

F R O S T & S U L L I V A N

FROST & SULLIVAN BEST PRACTICES AWARD

CANCER TREATMENT DEVICES - NORTH AMERICA

Technology Innovation 2019



FROST & SULLIVAN

2019

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Background and Company Performance

Industry Challenges

Liver cancer is among the most pervasive cancers globally. It ranks sixth on the list of most common cancer types, accounting for 4.7% of all new cancer cases reported across the globe in 2018.¹ According to the International Agency for Research on Cancer (IARC), an intergovernmental agency and affiliate of the World Health Organization (WHO), there were approximately 841,080 new liver cancer cases in 2018, which is expected to rise by a whopping 62% to reach 1,361,836 by 2040. Another area of grave concern is the survival rate associated with liver cancer, which is abysmally low as compared to other cancer types. According to the American Cancer Society, the 5-year relative survival rate for patients with liver cancer is 18% as against an average of 69% for other cancer forms.

Treatment for liver cancer involves use of invasive as well as minimally invasive methods. Though both methods provide curative treatment for the condition, they have their own share of drawbacks, which limits their use. Some of the limitations are summarized in figure 1.

Figure 1: Liver Cancer Treatment Continuum

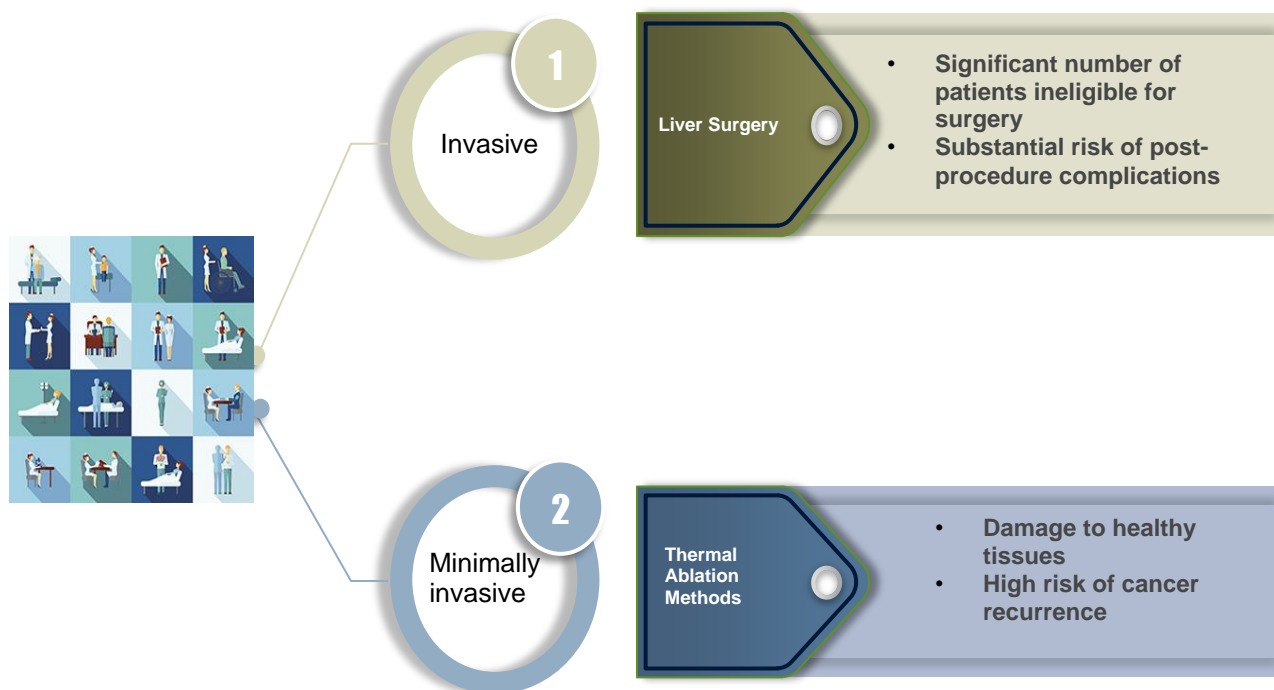


Image Source: Frost & Sullivan

Traditionally, liver surgery is performed to remove tumors through surgical resection. This open, or invasive, procedure involves removal of the affected part of the liver if the tumor size is small. However, most patients are ineligible for a surgical procedure due to anatomic distribution of the tumor, and if a large portion of the liver would have to be

¹ [International Agency for Research on Cancer](#)

excised. Moreover, the complications associated with surgery such as bleeding, risk of infection, and blood clots are major concerns for patients' safety.

