

PGDx

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MRD Industry Summary

Minimal Residual Disease (MRD) is a term used to describe detectable residual fragments of cancer in patients who have had cancer treatment with a curative intent (i.e. surgery, chemotherapy, etc.). The presence of these cancer fragments post treatment have been shown to put patients at a higher risk of cancer relapse. These MRDs can be of various types, and can be detected using specialized MRD assays. The most common biomarkers that the assays target are circulating tumor DNA (ctDNA), circulating tumor cells (CTC) and ctDNA/methylation. ctDNA is a clear frontrunner for MRD detection due to its detectability on an assay and comparatively higher presence in the body. However, ctDNA/methylation detection has recently been gaining traction by firms and shows potential for further research and development. Detection of ctDNA should enable more personalized treatment for each patient or even treatment before recurrence of the cancer.

Firms operating in the new and upcoming MRD detection and monitoring space are in the business of developing the assays required to detect these MRD for solid tumors. These assays are either foundationally dependent on polymerase chain reaction (PCR) or multiplex flow cytometry (MPFC). The determining factor for which is adopted lies primarily in the type of cancer from which the MRD emerges – hematological (blood-based) cancers or solid tumor cancers. The development of most of these assays, especially for the firms that develop personalised assays for patients, utilize tumor tissue to identify patient-specific tumor mutation targets that are built into the assay. These assays are known as tumor informed.

Several companies — ArcherDx, Genosity, Inivata, Natera — have taken similar approaches to developing MRD assays. Tumor and plasma samples are obtained from patients and undergo whole exome sequencing to detect 10-50 specific genetic mutations or variants found in the tumour. These mutation tags are used to design primers for the assays that are patient-specific. After the assay is developed, plasma samples can be taken from patients at any time point and run through the assay to detect and monitor the presence of MRD in the patient.

Some firms have taken different approaches to assay development for solid tumor MRD monitoring, some of them including Adaptive Biotechnologies, C2i Genomics, GRAIL and Savran Technologies. C2i has been going against the grain by opting for an extremely low (broad) coverage level, while GRAIL has utilized a methylation approach and Savran a CTC-based assay.

MRD assays require a very high specificity and sensitivity, since they guide neoadjuvant and adjuvant therapies, and this is the primary reason for why no firm's MRD assay has been FDA approved for commercial use. However, with an increasing

number of firms reporting positive performances for their assays, moving forward the success of all MRD tests will continue to rely on three factors – performance, manageability and cost efficiency. Firms are trying to estimate the frequency of testing as directed by clinicians through a patient’s treatment period in order to get better insight into the cost efficiency of their product as they gain approval and begin the commercialization process. Many of the bigger companies entering the market are valued well into the healthy, competitive and growing \$5-10 billion range, showing that these firms expect substantial returns from their investments into each of their prospective MRD platforms. As the first solid tumor assays gain approval, it will be interesting to witness the rise and emergence of this niche field in oncology.

Industry Overview

An overview of the companies leading the emerging MRD industry. Within each summary is an outline of each company’s respective technology platform, stage of commercialization and competitive placement within the marketplace.

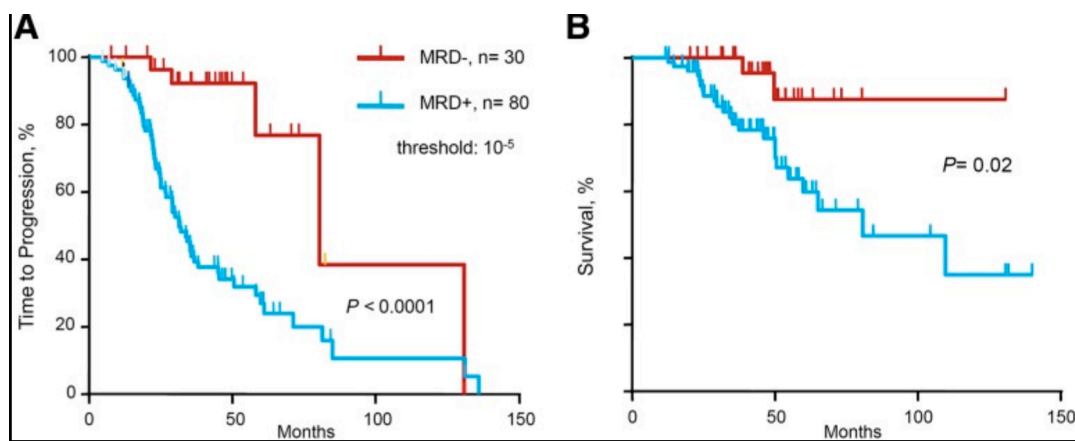
Adaptive Biotechnologies

Adaptive Biotechnologies is a commercial stage biotechnology company that aims to translate the genetics of the adaptive immune system into clinical products. Currently the leading company in development of plasma (ONLY) based assays for MRD testing; their current assay, ClonoSEQ, became FDA approved on September 28, 2018 to assess patients with CLL, MM, and B-ALL.

¹Adaptive’s ClonoSEQ assay utilizes Multiplex Polymerase Chain Reaction (MPCR) and Next Generation Sequencing (NGS). The ClonoSEQ’s NGS uses sequencing consensus primers, permitting standardization as it does not require the construction of patient specific reagents. Furthermore, each step is monitored by a corresponding control molecule – preventing false negatives. Every ClonoSEQ assay includes two sets of internal synthetic controls – panels of synthetic analogs of somatically rearranged BCR immune receptor molecules to address the inherent bias that occurs when DNA sequences are amplified using MPCR – which enable accurate and reproducible quantitation of MRD. Finally, the ClonoSeq assay uses an MPCR design which includes alternative Ig targets that are less prone to SHM, and NGS which has a higher sensitivity compared to standard approaches.

¹ The majority of the information in the next two paragraphs was obtained through this review paper on the ClonoSEQ assay: <https://sci-hub.se/https://www.tandfonline.com/doi/full/10.1080/14737159.2019.1627877?scroll=top&needAccess=true>

Rather than pursuing a highly specific or sensitive assay, Adaptive opted for a system with a minimum DNA requirement of between 500ng and 20ug. This works in tandem with their control molecules to ensure that no false negatives (or positives) occur. This broader scope of analysis allows them to avoid the problems other companies face when using highly specific technologies on low numbers of ctDNA. By combining their ClonoSEQ assay with Multiparameter Flow Cytometry (MPFC), Adaptive Biotechnologies was able to reach a sensitivity and specificity of 99.9999% (converted from a 1 in 1,000,000 detection value) with a Variant Allele Frequency (VAF) of .001%.²

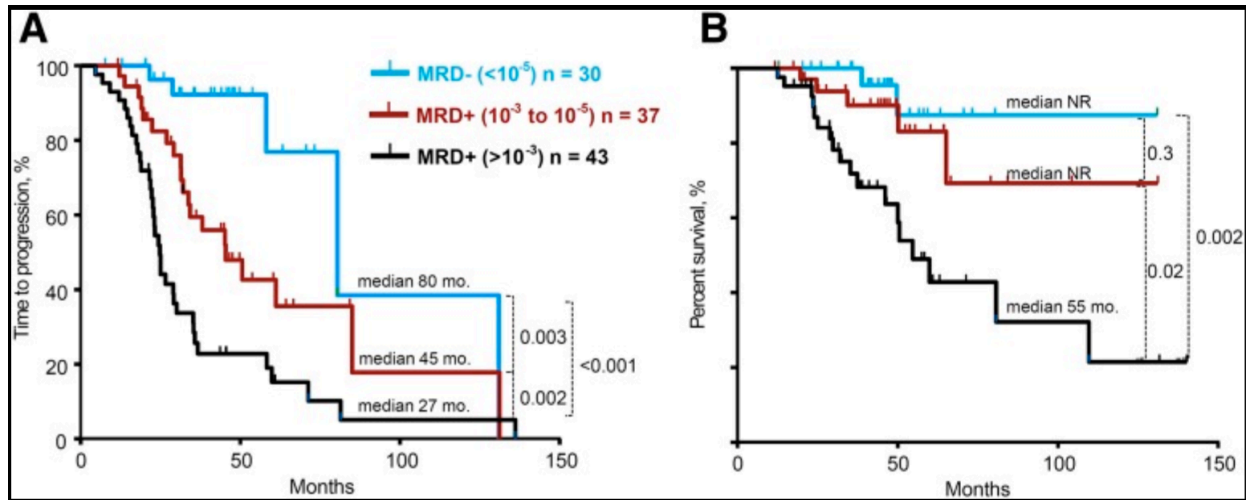


Due to this, Adaptive would most likely perform a follow up test yearly, the first test being between the 12th and 18th months following treatment and the next being between the 24th and 30th months.

