FROST & SULLIVAN

exosomics

2018 European Exosome-based Liquid Biopsy Enabling Technology Leadership Award

2018
BEST PRACTICES
AWARDS

Background and Company Performance

Industry Challenges

According to the World Health Organization, cancer is the second leading cause of death and accounts for nearly 1 in 6 deaths globally. In 2015 alone, cancer was responsible for 8.8 million deaths. Inaccessible diagnosis, advanced stage presentation, and delayed treatment are the primary reasons for the recorded deaths.[1]

Tissue biopsy, the current method for oncology diagnosis, provides limited diagnostic insights. Tissue samples represent the tumor non-heterogeneously. Restricted monitoring limits treatment decisions for therapy and personalized medication. The traditional biopsy is a painful, expensive, and complicated surgical procedure. While multiple screening methodologies exist, these tests are specific to certain kinds of cancer and are not broadly applicable. Moreover, the clinical utility of multiple cancer screening tests is poorly established due to incorrect assessment results, which then requires a subsequent investigation for further assessment and confirmation.[2] Testing for different cancer types bears a significant cost prompting an urgent need for a pan-cancer screening test.

A Compelling Need for an Enabling Technology to Assist Effective and Minimally Invasive Early Cancer Screening

Unfavorable treatment outcomes and a poor survival rate are common for cancer diagnosed at an advanced stage. The 5-year relative survival rate of patients diagnosed early with localized lung, colorectal, or breast cancer is 50%, 90%, and 98%, respectively—much higher than late-stage detection. Statistical evidence suggests early-stage cancer diagnosis before metastasis and incurability have a significant impact on enhanced cancer survival rate.[3] An early cancer screening of healthy and high-risk population improves the opportunity for therapy and healing manifold. There is a growing need for a minimally invasive early cancer detection technique to enable proper treatment of patients.[4]

A liquid biopsy is a minimally invasive, low-cost cancer screening technique, which gives in-depth insights into the molecular alterations in the tumor. Liquid biopsy is key to managing and prompting the treatment of most cancers as it facilitates early detection through tumor profiling and enabling critical invasive biopsy and clinical decision management.[5] However, a significant challenge that thwarts liquid biopsy efficiency

1 World Health Organization,"Cancer," http://www.who.int/news-room/fact-sheets/detail/cancer. (accessed August, 2018).
2Hsin-Yao Wang et al., "Cancers Screening in an Asymptomatic Population by Using Multiple Tumor Markers," PLoS One 11, no. 6 (2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4927114/. (accessed August, 2018).
3 Danni L. Meany et al., "Early Detection of Cancer: Immunoassays for Plasma Tumor Markers," Expert Opinion on Medical Diagnostics 3, no. 6 (2009), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2788950/. (Accessed August, 2018).
[4] *Innovations in Immunoassays, Cancer Detection, Ophthalmic Disease Detection, Vital Signs Monitoring, CT Systems, and Ultrasound Imaging Systems* (Frost & Sullivan, April 2018)
[5] *Innovations in Liquid Biopsy Techniques for Cancer Management* (Frost & Sullivan, August 2017)

relates to the lack of an enabling technology which could enhance the effectiveness of retrieval and culture of assay material used for biopsy.

Poor Assay Sensitivity Restricts Performance of Liquid Biopsy to Render Inferior Screening Result

Investigational assay material and analysis techniques affect liquid biopsy results appreciably. Liquid biopsy tests used for early detection are known to have low sensitivity owing to poor assay quality, which primarily depends on the source of material. Currently, used sources of liquid biopsy assay comprise of investigating circulating free DNA and RNA (cfDNA and cfRNA), circulating tumor cell (CTC) and exosomes. CfDNA is a tricky analyte due to fragmentation, the low yield of mutated DNA molecules, and an uneven amalgamation of normal DNA with the cfDNA, which challenges detecting genome anomalies and mutations responsible for tumors.[6] CTCs shed in blood are rare to retrieve and require expensive instrumentation. Poor assay quality with a limited molecular representation of tumor renders poor screening results. The third source of liquid biopsy material—exosomes, shed into the blood from tumor cells, are channels of robust information for multi-analyte analysis, cancer screening, monitoring, and studying drug resistance through its DNA, RNA, and protein. However, exosome-based liquid biopsy tests use generic exosomes that have poor sensitivity and specificity—lowering test effectiveness to offer marginal utility about treatment recommendations for early cancer detection.

There is a growing need for an exosomes-based early cancer screening test with a focus on a superior genomic and investigational technology to facilitate precise imaging and improve the potential to characterize highly specific tumor biomarkers for cancer detection.[7] An innovative technology that develops liquid biopsy assays with tumor-derived exosomes to detect tumor biomarkers will allow holistic tumor profiling and effective screening.