Minimally invasive treatment modalities such as radiofrequency ablation (RFA) offer a viable alternative owing to the less invasive nature of these procedures as compared to surgical resection. However, minimally invasive procedures suffer from a high recurrence rate of the cancer and can significantly damage healthy tissues that surround the tumor.

The limitations of current liver cancer treatment methods have driven demand for an option that is non-invasive or requires fewer incisions and involves minimal complications. Frost & Sullivan believes the success of a new treatment modality depends upon its ability to address patients' health, safety, and cost concerns while at the same time provide a comparable or more effective treatment than current modalities deliver.

Technology Attributes and Future Business Value

Industry Impact

Founded in 2009, with offices in Ann Arbor, Michigan, and Plymouth, Minnesota, HistoSonics, Inc. has developed a breakthrough non-invasive robotic platform aimed at overcoming the limitations of current modalities used to treat a variety of liver tumors and cancers today. The company has developed a novel beam therapy and new medical procedure called Robotically Assisted Sonic Therapy (RAST)[™] that can destroy targeted tissues, including solid tumors, at sub-cellular levels. RAST, uses the science of histotripsy and the pressure created by focused ultrasound to mechanically destroy and liquify diseased tissues and tumors at subcellular levels, creating an acellular, soluble slurry, allowing for rapid healing and resolution. The non-invasiveness of this technique eliminates the need to perform painful incisions as is typically required in current surgical and ablation methods, and significantly reduces the trauma patients must otherwise endure, in turn improving the overall patient experience.

Moreover, for patients undergoing thermal ablation methods such as RFA, or radiation therapy such as SBRT, there is always a risk of causing collateral damage as adjoining healthy tissues are also destroyed along with the tumor tissues. This leads to a host of post-procedure complications that may affect patients' health outcomes. RAST, in contrast, uses histotripsy and high pressure, micro-second ultrasound pulses that lead to mechanically induced cellular destruction of the target areas without damaging surrounding tissues, subsequently potentially eliminating the risk of many complications in patients. Specifically, these high-pressure pulses are focused to a singular point where it extracts micron and submicron sized gas bubbles which expand and collapse thousands of times per second. This precision "bubble cloud" can be tailored in size as needed but can be as small as 1-2mm and is robotically guided through a pre-planned volume destroying tumors and diseased tissues without damaging intervening tissue or critical structures outside the planned ablation volume.

Product Impact

Precise localization of tumors in the liver is essential because the risk of disease recurrence can ensue if targeted treatment is unsuccessful. Yet real-time monitoring during treatment is difficult when using existing modalities, which makes it extremely challenging for the performing physicians to gauge procedural outcomes. In order to overcome this challenge, the HistoSonics' system was designed to use a coaxially aligned diagnostic ultrasound transducer that enables physicians to visualize both the bubble cloud as well as the treatment effect in the tissue in real-time. This feature helps in accurate identification of the target site and provides vital information regarding tumor size, location, and tissue characteristics throughout the treatment. The acoustic energy required to destroy the tumor tissue is determined through a volumetric sensing pattern creating an energy-based personalized treatment plan that is then robotically guided to the specified target area to facilitate complete destruction of the tumor. Frost & Sullivan is impressed that HistoSonics has developed an image-guided system that uses histotripsy technology to ablate tissues with robotic precision.