Adaptive's key advantages lie in their ClonoSEQ's ability to utilize NGS to not need patient-specific reagents, allowing it to be a standardized platform. Furthermore, due to its minimum DNA requirements, Adaptive's ClonoSEQ assay never yields false negatives, ensuring that every reading is 100% accurate. Another key advantage is that each sample of the ClonoSEQ assay includes two sets of internal synthetic controls — enabling accurate and reproducible quantitation of MRD through BCR immune receptor molecules that address the inherent bias from DNA sequences being amplified by MPCR. The minimization of Somatic hypermutations (SHM) is one of the largest advantages the ClonoSEQ assay possesses. SHM can be a main cause for the incapacity to detect the clonal B cell population, especially in oligo/polyclonal repertoires, mature B cell malignancies, and

² Graphics obtained from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4023416/>

clonal evolution between diagnosis and relapse. Thus, the ClonoSE was designed with alternative Ig targets that are less prone to SHM to combat this.



Although Adaptive's ClonoSEQ assay possesses a plethora of advantages, many of them can also be taken as disadvantages. The most basic of these disadvantages is that Adaptive's ClonoSEQ assay is only functional for hematological cancers. Furthermore, while the ClonoSEQ assay does not return false negatives due to its minimum DNA requirements, these requirements restrict the assay from becoming more sensitive and detecting the MRD of these cancers at earlier stages. Another limitation of this assay is that it doesn't zero in on MRD, it utilizes the number of malignant cells to perform its readings; thus, the same MRD frequency would theoretically have lower precision at lower DNA amounts (false negatives could arise). The final disadvantage of the ClonoSEQ assay is that it isn't effective on all B-ALL cancer patients, specifically those lacking a rearranged immunoglobulin loci — these patients would need other MRD detection methods to be used to yield correct analysis.

Adaptive is currently the largest company involved in the "hematological only" approach with MRD research. With their various advantages listed above, their ability to stay as the current leader in this market is very likely. However, their current technologies are more expensive than current PCR methods. With this in mind, there is definitely room for other companies to develop more diverse methods and force adaptive to change direction from a massive minimum DNA requirement to reduce cost and increase sensitivity to stay relevant. This could pose a problem for the company as they currently seem to avoid going below these requirements since they return false negatives with the current depth of their technological advancements.

ArcherDx

ArcherDX is currently in a strategic collaboration with AstraZeneca to develop Personalized Cancer Monitoring (PCM) Assays for MRD testing. ArcherDX's process involves utilizing next-generation sequencing (NGS) device under development as a companion diagnostic (CDx) to detect neurotrophic receptor tyrosine kinase (NTRK) gene fusions that lead to the formation and growth of cancer. ArcherDX's NGS technology utilizes proprietary Anchored Multiplex PCR (AMP™) chemistry that captures DNA, RNA or ctDNA from both blood and tissue samples regardless of the location of the tumor. They received the breakthrough device designation by FDA in early 2019, putting them on a fast-track to receive FDA approval for their assay technology.³

ArcherDX will perform Whole Exome Sequencing (WES) of resected (ONLY) non-small cell lung cancer (NSCLC) patient samples and generate patient-specific circulating tumor DNA (ctDNA) assays (tissue and blood samples used). The minimum amount of cfDNA required is 10ng. They offer solutions for solid tumour monitoring such as nasopharyngeal carcinomas, colorectal carcinomas, rectal carcinomas, breast carcinomas, pancreatic carcinomas, and lung carcinomas.

Table 1. Summary of studies reporting ctDNA detection of Molecular Residual Disease (MRD) with corresponding clinical outcomes and accuracy data reported by the study authors

Tumor type	Study, Number of patients (n)	Clinical Outcomes in patients with ctDNA detected post treatment compared to ctDNA patients with no ctDNA detected	Reported data on accuracy of ctDNA testing for detecting MRD
Nasopharyngeal Carcinoma	Chan ATC, et al. 2002. (27) n=170(27)	High versus low EBV DNA: PFS at 1yr 48% versus 93%. RR for recurrence 11.9	Negative predictive value 83% Positive Predictive value 87%
Colorectal Carcinoma	Diehl F, et al. 2008. (28) n=18	Recurrence Rate with/without ctDNA statistically significant (p=0.006)	100% sensitivity 15/16 patients with ctDNA detected recurred
	Tie J, et al 2016. (29) n=230	No adjuvant chemotherapy group: RFS at 3 years 0% versus 90% HR for recurrence 18. Adjuvant chemotherapy group following completion of chemotherapy: HR for recurrence 11.	Sensitivity for recurrence at 36 months 48% Specificity 100% (in patients not treated with chemotherapy)
	Diehn M, et al. 2017. (32) n=145	2-year DFS 17% versus 88%. HR for recurrence 10.3 OS HR 3.4	92% of ctDNA detected patients recurred 7% of ctDNA not detected patients recurred
	Overman MJ, et al. 2017. (30) n = 54	2-year RFS 0% versus 47%. HR for recurrence 3.1	Sensitivity 58% Specificity 100%
	Scholer LV, et al. 2017. (31) n=27	RFS at 3 years 0% versus 73% HR for recurrence 37.7 5-year OS HR 6.7	Sensitivity 100% Specificity 100%
Rectal Carcinoma	Tie J, et al. 2018. (33) n=159	RFS at 3 years 33% versus 87% HR 13.0	11/19 (58%) with ctDNA detected recurred 12/140 (8.6%) ctDNA not detected recurred
Breast Carcinoma	Garcia-Murillas I, et al. 2015. (34) n=55	DFS 6.5 months versus NR. HR 25.1	6/12 (50%) patients relapsed had ctDNA detected. 96% of patients who did not relapse did not have ctDNA detected.
Pancreatic Carcinoma	Pietrasz D., et al. 2016. (35) n=31	DFS 4.6 versus 17.6 months OS 19.3 versus 32.2 months	4/6 patients with ctDNA detected relapsed
	Lee B., et al. 2018. (36) n = 42	DFS 5.4 versus 17.1 months HR 5.4 OS 10.6 versus NR months HR 4.5	Recurrence occurred in 13/13 patients with detectable ctDNA despite over half receiving chemotherapy
Lung Carcinoma	Chaudhuri AA, et al. 2017. (37) n=40	DFS at 36 months of 0% versus 93%. HR 43.4	One patient who recurred did not have ctDNA detected 100% specificity

³ArcherDX Receives Breakthrough Device Designation to Detect NTRK Gene Fusions

Based on the collaboration with the University College of London⁴, ArcherDx's Anchored Multiplex PCR (AMP) post-operative data points were analyzed from 90 patients. In patients whose cancer had relapsed and shed ctDNA, the ctDNA was detected at or before relapse with a median lead-time, or time from ctDNA detection to clinical relapse, of 164 days (range: 6 to 1,022 days) in the study tracking a median of 200 variants per patient. Furthermore, in non-relapse patients, the assay demonstrated 99.3% clinical specificity within the research data set. Results from the analytical validation of a 50-variant version of the research assay demonstrated 100% specificity with detection down to 0.003% variant fractions at high cell-free (cfDNA) input levels.

The company hopes to receive FDA approval soon, and will continue working with their collaborators to expand precision oncology into early-stage cancer when the cancer is typically easier to cure. On another note, their breakthrough device designation is a clear sign that their technology is on track to reach commercialization within the next couple years, indicating that more research on the efficacy of their platform will continue to be released throughout 2021 and 2022.

C2i Genomics

C2i Genomics is one of the newest competitors within the solid tumor MRD industry — commercializing the technology created by co-founder Dan Landau at Cornell and the New York Genome Center, and raising \$12 million in Series A funding in June of 2020. MRDetect is the name of C2i's premier MRD technology that can be used for lung, breast, osteosarcoma, melanoma, and colon cancers.