Technology Leverage and Customer Impact of Exosomics Siena S.p.A.

Founded in 2012, Exosomics Siena S.p.A. (Exosomics Siena) researched for several years before commercializing and launching its solution into the molecular diagnostic market. Exosomics Siena considers exosome-based liquid biopsy as the next generation cancer diagnostics mechanism, which will not only complement but surpass traditional biopsy in adoption owing to its superiority to present insights into the molecular genesis of the tumor and being easily repeatable and retrievable.

[6] http://mcr.aacrjournals.org/content/14/10/898
[7] https://www.ncbi.nlm.nih.gov/pubmed/25993143

Disruptive Technology Enables the Development of Superior Quality Tumor-Derived Exosome-based Liquid Biopsy Assays

Exosomics Siena's vision is creating best in class enabling technology to develop an excellent quality of tumor-derived assay material for cancer screening tests. The company believes that high-quality genomic material, as input for any downstream analytical assay (polymerase chain reaction—qPCR, ddPCR, and next-generation sequencing) is of utmost importance for superior test performance. Through its proprietary technology, Exosomics Siena harvests exclusive tumor-derived exosomes for selective isolation of tumor-derived protein, DNA, and RNA (miRNA), and meets a critical medical need. Unlike its competitors, who harvest generic exosomes that contain mostly confounding noise from non-tumor derived exosomes, Exosomics Siena assists in developing the finest quality cancer-screening assays.

Given that tumor-derived exosomes contain biomarkers identical to biomarkers expressed on a cancer cell surface and poorly expressed in healthy humans, Exosomics Siena engineers its technology to target Warburgian biomarkers expression. The positron emission tomography (PET) scans use Warburgian biomarkers to study tumor metabolism through changes in the respiration pattern of cancer cells. Exosomic Siena's technologies allow more efficacious cancer screening tests for cancer stratification, accurate staging, and early detection leading to improved patient outcomes, and understanding the resistance to particular therapy. The technology is robust in developing repeatable, high-quality assays to analyze even hard to track tumors, like in the pancreas where tumor genomic material extraction is challenging due to histological physiognomies of this malignancy.

Positioning Enabling Technologies across Molecular Diagnostic Continuum to Maximize Market Potential

The company follows cutting-edge best practices with the long-term goal to develop a pan-cancer test for asymptomatic patients (Cancer-rEVeal TM). Exosomics Siena's innovative model develops profitable proprietary technologies in the molecular diagnostic space that facilitate effective cancer screening. The technology development encompasses three stages that contribute towards enhanced early cancer screening. The first stage includes a novel solution for plasma collection. Exosomics Siena's technology establishes standardization of plasma collection in the cancer screening molecular diagnostic industry. The company's proprietary technology prototype concept supersedes other techniques in cost-effectiveness, simplicity, and homogenizes and will harmonizes the plasma collection process with a standardized centrifuge-free procedure.

The second stage, which has patents granted for an aspect of technology, provides low-cost molecular screening with a proprietary exosome-based immunoassay, based on higher specificity and sensitivity. This stage gives either a positive or negative result. A positive result leads to the third stage that involves cancer confirmation and typing.

Exosomics Siena's third-stage molecular diagnostic technology under development for early cancer screening is based on RNA signatures and confirms and localizes tumors. The company leverages diagnostics based on miRNA and RNA analysis for better insights into cancer. Being a robust molecular diagnostic assay, it studies and analyzes several cancer categories each with a unique expression pattern and enables segregation to recognize one or more cancer types. The company has secured an exclusive license for the assay technology.

Frost & Sullivan asserts that Exosomics Siena's technology is the superior molecular diagnostics for early cancer screening and monitoring with its multiple stage diagnosis—from plasma separation to cancer confirmation and typing. Additionally, the company's long-term goal to develop a pan-cancer test will fulfill a critical unmet medical need by enabling screening and localization of multiple cancer types.

Optimizing Experiences of Diagnostic Kit Developers, Laboratory Service Providers, and Big Pharma

Exosomics Siena's optimizes customer experience through a range of original equipment manufacturer (OEM) solutions for best quality analytical assay development and reliable reporting. An entire pipeline of diagnostic solutions caters to blood processing, nucleic acid extraction, and assay development from bio fluids.

Diagnostic lab services providers (cancer research and hospital) and diagnostic kit manufacturers will benefit from the company's expertise in blood processing and plasma separation harmonizer.