Another challenge healthcare providers face involves the time required to execute liver cancer treatment. On average, the estimated time to complete a procedure ranges between 80 minutes in case of RFA to several hours in case of liver surgery, depending on the size and location of the tumor. The procedures are not only time consuming but costly for patients. HistoSonics has managed to address this challenge by developing a system that can execute the entire therapeutic procedure within a span of 30 minutes, providing a rapid and cost-effective option for treating liver tumors.

Application Diversity

In addition to liver cancer, HistoSonics is developing its robotic system and RAST procedure for treatment of kidney and pancreatic tumors, as well as other underserved solid tumors. According to IARC, the number of new cases of the three types of cancer totaled 1.7 million in 2018. The number is expected to swell to 2.8 million by 2040, providing a large addressable market for the company.

The use of focused ultrasound pulses to accurately target tumor sites has created new application opportunities for different types of cancer treatment. For instance, the company believes that mid-term opportunities exist in treating tumors in organs such as thyroid and breast, and long-term in brain and lung, with proof of concept in all.

Customer Acquisition

A recent clinical study carried out to evaluate the technical effectiveness and safety of the HistoSonics' system has demonstrated favorable outcomes for patients. Results from the first-in-human clinical trial made public in June 2019 indicate that all 8 patients who underwent a RAST procedure were successfully treated —successfully destroying the planned volume of targeted tissue. None of the patients reported discomfort from the procedure at any timepoint including follow-up, and the average treatment time was 24 minutes.

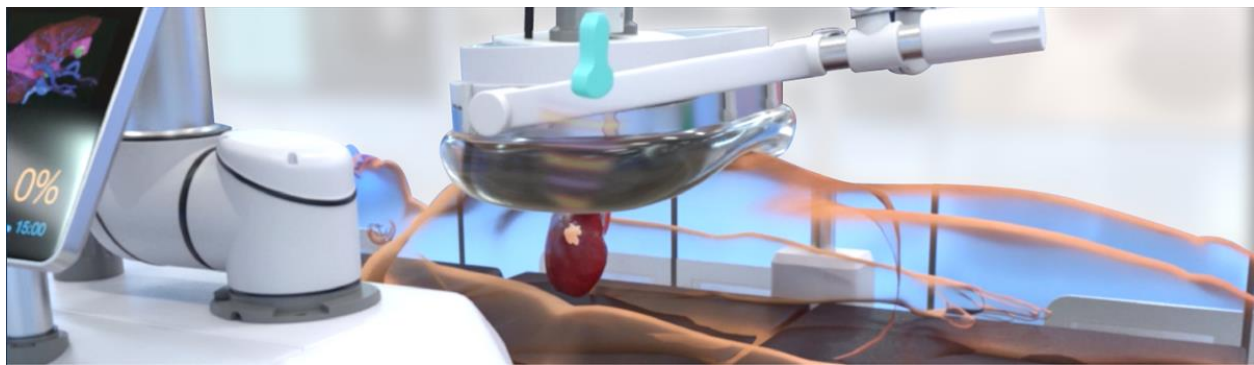
The promising study results have impressed the medical fraternity about RAST's success potential in safely and effectively treating cancerous tissues in a single treatment session. Moreover, data from preclinical studies highlight the ability of RAST to stimulate potent local, regional, and systemic tumor-specific immune responses at a far greater scale as compared to thermal or radiation ablation-based methods. Frost & Sullivan recognizes that these preclinical observations demonstrate the technology's potential to target tumor neoantigens through activation of the immune system by immunostimulatory effects. The ability to generate antitumor response to the intended primary tumor targets along with distant cancerous cells is expected to provide patients with a far more effective option for cancer treatment.

Brand Loyalty

Frost & Sullivan finds that a key differentiator offered by HistoSonics' platform system is its ability to provide rapid recovery for patients. Target areas that are subjected to RAST treatments have exhibited faster healing as compared to the current invasive and minimally invasive procedures. The swift recovery process is likely to drastically change the current standard of follow-up care by reducing frequent post-procedure physician visits. This shift is expected to not only decrease patient anxiety levels and recovery time but also grant them significant cost savings, all of which are factors expected to play a pivotal role for the market adoption of HistoSonics' groundbreaking system upon commercialization, which is anticipated to occur in 2020.