⁵⁶MRDetect is a tumor-informed liquid biopsy assay and begins its process by sequencing resected tumor tissue to create a personalized tumor “fingerprint” — representing thousands of mutations for each individual patient. Then it uses whole genome sequencing (WGS) to identify cfDNA somatic variants that are detected by shallow whole genome sequencing of blood (without filtering). Since substantial aneuploidy is present in 88% of cancers — large portions of the genome undergo amplification and deletion - MRDetect utilizes this and scans for the amplified and deleted regions. By doing this in combination with WGS, it creates a greater read depth in amplification regions and lower read depth in deleted regions; this allows

⁴ <https://apnews.com/press-release/pr-newswire/4749628169ea12208956106af79d7966>

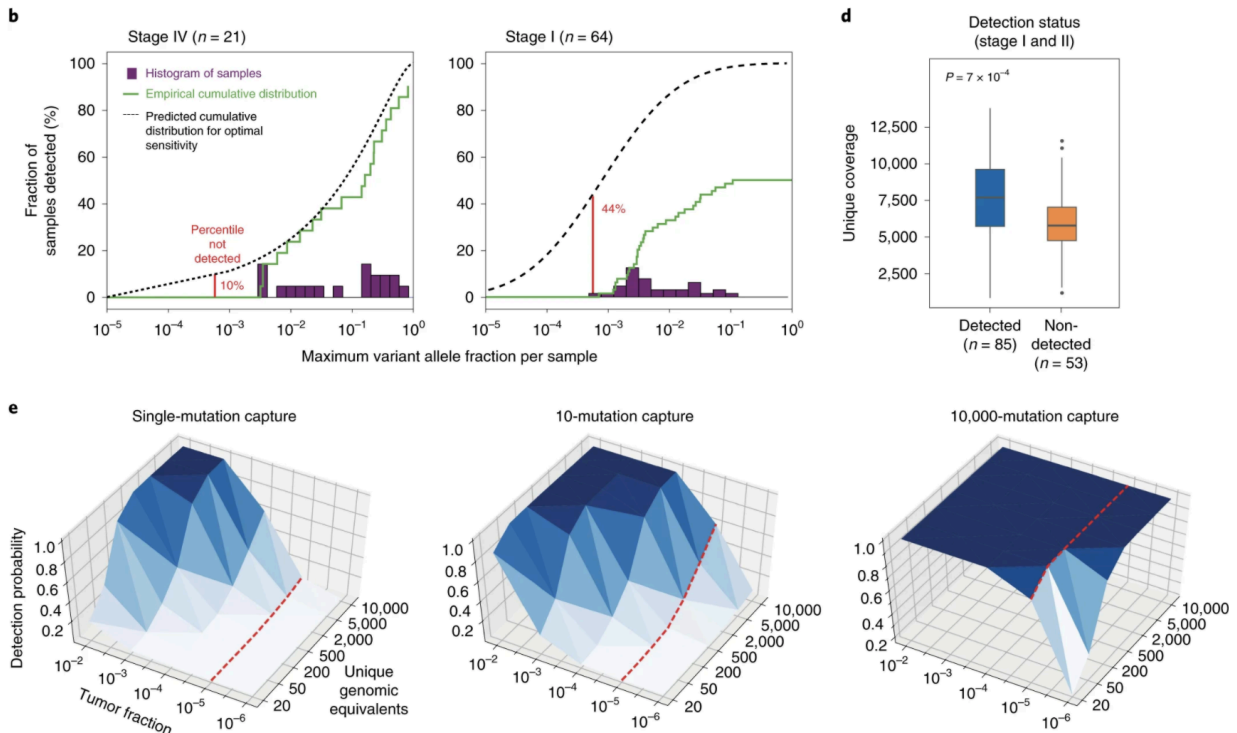
⁵All of this information came from C2i's only self-published peer-reviewed paper. Although it was comprehensive, and likely led to their series A, the results have yet to be corroborated in other head-to-head studies. In addition, we were unable to find any more existing informational materials regarding the MRDetect technology as of November 2020

⁶ <https://www.nature.com/articles/s41591-020-0915-3>

for easy identification of ctDNA as there will be a skewed portion in the reading of cfDNA due to the ctDNA present.

Instead of vying for ultra-high coverage, C2i is opting for lower coverage — giving the assay more breadth, detection sites, and input material. This allows the assay to bypass the struggle of dealing with low amounts of cfDNA in plasma samples. In addition, the researchers utilized a support vector machine to overcome the noise caused by sequencing errors — reducing error to 1 in every 10,000 base pair, and yielding a 95% specificity at a .00001 tf value. The sequencing kit used was for a DNA requirement between 1-5(+) ng, however it was unclear how these values differ among different coverage values. Their website claims to need as little as 2 ml of plasma per assay.

In their in-silico⁷ trial, Dan Landau and his team found that 35x coverage yielded detection of tumor fraction as low as .00001, a sensitivity in between 90 and 99%⁸, and a specificity of 95%. C2i claims to be able to work between a range of 10-120x coverage, and cited that their 120x coverage yielded a .000001 tf at the expense of a larger minimum DNA requirement. Furthermore, By using ctDNA fragments of approximately 165 base pairs, along with their WGS techniques and tech, they reduced the sequencing error rate to 4.96×10^{-5} with a specificity of 99.85% per locus sequenced at 30x sensitivity.



⁷ All trials in this paper were in-silico

⁸ Trials indicated that using a 20x coverage yielded a >85% sensitivity, while a 50x coverage yielded a >99% sensitivity

On a broader level, C2i is probably the smallest and most nimble out of all the companies we have identified to be leaders within the solid tumor MRD industry. Their unique broad coverage method seems to yield impressive sensitivity levels — however, that may come at the cost of a higher DNA input requirement, subsequently raising their prices for testing. As no other news or publications have been released about C2i (or their technology) since Q2 of 2020, we highly recommend keeping updated on the company throughout 2021, as more data and information on their platform will likely become available as they gear up to commercialize.

Genosity

Genosity is a biotechnology company located in New Jersey offering both lab services and software platform installation. They are currently developing a 3 step MRD platform: Astra Profile, Astra One and Astra Next. In August 2020, they received CLIA approval for AsTra Profile and AsTra Next and were cleared to begin working with human tissue. Astra, which stands for assessment and tracking⁹, uses tumor exome sequencing to derive a panel of patient-specific genomic targets. These are then used to design a unique liquid biopsy assay for the detection and monitoring of minimal residual disease in each cancer patient.

The first step in the MRD testing platform is the Astra Profile¹⁰, and it involves whole-exome sequencing using the Illumina NovaSeq 6000 platform. It is clinically indicated for patients with solid tumor neoplasms irrespective of tumor type. This assay allows for the identification of tumor specific alterations of clinical significance as well as a determination of tumor mutation burden. It leverages this identification of a larger number of tumor specific variations available only from whole exome sequencing to generate a patient specific ctDNA panel.

The next step is the Astra One test, which utilizes the custom ctDNA panel designed based on specifically selected 50 to 200 patient tumor specific mutations to detect the tumor's unique signature and provide initial MRD assessment through non-invasive liquid biopsy.

The final step is the Astra Next test, this liquid biopsy test can be utilized to determine effectiveness of tumor reduction in patients undergoing treatment as well as detect recurrence. Using the same patient specific tumour's signature, MRD

⁹https://www.genomeweb.com/liquid-biopsy/genosity-latest-entrant-growing-ctdna-residual-disease-monitoring-market?utm_source=ad&utm_medium=email&utm_campaign=genosity-latest-entrant-growing-ctdna-residual-disease-monitoring-market

¹⁰Most information regarding the MRD testing platform was taken from Genosity's site, we found little published academia

presence or absence is reported separately for each sequential plasma sample that is tested.

Due to the fact that Genosity received CLIA approval 3 months ago (as of December 2020) to begin testing with human tissue, they have published little qualitative data on their platform. However, they have been able to successfully run a 500x exome off of circulating tumor material, and have hopes of reaching a coverage of 20,000x, but acknowledge that a higher coverage is not cost effective given current circumstances.

GRAIL

As of September 14th 2020 (¹¹SEC Filing), the Jeff Bezos backed GRAIL is planning to expand the range of their technology to include monitoring for residual disease. They claim that their MRD test will be a non-personalized plasma methylation assay that may or may not use a tissue sample. GRAIL's precursor cancer detection technology, which is currently undergoing an NHS pilot in the UK (165,000 patients), Galleri (planned for 2021 commercialization), is likely to be the most technologically similar to their upcoming MRD platform. According to their IPO SEC filing in the beginning of September, GRAIL stated that their future MRD platform could deliver results in approximately 10 days and “overcome the operational complexities of existing MRD technologies”. In addition, they are planning to develop an approach that would be able to be informed by a tissue sample — allowing them to reach the standard sensitivity levels of current bespoke assays. They anticipate seeking scientific validation and publishing data from initial studies testing their platform throughout Q1 and Q2 of 2020.