Another offering is the Molecular Dx Kit Line, which is a pre-analytical solution suite that facilitates enrichment and analysis of tumor-derived exosomes for analytical assay development. The solution suite comprises of the SeleCTEV™DNA and the SoRTEV™ RNA kits (the "Enrichment Kits") and can be combined with an analytical assay solution from a partner or provided by Exosomics if a partner does not have such a solution. The Enrichment Kits for selective exosomes isolation of DNA and RNA are designed by use of a battery of proprietary products, which binds to exosomes to harvest pure tumor-derived RNA. Additionally, for market players using exosomes-based liquid biopsy, the company offers ExoRefs—the exosomes reference standard solution to enable benchmarking.

Exosomics Siena caters to the entire continuum of molecular diagnostic know-how—biophysical, biochemical, and molecular biology analysis to characterize content and facilitate tumor detection. Its superior molecular diagnostic expertise and pipeline of an end-to-end molecular diagnostic solution suite promises new customer acquisition both in diagnostic and in therapeutic fields. In fact, for big pharma, contract development and manufacturing organizations, Exosomics Siena's platform and knowledge in isolating the right biomarkers should help to develop the next generation of exosome disease-driven companion diagnostics. The company seeks to revamp the skewed perception of

diagnostic kit developers by aiming to educate them about the significance of the quality of the input material in determining test results for better patient outcomes rather than focusing mainly on the performance of analytical part.

Building Brand Equity through Strategic Collaboration with Key Industry Leaders

Exosomics Siena positions its brand in the multi-cancer testing segment for asymptomatic patients (long-term) and the molecular diagnostics market (medium-long term). The company actively publicizes itself on the most followed channels for exosome-based oncology diagnostics and aggressively participates in cancer-related conferences and exhibits in healthcare congresses.

Having received a strategic investment and active participation in formulation of commercial and business strategy from Lonza, one of the world's leading suppliers to the pharma and life-science industry, Exosomics Siena benefits from a joint synergy for brand development while appealing to Lonza's clinical interests in supporting the exosome-based life-science applications. Exosomics Siena is in a starting phase of the preparation of its next round of financing. The company intends to start its discussions with strategic and investment partners to successfully commercialize its launched solutions for the diagnostics market with brand building, while completing its development of early cancer-screening products. The company seeks to collaborate with analytical assay developers and become the most preferred supplier of OEM diagnostic solutions for their analytical assay kits. Exosomics Siena aims to synergize efforts with diagnostic kit developers for co-marketing to hospitals and research laboratories. By demonstrating usability and application of DNA and RNA enrichment technology commercially in the molecular diagnostics industry, the company aims to validate simultaneously its method and approach for its pan-cancer screening technology. The pending validation will shape positive perceptions and strengthen consumer and investor confidence to boost brand equity, positioning and market acceptance.

Conclusion

Exosomics Siena's novel proprietary technology enables an exosome-based diagnostic solution development for liquid biopsy screening. Its range of molecular diagnostic solutions provides its customers the ability to formulate the best quality of analytical assays with the highest sensitivity and specificity for prognosis, screening, and monitoring by working on high quality relevant tumor material. With the detection of tumor biomarkers through isolation and characterization of tumor-derived exosomes, Exosomics Siena's technology allows early cancer diagnosis and treatment decisions to improve survival rate. Due to its strong focus on radically changing and developing a new class of liquid biopsy assays, and an aim to design a pan-cancer screening test to detect cancer in asymptomatic patients, Exosomics Siena earns Frost & Sullivan's 2018 Europe Enabling Technology Leadership Award in the exosome-based liquid biopsy market.

Significance of Enabling Technology Leadership

Ultimately, growth in any organization depends upon customers purchasing from a company and then making the decision to return time and again. In a sense, then, everything is truly about the customer—and making those customers happy is the cornerstone of any long-term successful growth strategy. To achieve these goals through enabling technology leadership, an organization must be best-in-class in three key areas: understanding demand, nurturing the brand, and differentiating from the competition.

Understanding Enabling Technology Leadership

Product quality (driven by innovative technology) is the foundation of delivering customer value. When complemented by an equally rigorous focus on the customer, companies can begin to differentiate themselves from the competition. From awareness, to consideration, to purchase, to follow-up support, best-practice organizations deliver a unique and enjoyable experience that gives customers confidence in the company, its products, and its integrity.

Key Benchmarking Criteria

For the Enabling Technology Leadership Award, Frost & Sullivan analysts independently evaluated two key factors—Technology Leverage and Customer Impact—according to the criteria identified below.