Visionary Innovation

Currently, ultrasound is deployed in cancer treatment through use of techniques such as high intensity focused ultrasound (HIFU). This method uses high frequency sound waves to heat and subsequently kill cancer cells. However, HIFU is not able to precisely ablate tumors and can only be used for specific cancers. To overcome these limitations, HistoSonics has combined histotripsy with advanced visualization and robotics technology that facilitates precise local ablation of the diseased tissues and has the potential to be easily used for many types of tumors. Moreover, the system uses proprietary software for pre-procedure planning that prepares physicians with a 3-D outline of the target tissues that need to be ablated. Frost & Sullivan believes this development is a testament of the innovative strategy adopted by HistoSonics that delivers a technology platform closely aligned to market needs. In fact, the company's visionary thinking has been greatly supported by the investor community that has vigorously channeled funding to the tune of \$83 million since HistoSonics' inception.



Conclusion

Based on Frost & Sullivan analysis of the cancer treatment devices market, HistoSonics stands out for its development of a revolutionary platform that uses a first-of-its-kind non-invasive robotic technique and non-thermal acoustic cavitation for destruction of diseased tissue and tumors.

Frost & Sullivan lauds the company's successful delivery of a system that is non-invasive, provides quicker patient recovery, and is more cost-effective as compared to current cancer treatment modalities. Moreover, the system can accurately ablate the diseased tissues in certain anatomic structures that are inaccessible by current cancer treatment methods. For patients, it provides a quick and effective treatment option that eliminates complications from standard invasive surgery, thermal or radiation procedures. Through use of robotics and real-time visualization technology, the system has emerged as a potentially superior alternative to existing open and minimally invasive procedures in terms of providing better outcomes for patients.

For its strong overall performance, HistoSonics has earned Frost & Sullivan's 2019 Technology Innovation Award in the North American cancer treatment devices industry.

Significance of Technology Innovation

Ultimately, growth in any organization depends on finding new ways to excite the market and maintaining a long-term commitment to innovation. At its core, technology innovation, or any other type of innovation, can only be sustained with leadership in 3 key areas: understanding demand, nurturing the brand, and differentiating from the competition.



Understanding Technology Innovation

Technology innovation begins with a spark of creativity that is systematically pursued, developed, and commercialized. That spark can result from a successful partnership, a productive in-house innovation group, or a bright-minded individual. Regardless of the source, the success of any new technology is ultimately determined by its innovativeness and its impact on the business as a whole.

Key Benchmarking Criteria

For the Technology Innovation Award, Frost & Sullivan analysts independently evaluated 2 key factors—Technology Attributes and Future Business Value—according to the criteria identified below.

Technology Attributes

- Criterion 1: Industry Impact
- Criterion 2: Product Impact
- Criterion 3: Scalability
- Criterion 4: Visionary Innovation
- Criterion 5: Application Diversity

Future Business Value

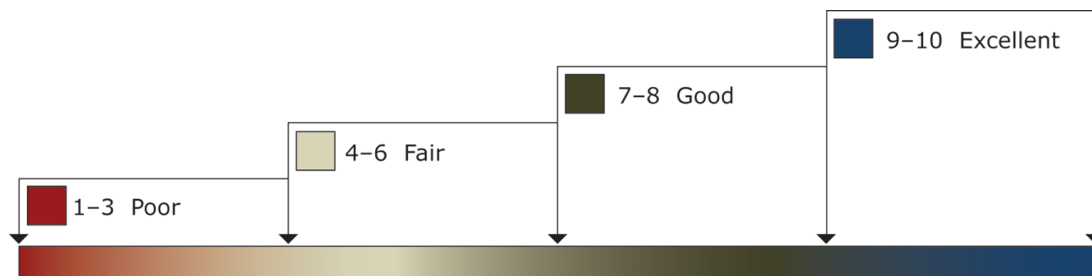
- Criterion 1: Financial Performance
- Criterion 2: Customer Acquisition
- Criterion 3: Technology Licensing
- Criterion 4: Brand Loyalty
- Criterion 5: Human Capital

Best Practices Award Analysis for HistoSonics, Inc.