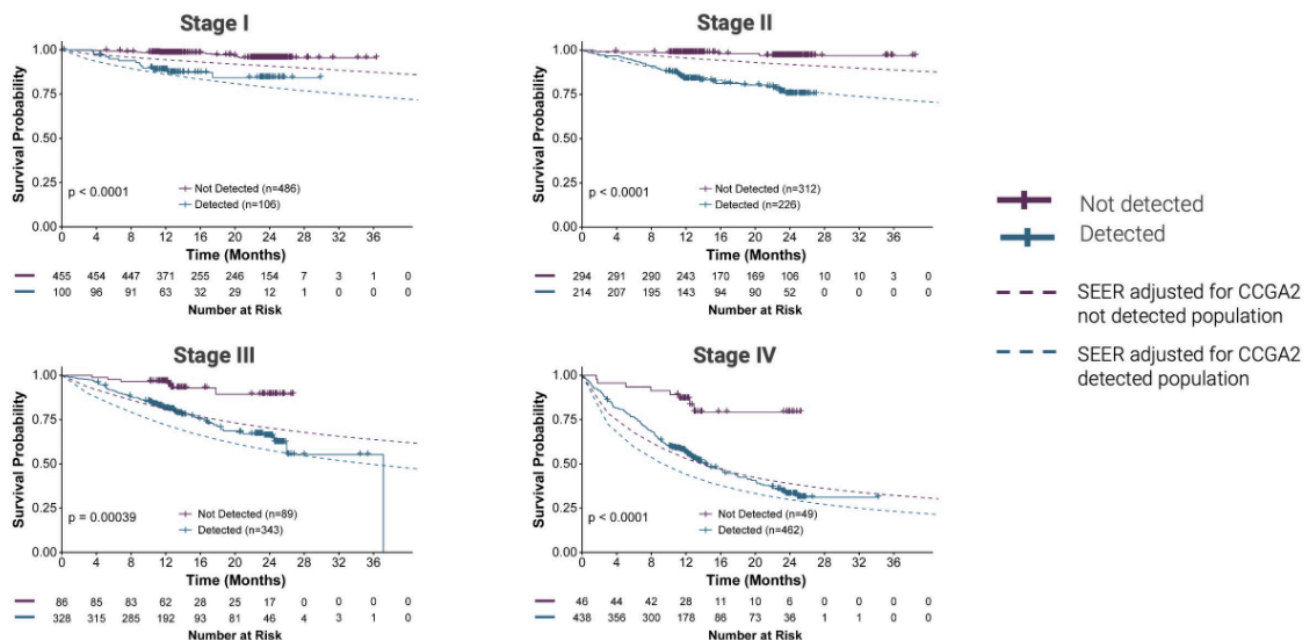
Their Galleri platform was outlined in the ¹²Annals of Oncology journal in June of 2020 — indicating that their target methylation approach could accurately detect more than 50 types of unscreened cancers across stages. Galleri uses methylation rather than the traditional NGS methods of other tech and assays. By scanning the 30 million methylation sites in the genome, Galleri has a large, ubiquitous, rich signal for detecting cancers. Galleri utilizes the highly informative and low-noise methylation regions for optimal signal detection and localization capabilities. Galleri targets these regions allowing early cancer detection as well as sensitive MRD detection even when there is low ctDNA circulating in the blood. Galleri has a false positive rate of less than 1%, and, upon cancer detection is able to localize the cancer signal with “high accuracy” (93% correctness in older trials, no value given

¹¹ <https://www.sec.gov/Archives/edgar/data/1699031/000162827920000227/grails-1.htm>

¹² [https://www.annalsofoncology.org/article/S0923-7534\(20\)36058-0/fulltext](https://www.annalsofoncology.org/article/S0923-7534(20)36058-0/fulltext)

for newer trials) from one blood sample. According to GRAIL's data on the performance of Galleri in their CCGA-2 study coupled with data from SEER, their models predict that by adding Galleri diagnosis to usual care there is a 70% chance to detect cancers that result in death within 5 years at earlier stages, reducing the death toll of these cancers by 39%. Galleri would offer blood-based MRD testing without a personalized assay. Furthermore, results would be available in roughly 10 days. Galleri will utilize a flexible approach that can perform personalized analysis after being informed by a baseline plasma or tissue (when available).

Their Galleri platform was able to achieve a specificity of 99.3% at a 95% confidence interval, a 39% sensitivity in stage I, 69% sensitivity in stage II, 83% specificity in Stage III, and 92% in stage IV when the cancers were pre-specified. When non-specified, the specificity remained the same, but the sensitivity became 18% in stage I, 43% in stage II, 81% in stage III, and 93% in stage IV. Furthermore TOO was predicted in 96% of samples with cancer-like signals and the localization of TOO was accurate in 93% of those samples. They also claimed that methylation not only outperformed WGS and targeted mutation panels in cancer detection and TOO localization, but that the methylation also proved to be more pervasive compared with canonical mutation sites that would typically be interrogated in traditional liquid biopsy approaches.¹³



¹³ <https://www.sec.gov/Archives/edgar/data/1699031/000162827920000227/grails-1.htm>

GRAIL's methylation approach to early cancer detection will likely prove to be an industry disruptor — allowing the company to gain momentum in launching their methylation-based MRD assay, which may prove to be an equally dangerous challenger to companies utilizing more traditional sequencing assays in the MRD market. The September 2020 acquisition by Illumina valued GRAIL at nearly \$8 billion, quite a pretty penny above the initially planned \$100 million IPO announced just weeks before the acquisition — showing that this is a serious gamble on Illumina's part to break into detection and likely MRD. Galleri is slated to reach commercialization by 2021, meaning that it is likely GRAIL's MRD platform will not enter commercialization discussions until at least 2022 or 2023 — making it important to keep a watchful eye out for emerging publications, studies and marketing materials outlining the tech throughout the end of 2021 and into 2022.

Inivata

Inivata is a market leader in molecular profiling using liquid biopsies through their highly sensitive and proprietary InVision®Platform. This platform was being used primarily for Inivata's only product, InVisionFirst-Lung, which is a clinical diagnostic test used by clinicians to accurately identify genomic alterations in 37 genes that help support treatment decisions in patients diagnosed with advanced non-small cell lung cancer (NSCLC).¹⁴ However, Inivata recently entered the MRD detection and monitoring space with their new product, the RaDaR™ assay, which incorporates their InVision®liquid biopsy platform technology, and allows them to exploit the existing technology's FDA approved built-in controls and error-correction to obtain highly sensitive and specific variant detection for numerous solid tumors, such as breast, colon, melanoma and lung cancers.¹⁵

The RaDaR™ assay is a personalised tumor-informed assay optimized to detect circulating tumor DNA (ctDNA), allowing both detection of residual disease following curative intent or definitive treatment and early detection of relapse. Tumor-specific variants are identified using Whole Exome Sequencing of tumor tissue samples and primer panels that target mutated loci are designed. Then their InVision®liquid biopsy platform technology (which requires a minimum plasma concentration of 78ppm) captures and amplifies up to 48 patient-specific tumor variants in cfDNA from a liquid biopsy using a multiplex high-fidelity PCR. This is followed by high depth next generation sequencing using Illumina NovaSeq to a

¹⁴ <https://www.inivata.com/invisionfirst-lung/>

¹⁵ <https://www.inivata.com/radar-residual-disease-and-recurrence/>

depth >100,000 reads per locus, after which proprietary algorithms compare patient-specific sequencing data to controls, and integrate information across variants and replicates to detect trace levels of tumor-derived signals. The method is currently available for research use only (RUO).¹⁶

Using 48 variants allows the RaDaR™ assay to obtain a mean sensitivity of 100% at 20 parts per million (20 ppm, equivalent to a VAF of 0.002%) and sensitivity of 70% at 10 ppm (0.001%) with an overall specificity of 100%.¹⁷ An experiment correlating number of targeted variants and assay performance concluded that when using only 16 variants, the assay had a mean sensitivity of 95% at 40 ppm (0.004%), 64% at 20 ppm (0.002%) and 22% at 10 ppm (0.001%) with specificity 99.99%. Using 48 variants therefore enhances this already high sensitivity.^{18,19}