Technology Leverage

Criterion 1: Commitment to Innovation

Requirement: Conscious, ongoing adoption of emerging technologies that enables new product development and enhances product performance

Criterion 2: Commitment to Creativity

Requirement: Technology leveraged to push the limits of form and function in the pursuit of "white space" innovation

Criterion 3: Stage Gate Efficiency

Requirement: Adoption of technology to enhance the stage gate process for launching new products and solutions

Criterion 4: Commercialization Success

Requirement: A proven track record of taking new technologies to market with a high rate of success

Criterion 5: Application Diversity

Requirement: The development and/or integration of technologies that serve multiple applications and can be embraced in multiple environments

Customer Impact

Criterion 1: Price/Performance Value

Requirement: Products or services offer the best value for the price, compared to similar offerings in the market.

Criterion 2: Customer Purchase Experience

Requirement: Customers feel they are buying the most optimal solution that addresses both their unique needs and their unique constraints.

Criterion 3: Customer Ownership Experience

Requirement: Customers are proud to own the company's product or service and have a positive experience throughout the life of the product or service.

Criterion 4: Customer Service Experience

Requirement: Customer service is accessible, fast, stress-free, and of high quality.

Criterion 5: Brand Equity

Requirement: Customers have a positive view of the brand and exhibit high brand loyalty.

Best Practices Recognition: 10 Steps to Researching, Identifying, and Recognizing Best Practices

Frost & Sullivan analysts follow a 10-step process to evaluate Award candidates and assess their fit with select best practice criteria. The reputation and integrity of the Awards are based on close adherence to this process.

STEP		OBJECTIVE	KEY ACTIVITIES	OUTPUT
1	**Monitor, target, and screen**	Identify Award recipient candidates from around the globe	• Conduct in-depth industry research • Identify emerging sectors • Scan multiple geographies	Pipeline of candidates who potentially meet all best-practice criteria
2	**Perform 360-degree research**	Perform comprehensive, 360-degree research on all candidates in the pipeline	• Interview thought leaders and industry practitioners • Assess candidates' fit with best-practice criteria • Rank all candidates	Matrix positioning of all candidates' performance relative to one another
3	**Invite thought leadership in best practices**	Perform in-depth examination of all candidates	• Confirm best-practice criteria • Examine eligibility of all candidates • Identify any information gaps	Detailed profiles of all ranked candidates
4	**Initiate research director review**	Conduct an unbiased evaluation of all candidate profiles	• Brainstorm ranking options • Invite multiple perspectives on candidates' performance • Update candidate profiles	Final prioritization of all eligible candidates and companion best-practice positioning paper
5	**Assemble panel of industry experts**	Present findings to an expert panel of industry thought leaders	• Share findings • Strengthen cases for candidate eligibility • Prioritize candidates	Refined list of prioritized Award candidates
6	**Conduct global industry review**	Build consensus on Award candidates' eligibility	• Hold global team meeting to review all candidates • Pressure-test fit with criteria • Confirm inclusion of all eligible candidates	Final list of eligible Award candidates, representing success stories worldwide
7	**Perform quality check**	Develop official Award consideration materials	• Perform final performance benchmarking activities • Write nominations • Perform quality review	High-quality, accurate, and creative presentation of nominees' successes
8	**Reconnect with panel of industry experts**	Finalize the selection of the best-practice Award recipient	• Review analysis with panel • Build consensus • Select recipient	Decision on which company performs best against all best-practice criteria
9	**Communicate recognition**	Inform Award recipient of Award recognition	• Present Award to the CEO • Inspire the organization for continued success • Celebrate the recipient's performance	Announcement of Award and plan for how recipient can use the Award to enhance the brand
10	**Take strategic action**	Upon licensing, company is able to share Award news with stakeholders and customers	• Coordinate media outreach • Design a marketing plan • Assess Award's role in future strategic planning	Widespread awareness of recipient's Award status among investors, media personnel, and employees

The Intersection between 360-Degree Research and Best Practices Awards

Research Methodology

Frost & Sullivan's 360-degree research methodology represents the analytical rigor of our research process. It offers a 360-degree-view of industry challenges, trends, and issues by integrating all 7 of Frost & Sullivan's research methodologies. Too often companies make important growth decisions based on a narrow understanding of their environment, leading to errors of both omission and commission. Successful growth strategies are founded on a thorough understanding of market, technical, economic, financial, customer, best practices, and demographic analyses. The integration of these research disciplines into the 360-degreeresearch methodology provides an evaluation platform for benchmarking industry participants and for identifying those performing at best-in-class levels.

360-DEGREE RESEARCH: SEEING ORDER IN THE CHAOS

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