Decision Support Scorecard

To support its evaluation of best practices across multiple business performance categories, Frost & Sullivan employs a customized Decision Support Scorecard. This tool allows research and consulting teams to objectively analyze performance according to the key benchmarking criteria listed in the previous section, and to assign ratings on that basis. The tool follows a 10-point scale that allows for nuances in performance evaluation. Ratings guidelines are illustrated below.

RATINGS GUIDELINES



The Decision Support Scorecard considers Technology Attributes and Future Business Value (i.e., the overarching categories for all 10 benchmarking criteria; the definitions for each criterion are provided beneath the scorecard). The research team confirms the veracity of this weighted scorecard through sensitivity analysis, which confirms that small changes to the ratings for a specific criterion do not lead to a significant change in the overall relative rankings of the companies.

The results of this analysis are shown below. To remain unbiased and to protect the interests of all organizations reviewed, Frost & Sullivan has chosen to refer to the other key participants as Competitor 1 and Competitor 2.

<i>Measurement of 1–10 (1 = poor; 10 = excellent)</i>			
Technology Innovation	Technology Attributes	Future Business Value	Average Rating
HistoSonics, Inc.	9.6	9.7	9.7
Competitor 1	6.2	5.9	6.1
Competitor 2	4.1	5.0	4.6

Technology Attributes

Criterion 1: Industry Impact

Requirement: Technology enables the pursuit of groundbreaking ideas, contributing to the betterment of the entire industry.

Criterion 2: Product Impact

Requirement: Specific technology helps enhance features and functionalities of the entire product line for the company.

Criterion 3: Scalability

Requirement: Technology is scalable, enabling new generations of products over time, with increasing levels of quality and functionality.

Criterion 4: Visionary Innovation

Requirement: Specific new technology represents true innovation based on a deep understanding of future needs and applications.

Criterion 5: Application Diversity

Requirement: New technology serves multiple products, multiple applications, and multiple user environments.

Future Business Value

Criterion 1: Financial Performance

Requirement: Potential is high for strong financial performance in terms of revenue, operating margins, and other relevant financial metrics.

Criterion 2: Customer Acquisition

Requirement: Specific technology enables acquisition of new customers, even as it enhances value to current customers.

Criterion 3: Technology Licensing

Requirement: New technology displays great potential to be licensed across many verticals and applications, thereby driving incremental revenue streams.