Sensitivity for high (48) and low (16) numbers of variants at high input copies

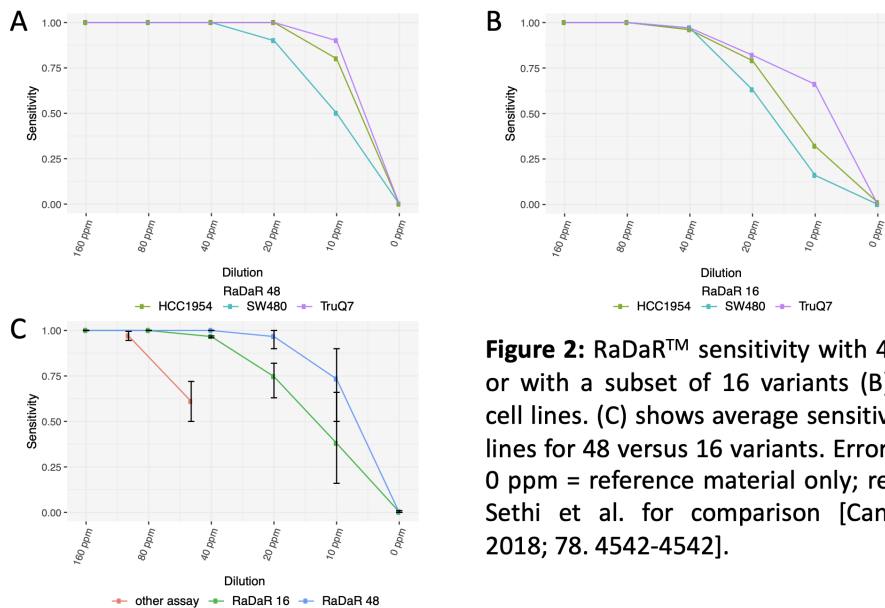


Figure 2: RaDaR™ sensitivity with 48 variants (A) or with a subset of 16 variants (B) for different cell lines. (C) shows average sensitivity across cell lines for 48 versus 16 variants. Error bars = range; 0 ppm = reference material only; red line is from Sethi et al. for comparison [Cancer Research 2018; 78. 4542-4542].

Inivata's In-Vision Platform technology serves as a great advantage for the firm as they move forward with the development of their RaDaR™ assay. With the technology recently approved and commercially available, integrating it into their MRD detection and monitoring pipeline gives Inivata a unique advantage over its competitors, with potential to fast-track approval of the RaDaR™ assay. As of October 2020, Invita has partnered with Maverick Therapeutics to use their

¹⁶ https://www.inivata.com/wp-content/uploads/2020/06/AACR_2020_poster_3097.pdf

¹⁷ https://cancerres.aacrjournals.org/content/80/16_Supplement/3097

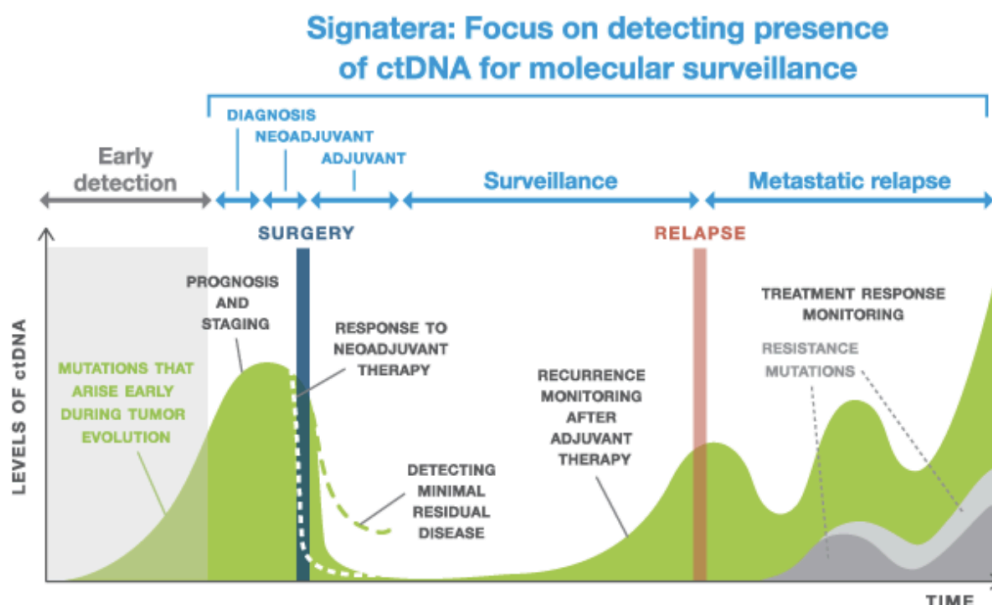
¹⁸ https://www.inivata.com/wp-content/uploads/2020/06/AACR_2020_poster_3097.pdf

¹⁹ https://cancerres.aacrjournals.org/content/80/16_Supplement/3097

RaDaR™ assay to detect and monitor ctDNA from multiple tumor types in patients enrolled in Maverick's Phase I/II clinical study for its MVC-101 drug candidate following treatment. The study is said to provide “valuable early insights into the effectiveness of Radar”.²⁰ This partnership displays a new application of MRD assays in streamlining clinical trials and Inivata is one of the first firms to enter into this space. Going forward, it will be noteworthy to track how the RaDaR™ assay performs in this clinical trial setting (whether its high sensitivity and specificity holds up), and understand this new and potentially lucrative application for MRD assays in clinical trials.

Natera

Natera is a genetic testing company that operates a CLIA-certified laboratory in San Carlos, California. Its oncology pipeline features their solid tumor minimal residual disease test — Signatera. Signatera is a personalized, tumor-informed assay optimized to detect circulating tumor DNA (ctDNA) for molecular residual disease (MRD) assessment and recurrence monitoring for patients previously diagnosed with cancer. Tumor-informed indicates that it uses both tissue and plasma to develop personalized assays anMRD assessment, after which solely plasma samples are sufficient for treatment monitoring.²¹



²⁰<https://www.genomeweb.com/molecular-diagnostics/maverick-therapeutics-use-inivatas-liquid-biopsy-assay-phase-iii-clinical#.X8glwBNKi3K>

²¹ <https://www.natera.com/oncology/signatera-advanced-cancer-detection>

Preparation of the assay requires primary tissue (if whole exome sequencing data has not already been collected) and blood samples. The optimum amount of tissue required is either a tissue block and 1 H&E slide (preferred), 10, 5micron slides with a $>5\text{mm}^2$ tumor at $>20\%$ tumor content, or 4-6 core needle biopsies and 1 H&E slide. The minimum amount of plasma required is 2mL of plasma with 15ng of DNA (lower than most of its competitors), but ideally 2 tubes of whole blood in Streck/EDTA tubes, or 10mL of double-spun plasma is used. These samples are collected and whole-exome sequencing is performed and analysed to find the full complement of patient-specific somatic tumor derived mutations. These are filtered based on clonality, detectability, and frequency of mutations to identify the top 16 somatic variants. PCR primers are then designed for each of these 16 variants to develop the assay.²²

After the preparation of the assay, at any given time point, plasma samples are isolated and cfDNA is extracted from the sample. This is then assayed with the patient specific 16-plex PCR pool. Following multiplex PCR amplification, ultra-deep next generation sequencing is performed, with a 100,000X coverage of each target (higher than most of its competitors), and analyzed to detect the presence of ctDNA.²³

The Signatera test has been clinically validated across all solid cancer types such as colorectal, non-small cell lung, prostate, breast, gastrointestinal, esophageal and bladder cancers. It was awarded the Breakthrough Devices designation by the U.S. Food and Drug Administration in 2019 for its significant advantages over other firms in terms of technological prowess. They are able to detect the presence of ctDNA at a variant allele frequency (VAF) of 0.01% (lower than most of its competitors) because of their approach to target 16 patient-specific mutations to develop their assay. The dependence on the number of somatic SNVs for clinical sensitivity of MRD detection was demonstrated in a clinical study. In addition, the Signatera RUO assay has a 99.9% sensitivity on an SNV level, and a greater than 95% sensitivity at 0.01% tumor fraction, nearly 100% sensitivity at 0.03% tumor fraction, and 100% sensitivity at 0.05% and above tumor fraction on a sample-level. The test is validated across multiple cancer types to detect molecular residual disease (MRD) up to 2 years earlier than standard diagnostic tools, 2-5 with virtually no false positives ($<0.3\%$).²⁴

