 gene panels address therapy selection and surveillance by identifying guideline-related and emerging markers. Although these tests are currently designated for research use only, Roche is gathering and presenting data on validity and utility that it will likely use to push the product towards approval.

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Regulatory Approval Strategy

It’s unclear what the optimal long-term regulatory approval strategy will be for liquid biopsy products but currently, LDTs appear to be sufficient.

The market is dominated by service providers that offer LDTs; this option can quickly get the product offering to market and can minimize the regulatory hurdles involved without necessarily compromising product success (adoption and reimbursement) – Genomic Health’s Oncotype Dx Breast Cancer Assay for solid tumor testing, estimated to have 90% market share in 2013\(^1\) and incorporated into multiple treatment guidelines (including ASCO, NCCN, ESCO), is an example of a highly successful product that has not seen a need to move beyond its LDT status for over a decade. Primary interviewees who were oncologists were not weary of LDTs as long as clinical evidence is clear.

ADVANTAGES & DISADVANTAGES OF REGULATORY APPROVAL STRATEGIES

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<thead>
<tr>
<th>ADVANTAGES</th>
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<tr>
<td><strong>IVD</strong></td>
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<tr>
<td>+ Very few liquid biopsy tests in oncology have obtained IVD status; doing so could provide product differentiation</td>
<td>– Requires extensive amounts of time and financial investment</td>
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<tr>
<td>+ Ability to back claims regarding the clinical validity of their tests with data, bolstering credibility</td>
<td>– Reimbursement is not guaranteed, even after approval</td>
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<td><strong>LDT</strong></td>
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<td>+ Reduced development timeframe to offer product on the market</td>
<td>– May be more difficult to garner trust from clinicians compared to FDA-approved or CE-marked products</td>
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<tr>
<td>+ Reduced cost associated with an extensive validation and approval process</td>
<td>– The burden of proof (validation and verification) as well as communication of a product’s analytical performance falls on the vendor</td>
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Market Moderators

While we expect liquid biopsies to have a significant impact in the cancer care continuum in the long-term, current market moderators must be overcome for more widespread adoption.

Moderator 1: There is lack of understanding of liquid biopsy as a technique, and the value it adds to cancer care

Querying circulating materials could be an appealing alternative to more invasive tissue biopsies, but the field is still very much in its nascent stages. For one, at its core, liquid biopsy is based on the belief that the genetic mutation is more important than tumor origin, but tumor agnostic testing has not yet gained widespread acceptance. Additionally, many questions still stand with respect to the interpretation of liquid biopsy results, including, but not limited to:

- What is the biomarker concentration threshold for distinguishing between a healthy patient sample and a diseased-state sample (e.g., false positives)? What should be the threshold for clinical intervention?
- Are cells and nucleic acids identified in a blood sample representative of those found in a solid tumor?
- How should results be interpreted when a discrepancy exists between solid tumor and liquid biopsy results?

Much of this uncertainty around liquid biopsies will dissipate as more research is conducted and the field matures. However, companies can also drive the field of research by demonstrating clinical utility for both tumor agnostic testing and liquid biopsy as a technique. Now, the validity of tumor agnostic testing is only answered for microsatellite instability (MSI) with the approval of Merck’s immunotherapy drug Keytruda, but other products in the approval pipeline, like Loxo Oncology’s larotrectinib, or Ignyta’s entrectinib will also be helping drive this paradigm shift.

Another way companies can drive adoption of liquid biopsy techniques is to identify a robust, clearly defined use-case for their product with clear patient benefit. For example, Roche’s cobas EGFR v2 kit is well-positioned to address NCCN guidelines that recommend EGFR mutation testing for patients with metastatic non-small cell lung cancer, and also acts as a companion diagnostic for tyrosine kinase inhibitors Tarceva (erlotinib) and TAGRISSO (osimertinib). Providing clinicians with a test that produces meaningful and tangible implications for patient care, particularly for cancer types where the driver mutations are well understood, is one accessible entry point into the space. Another entry point involves offering a test where liquid biopsy may be the only option, as in cancer types for which a tissue biopsy is not easily accessible (i.e., lung and pancreatic cancers) or treatment scenarios where tissue biopsies may prove harmful to the patient (i.e., after chemotherapy, or in late stage cancers).
**Moderator 2: The market landscape is convoluted:**

The sheer number of players in the liquid biopsy space and difficulty in tracking the characteristics and limitations of each assay can deter adoption by clinicians. Several factors are contributing to a convoluted consumer information problem in the liquid biopsy space: a wealth of players in the liquid biopsy space, limited publications validating the sensitivity of their assays, the lack of a perfect control to compare each assay to, the scarcity of tests holding IVD status, and an abundance of bold claims surrounding each product. Just recently, Guardant Health sued Foundation Medicine for false advertising around claims that FoundationACT is the "only commercially available molecular information platform that comprehensively assesses cancer simultaneously for all four classes of genomic alterations . . . across all cancer-related genes with the sensitivity and specificity required for routine medical practice." Furthermore, workflows for liquid biopsy tests have not been standardized; questions from how to properly collect samples, purify DNA, and analyze and interpret the data still varies from among different companies and academic institutions. Granted, several research groups, are working on standardizing procedures by comparing a number of platforms, technologies, kits, and extraction methods. As adoption of liquid biopsy increases, regulatory authorities may also step in to ensure standardization, but until then, clinicians may continue to be overwhelmed by the options and receive little guidance to base their adoption decisions upon.

At present, companies can strive to gain the trust of clinicians by producing data that demonstrate the robustness of their tests, clearly communicating the benefits and drawbacks of their products, and provide easy-to-understand actionable reports to provide their consumers peace-of-mind.

**Moderator 3: High costs and lack of reimbursement**

Reimbursement by payors will be a key adoption driver. Currently reimbursement is limited. Liquid biopsy is still a novel, unproven technique, and it may take many years before it can garner more widespread acceptance of techniques.

Even with sequencing and dPCR costs decreasing over time, hence making liquid biopsies more cost effective, payors are going to be closely scrutinizing the clinical utility of liquid biopsies, and weighing it against the cost. As mentioned earlier, identifying a well-defined use case for a product will be essential in driving adoption and demonstrating clinical value, bolstering the argument for reimbursement of such a test. Having the relevant biomarkers, techniques and products incorporated into cancer care guidelines (i.e., NCCN, ESCO) will also place additional pressure on payors to reimburse.

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Future Trends & Conclusions

The demand for liquid biopsies has risen significantly due to the non-invasive nature of the test and its ability to offer more granular insight into disease process and progression. Liquid biopsies have been particularly successful in NIPT, with over 2.5M tests conducted worldwide in 2016, and cancer seems to be poised to follow these trends as oncology shifts away from a “one-size-fits-all” treatment regime toward personalized medicine.

Initial adoption may be slow due to market moderators, but highly attractive applications and use cases of liquid biopsy will no doubt overcome these barriers in the long-term. Within the next decade, however, liquid biopsy will become an essential complement to, but most likely not a replacement for, tissue biopsies and imaging, which will continue to serve as the standards of care in most cancer types.

If you are looking for strategic insights or interested in understanding more about the liquid biopsy market, contact us about our off-the-shelf competitive intelligence tool and our consulting services.
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