Criterion 4: Brand Loyalty

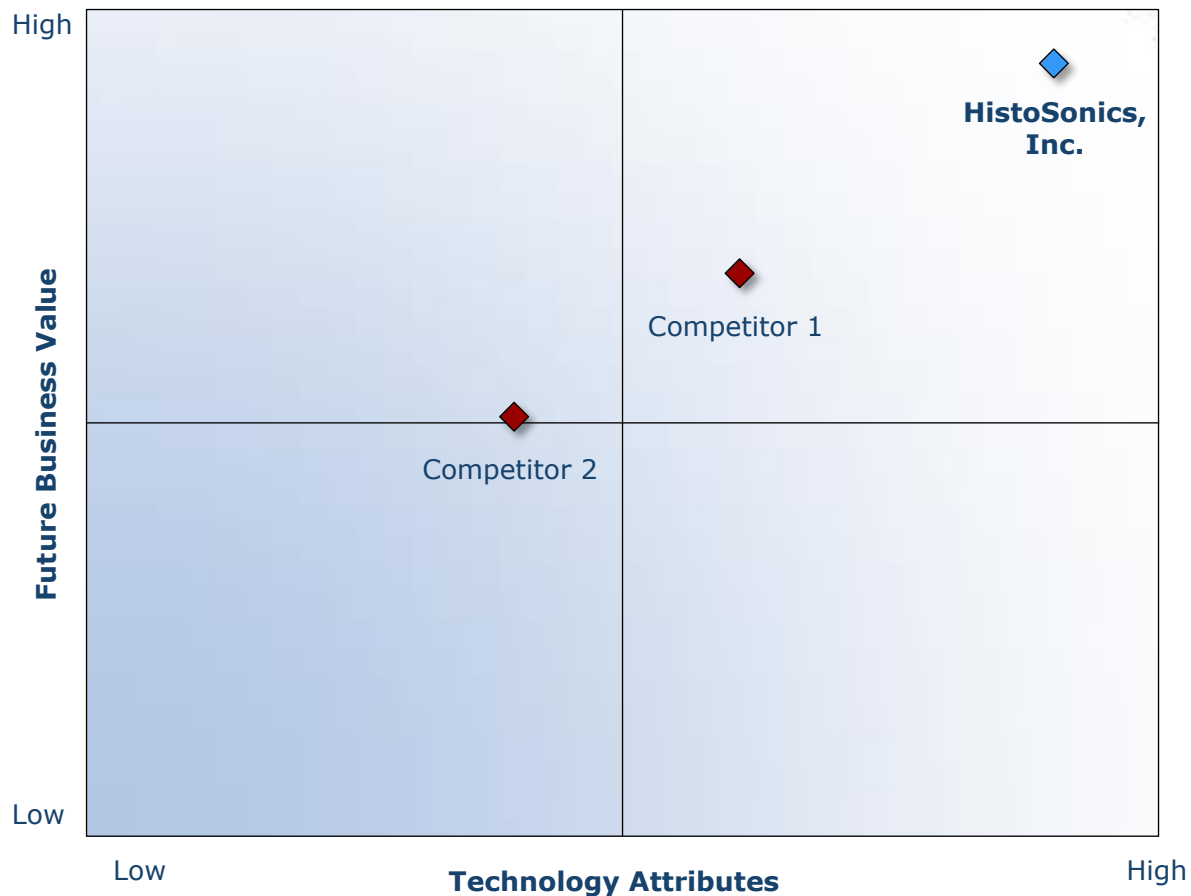
Requirement: New technology enhances the company's brand, creating and/or nurturing brand loyalty.

Criterion 5: Human Capital

Requirement: Customer impact is enhanced through the leverage of specific technology, translating into positive impact on employee morale and retention.

Decision Support Matrix

Once all companies have been evaluated according to the Decision Support Scorecard, analysts then position the candidates on the matrix shown below, enabling them to visualize which companies are truly breakthrough and which ones are not yet operating at best-in-class levels.



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 practices 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 world	<ul style="list-style-type: none"> • Conduct in-depth industry research • Identify emerging industries • Scan multiple regions 	Pipeline of candidates that potentially meet all best practices criteria
2 Perform 360-degree research	Perform comprehensive, 360-degree research on all candidates in the pipeline	<ul style="list-style-type: none"> • Interview thought leaders and industry practitioners • Assess candidates' fit with best practices 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	<ul style="list-style-type: none"> • Confirm best practices 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	<ul style="list-style-type: none"> • Brainstorm ranking options • Invite multiple perspectives on candidates' performance • Update candidate profiles 	Final prioritization of all eligible candidates and companion best practices positioning paper
5 Assemble panel of industry experts	Present findings to an expert panel of industry thought leaders	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 practices award recipient	<ul style="list-style-type: none"> • Review analysis with panel • Build consensus • Select recipient 	Decision on which company performs best against all best practices criteria
9 Communicate recognition	Inform award recipient of recognition	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Coordinate media outreach • Design a marketing plan • Assess award's role in 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 the 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, resulting in 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-degree research 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



About Frost & Sullivan

Frost & Sullivan, the Growth Partnership Company, helps clients accelerate growth and achieve best-in-class positions in growth, innovation, and leadership. The company's Growth Partnership Service provides the CEO and the CEO's growth team with disciplined research and best-practices models to drive the generation, evaluation, and implementation of powerful growth strategies. Frost & Sullivan leverages nearly 60 years of experience in partnering with Global 1000 companies, emerging businesses, and the investment community from 45 offices on 6 continents. To join Frost & Sullivan's Growth Partnership, visit <http://www.frost.com>.