²²https://www.natera.com/sites/default/files/SGN_WP_2019_05_22_NAT-801919_DOWNLOAD.pdf?src=www.aushev.name/cv/ctDNA.pdf

²³https://www.natera.com/sites/default/files/SGN_WP_2019_05_22_NAT-801919_DOWNLOAD.pdf?src=www.aushev.name/cv/ctDNA.pdf

²⁴https://www.natera.com/sites/default/files/SGN_WP_2019_05_22_NAT-801919_DOWNLOAD.pdf?src=www.aushev.name/cv/ctDNA.pdf

As of September 2020, Natera has been granted final medicare coverage for MRD testing for patients with stage II and III colorectal cancer (CRC). In patients with CRC, MRD detection rates were observed to be low within 2 weeks post-surgery, whereas the background cfDNA levels were found to be elevated. This suggested that this time point is suboptimal for MRD detection due to the increased cfDNA load from surgery. Therefore, the Signatera test for MRD detection is conducted at an optimal time point of 6 weeks after surgery, when the cfDNA levels have normalized close to the baseline.²⁵

Figure 4: Relapse-free survival of locoregional breast cancer patients, stratified by ctDNA status

Detection of positive ctDNA after surgery and after adjuvant chemotherapy is associated with higher risk of relapse.

- Molecular relapse was detected at an average of 9.5 months

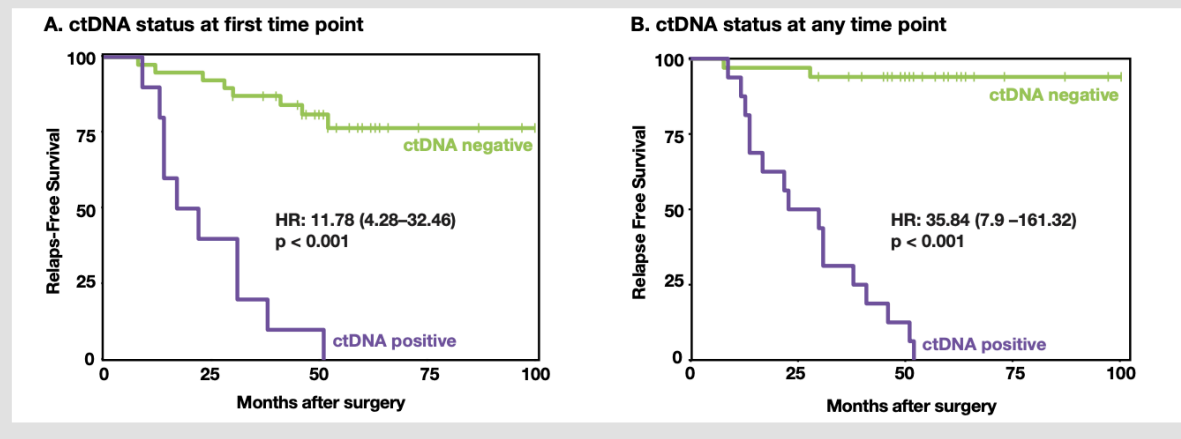
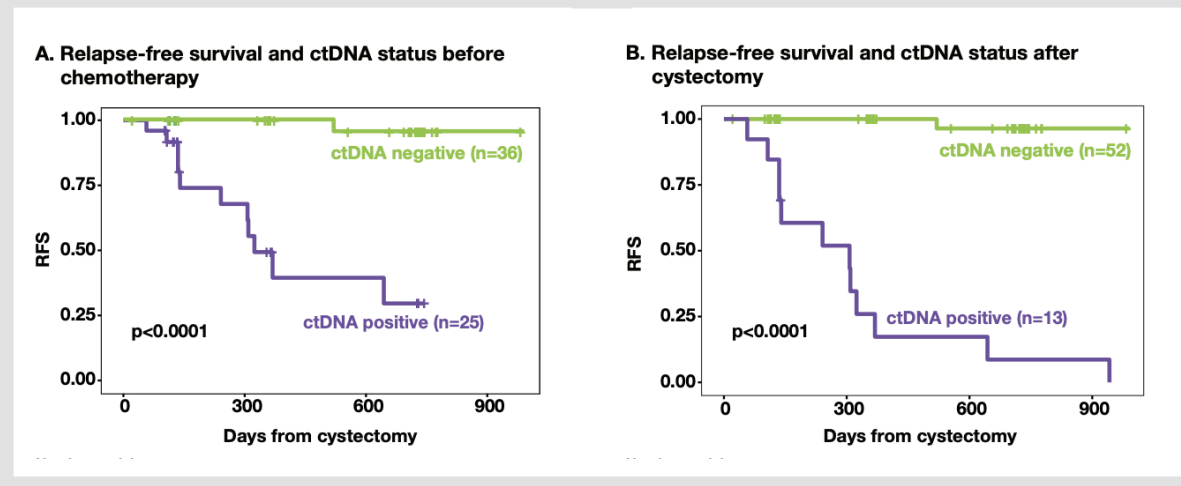


Figure 5: Relapse-free survival of MIBC patients, stratified by ctDNA status

Significantly shorter relapse-free rates were observed for patients who are ctDNA-positive at diagnosis and post cystectomy.

- Molecular relapse was detected at an average of 2.8 months before clinical relapse



²⁵https://www.natera.com/sites/default/files/ASCO%202020%20-%20Clin%20Experience%20Poster_Kasi_15%20May%202020.pdf

On another note, it is important to acknowledge that Natera has an ongoing consolidated lawsuit against ArcherDx and Genosity over patent infringement (Patent No. 10,732,220 - “Methods for Simultaneous Amplification of Target Loci”). The original suit against ArcherDx was filed in August of 2020, and the suit against Genosity was filed in early October of 2020. According to an article written by GenomeWeb, “Natera claimed that Genosity... does not have freedom to operate its AsTra products for minimal residual disease and personalized cancer monitoring” and that the company infringes Natera’s “‘220 patent” (GenomeWeb, 2020). As of December 2020, Natera has consolidated their lawsuit against Archerdx (originally filed in August) with one against Genosity for patent infringement in January and October 2020 respectively. This was the third patent infringement lawsuit initiated by Natera this year, after suing CareDx for infringing a different patent in early January. Natera has asked for a jury trial — however their request has yet to be fulfilled as far as the internet/public is aware. Patent jury trials have become far less prevalent over the years due to the sheer amounts of “no-discovery” claims and because the discovery processes tend to be incredibly time-consuming and expensive. Thus, this may likely be an attempt by Natera to bleed out Genosity and ArcherDx, companies with far smaller balance sheets and subsequently less time, money and resources to pour into a potentially frivolous lawsuit.^{26 27}

Savran Technologies Inc.

Savran Technologies is a biotechnology company based in Massachusetts. Savran is attempting to modify the current non-invasive diagnostics of multiple cancers: heavily focusing on breast while also being able to monitor lung, prostate, and colorectal cancers. Savran is using unique micro-fluidic designs and processes to offer as many advantages as possible in a scalable rare cell detection platform: utilizing centrifuge-free operation with streamlined workflow, rapid processing, high capture efficiency and purity, and individual cell delivery for downstream analysis.²⁸ Savran announced the completion and conduction of their “Phase 2” multi-center clinical trials in twenty different sites around the country on October 15, 2020.²⁹

Savran’s Tech uses a unique and patented technology to capture rare (~ 1 in a billion) cells from a tube of unprocessed blood samples. CTC are detected using an

²⁶<https://www.genomeweb.com/business-news/natera-sues-archerdx-infringement-new-target-amplification-patent#.X8rBU RNKiEs>

²⁷<https://www.genomeweb.com/sample-prep/natera-sues-genosity-patent-infringement-relating-archerdx-products#.X8rBgB NKiEs>

²⁸<https://www.businesswire.com/news/home/20201015005035/en/Savran-Technologies-Inc.-Rare-Cell-Detection-Platform-Contributes-to-Successful-Clinical-Trial-for-Detecting-Breast-Cancer-Recurrence>

²⁹<https://www.precisiononcologynews.com/molecular-diagnostics/savran-technologies-target-breast-cancer-recurrence-circulating-tumor-cell#.X8m0X6pKhb8>

epithelial cell adhesion molecule-based positive-selection microfluidic device. Specifically, after receiving standard neoadjuvant treatment, 10 ml of a patient's blood are extracted, then, Savran uses magnetic beads conjugated with antibodies against a specific antigen to capture cells overexpressing the antigen. The target-bound beads then flow through a silicon microfluidic chamber and are drawn to a microchip by an external magnetic field. Then, Savran uses another company's biopsy in tandem with the microfluidic device to profile the ctDNA and enumerated CTC using fluorescent microscopy.

The company published a paper in ³⁰JAMA Oncology, which is the largest of its kind to date, regarding usage of circulating biomarkers with triple negative breast cancer patients who had residual disease. Results demonstrated that circulating markers were more successful in predicting relapse than other, more commonly used clinical markers such as tumor size, lymph node status, grade and stage. Augmenting a ctDNA analysis with Savran Technologies' CTC analysis platform improved the sensitivity of predicting relapse to 90%. Savran chose to use CTC's as a biomarker because they can be isolated in plasma when the index mutations are not covered by the ctDNA assay, or have low concentrations and/or shedding of ctDNA. Hence, using both CTC's and ctDNA as biomarkers provides insurance that minimal residual disease will be identified. ³¹Savran had a CTC detection capability of roughly 41% (on average) during their study. By combining their individual tests of ctDNA and CTC into a joint test, Savran was able to boost their sensitivity from 79% with only ctDNA and 62% with only CTC to 90% using both. It should also be noted that when these tests are used in tandem, the ctDNA acts as a safety net for the CTC and vice versa - this allows for multiple DDFS curves (+CTC -ctDNA, +ctDNA -CTC, and +CTC +ctDNA), giving more specific testing times and requirements for follow ups as well as making it easier to monitor and track the progression of the residual disease (Figure 2. Survival of Study Patients With vs. Without Circulating Tumor DNA (ctDNA) and Circulating Tumor Cells).

However, we believe it is important to understand that although their July 9th (2020) paper indicated that CTC's could be used in conjunction with ctDNA to monitor recurring disease, Savran is currently only focused on the CTC side of operations. As of November 9th 2020 (Precision Oncology, 2020), the company is planning to commercialize by 2022, but will require a liquid biopsy partner to combine Savran's CTC microfluidic chip platform with this partner's ctDNA assay in order to bring the fully executed product to market. The company's CEO also believes that they will likely seek breakthrough device designation from the FDA in

³⁰ http://savranlab.org/wp-content/uploads/2020/07/savran_milan_JAMA.pdf

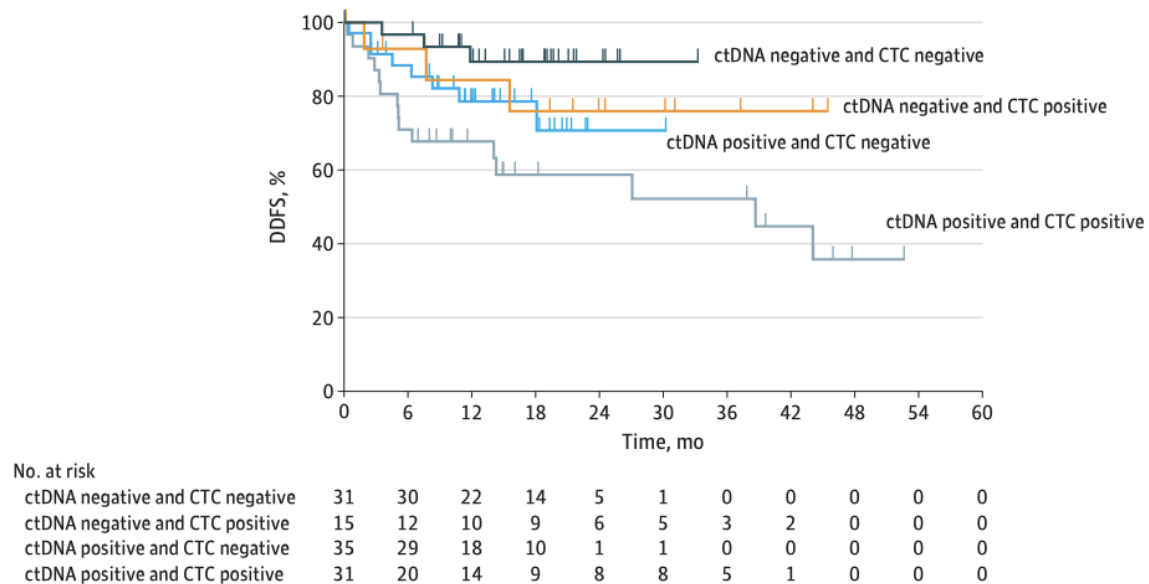
³¹ <https://sci-hub.se/https://jamanetwork.com/journals/jamaoncology/article-abstract/2768007>

lieu of 501(k) clearance or the offering of a lab-developed test — believing that CTC-capture platforms are becoming more applicable to cancer recurrence monitoring and MRD detection technologies. Angle (Parsotix technology), Menarini-Silicon Biosystem (CellSearch technology), and Cellular Analytics (CytoFind technology) appear to be a few companies working on similar CTC assays.

Median follow-up testing is around the 17 month marker as the DDFS after this point begins to lower more rapidly.

Figure 2. Survival of Study Patients With vs Without Circulating Tumor DNA (ctDNA) and Circulating Tumor Cells (CTCs)

A Association of ctDNA and CTCs with DDFS



Savran’s unique micro-fluidic designs and processes place them in a unique category among other solid tumor MRD monitoring companies. As they themselves are not developing an assay, but an accompaniment, Savran has the capability to work with existing FDA approved assays. This places Savran on a fast track to bring their technology to market — tentatively planning to commercialize by 2022, requiring a liquid biopsy partner to combine their CTC microfluidic chip platform with a ctDNA assay. Savran’s microchip platform will utilize both ctDNA and CTC (once the partnership is established), a unique approach that has not been seen by any of the other companies currently in the market. Monitoring Savran’s movements and partnerships in the near future will shed light on the direction they are taking (along with their partner) towards furthering sensitivity and specificity of MRD detection.

Performance Requirements

Company	Precursor	MRD Sequencing	Tech Platform
Adaptive Biotechnologies (plasma)	—	Multiplex Polymerase Chain Reaction & Next Generation Sequencing	Uses MPCR and NGS – does not require the construction of patient specific reagents; each step is monitored by corresponding molecule (no false negatives)
ArcherDx (tissue & plasma)	✓	Whole Exome Sequencing	WES of resected (ONLY) non-small cell lung cancer patient samples to generate patient-specific circulating tumor DNA (ctDNA) assays
C2I Genomics (tissue & plasma)	—	Whole Genome Sequencing	Sequence whole tumour, shallow whole genome sequencing of the blood, non-personalized MRD assay
Genosity (tissue & plasma)	✓	Whole Exome Sequencing	3 step testing platform. Astra Profile: sequences exome, generates ctDNA assay; Astra One: initial MRD assesment; Astra Next: ongoing monitoring and MRD assesment
GRAIL (tissue & plasma)	✓	Methylation	Galleri platform: scans 30 million methylation sites within the genome and utilizes informative and low-noise methylation regions for optimal signal detection and localization – overcoming low ctDNA levels in samples
Inivata (tissue & plasma)	✓	Whole Exome Sequencing	InVisionFirst® technology (uses WES) performed on tissue to identify, rank and prioritize 48 somatic variants which are used to design personalized assays that detect ctDNA
Natera (tissue & plasma)	—	Whole Exome Sequencing	Breakthrough Devices designation by FDA and positive medicare coverage for stages II&III of CRC. Uses WES of tumor tissue to identify 16 variants to design personalized assays that detect ctDNA
Savran Technologies (tissue & plasma)	—	Circulating Tumor Cell Detection*	CTC capture technology using epithelial cell adhesion molecule-based positive-selection microfluidic device, allows magneted beads to capture cells overexpressing specific cancer marking antigens

Table 1: Competitive analysis of each firm's technology platforms for solid tumor MRD detection and monitoring. For some companies, we could not find published figures for existing MRD technology due to the technology's ongoing development. However, we were able to find published material surrounding their precursor cancer detection technologies. These technologies will ultimately prove to be extremely similar to those used in the MRD monitoring technology each company plans to commercialize.

	Tech Platform	Min DNA	Coverage	Sensitivity	Specificity	VAF
Adaptive Biotechnologies (plasma)	MPCR and NGS	500ng - 20ug	22,224 MRD measurements	99.9999%	100%	0.001%
ArcherDx (tissue & plasma)	WES	10 ng	14,000x of ctDNA	58-100%**	100%	0.003%
C2I Genomics (tissue & plasma)	WGS	1-5 ng	35x of cfDNA	85%	99%	.001%***
Genosity (tissue & plasma)	WES	—	500x of WES	—	—	—
Inivata (tissue & plasma)	WES	6.6-53 ng	>100,000 reads per locus	97%	100%	0.06 - 0.08%
Natera (tissue & plasma)	WES	15 ng	100,000x of ctDNA	99.90%	95%	0.01%
Savran Technologies (tissue & plasma)	CTC*	—	—	90%	—	—

*Savran does not have an assay and does not utilize any of the normal techniques, they provide accompaniment to the assays with a microfluidic device via fluorescent microscopy

**Refer to the table in paper regarding range in sensitivity

***C2i reports using TF (tumor fraction) values rather than VAF; their TF values range from .0001% - .00001%

Table 2: Summary of the quantitative metrics of each company's technology, measurement specifications and quoted performances.

Disease Types

	Breast	Bladder	Colon	Colorectal	Lung	Melanoma
ArcherDx (tissue & plasma)	✓			✓	✓	
C2I Genomics(tissue & plasma)	✓		✓		✓	✓
Genosity (tissue & plasma)	✓				✓	
Inivata (tissue & plasma)	✓		✓		✓	✓
Natera (tissue & plasma)	✓	✓		✓	✓	
Savran Technologies (tissue & plasma)	✓			✓	✓	

Table 3: Most common solid tumor cancers targeted by firms for MRD detection. Breast and Lung cancer appear to be the most commonly targeted tumors for companies entering, or looking to enter the industry.

	Nasopharyngeal	Osteocarcoma	Ovarian	Pancreatic	Prostate	Rectal	Hematological
Adaptive Biotechnologies (plasma)							✓
ArcherDx (tissue & plasma)	✓			✓		✓	
C2I Genomics(tissue & plasma)		✓					
Genosity (tissue & plasma)			✓				
Savran Technologies (tissue & plasma)					✓		

Table 4: Less commonly targeted solid tumors for MRD detection.

Financial Valuations

Company	Financial Valuation	Valuation Type
Adaptive Biotechnologies (US)	\$6.4 billion	<i>Market Capitalization</i>
ArcherDx (US)	\$1.4 billion; \$8.8 billion	<i>Acquisition Value; Parent Co. MC</i>
BGI Genomics (China)	\$7.8 billion	<i>Market Capitalization</i>
C2i Genomics (US)	\$12 million	<i>Series A</i>
Genetron Health (China)	\$1.2 billion	<i>Market Capitalization</i>
Genosity (US)	> \$150k-350k	<i>Loan in 2020</i>
GRAIL (EU and US)	\$8 billion; \$50.5. billion	<i>Acquisition Value; Parent Co. MC</i>
Inivata (EU and US)	\$45 million	<i>Series A</i>
Natera (US)	\$7.5 billion	<i>Market Capitalization</i>
Roche (EU)	\$285.3 billion	<i>Market Capitalization</i>
Savran Technologies (US)	\$233k	<i>Angel Funding</i>

Table 5: Rough estimate of financial muscle, commercialization abilities and scalability capabilities. Companies such as GRAIL and ArcherDx are now backed by mega-cap biotechnology companies with strong balance sheets, indicating that commercialization and scale will occur much more quickly and easily than smaller, leaner and more nimble companies such as C2i Genomics.

International Competition

UK (EU) — GRAIL

³²As of November 26th 2020, GRAIL announced a commercial partnership with the NHS England and the UK Government to confirm Galleri's clinical and economic performance in the NHS system as a precursor to its routine use by the NHS. The partnership program will involve approximately 165,000 people in the UK and will include two groups — one of people over the age of 50 with no cancer suspicion and the other of people aged 40 and above with cancer suspicions. The data from this program will hopefully allow the test to be expanded to nearly one million people in the UK across 2024 and 2025. GRAIL will likely begin its initial commercialization efforts for Galleri in the UK, indicating that their MRD platform may also begin commercialization in the UK.

UK (EU) — Inivata

Inivata is co-headquartered in the United Kingdom, and much of their research and development is done in their UK labs. They have previously collaborated with the UK government and its institutions for trials — indicating that they will have a strong presence in the nation for the commercialization of their MRD assay (and likely the EU).

China (Asia) — BGI Genomics

³³BGI Genomics (Beijing Genomics Institute) partnered with Natera in March of 2019 for a 10 year commercialization of Natera's Signatera MRD assay in China. The deal is estimated to be worth approximately \$50 million.

³² <https://www.yahoo.com/now/grail-uk-government-galleri-multi-005900582.html>

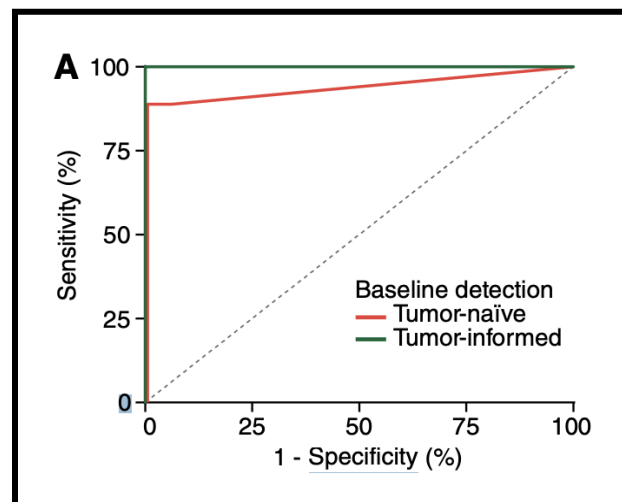
³³ <https://www.natera.com/press-releases/natera-and-bgi-genomics-announce-50m-partnership-commercialize-signatera-oncology>

China (Asia) – ImmuQuad and Genetron Health

Genetron Health has entered into an exclusive global licensing agreement to “research, develop, commercialize and manufacture ImmuQuad’s Seq-MRD” assay according to an article written by ³⁴NASDAQ on October 22nd 2020. They claim that “ImmuQuad is a leading biotechnology company in China focused on developing an immune profiling platform for clinical diagnostics and life sciences research. The Company’s proprietary immunomics platform employs next-generation sequencing (NGS) technology to read and decode the diverse genetic code of a patient’s adaptive immune system and applies it in key areas, encompassing MRD monitoring for hematologic cancers (i.e. Seq-MRD), early disease detection and cellular therapies discovery and development” (NASDAQ, 2020). It should be noted that the Seq-MRD assay is currently only being used for hematological cancers.

Switzerland (EU) – Roche

In 2015, CAPP Medical was acquired by Roche for its CAPP-SEQ platform — a ctDNA detection technology spun out of the Stanford University School of Medicine that has applications for monitoring minimal residual disease in non-small cell lung cancer. The Capp-SEQ is an NGS based assay that can sensitively track ctDNA while maintaining a relatively high specificity. Capp-SEQ possesses integrated digital error suppression for improved detection of ctDNA. It should be noted that Roche has yet to put their Capp-SEQ to an actual test, all of this is all in silico. Capp-SEQ can perform with up to a maximum of 32ng of cfDNA or 32ng of sonicated DNA from plasma depleted whole blood. The Capp-SEQ detected the presence of ctDNA by monitoring tumor mutations, overlapped with the Capp-SEQ selector and Monte Carlo-based ctDNA detection index (cutoff point → $P \leq .05$). Capp-SEQ can be utilized for both tumor informed and tumor naive scenarios, although its performance rate does drop for those tumor naive scenarios. The sensitivity for tumor informed cancers is $\geq 95\%$, while the sensitivity for tumor naive cancers drops to 89%.



³⁴<https://www.nasdaq.com/press-release/genetron-health-enters-exclusive-global-licensing-agreement-with-immuquad>

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