FROST & SULLIVAN BEST PRACTICES AWARD

DIGITAL PATHOLOGY SOFTWARE SOLUTIONS - GLOBAL

Company of the Year 2019
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Background and Company Performance

Industry Challenges

Tissue-based Cancer Diagnostics: Over a Century-old Gold Standard

Tissue-based diagnostics’ basic processes have remained relatively unchanged over the last 150 years. Subjective, inconsistent, and semi-quantitative, conventional microscopy is the primary diagnostic tool assisting pathological examinations. Despite its limitations, no other technology captures the complex biological context of solid tumors and the critical parameters factoring into patient outcomes as tissue-based cancer diagnostics.

Traditionally, pathologists look at hematoxylin-eosin (H&E)-stained biopsy specimens microscopically for routine analysis, using abnormalities in cell structure and staining patterns as the basis for interpretation. Advanced staining techniques such as immunohistochemistry (IHC) and in situ hybridization (ISH) yield important additional insights into tumor biology. IHC methods detect cancer-related protein biomarkers’ distribution, localization, and differential expression in the proper tissue context. Likewise, ISH techniques deliver temporal and spatial configurations about gene expression and genetic loci. Both IHC/ISH protocols use chromogenic and fluorescent visualization. Nonetheless, the biological context of the tumor microenvironment (TME) complicates histopathological examinations. Moreover, both IHC/ISH techniques are inherently subjective with limited reproducibility and accuracy—mainly due to inter- and intra-reader variability and semi-quantitative scoring methods, i.e., pathologist visual scoring.

Beyond tissue analysis, the patient-to-pathologist histology workflows require consistency for diagnostic accuracy. Tissue-based diagnostics is one of the most labor- and time-intensive processes in clinical diagnostic testing, relying mostly on manual procedures—approximately 70% of the workflow in histology laboratories (labs). High dependent on the personnel skill level, these functions are prone to errors, introducing inefficiencies and inaccuracies to the analytical process, with a potentially significant impact on diagnostic decisions and subsequent patient outcomes. Moreover, pathologist’s demand is evolving faster than supply capability and exacerbated by global workforce shortage driven by an aging population, rising cancer prevalence, and widening applications, e.g., diagnostics, therapeutic response, biomarker discovery, and drug development.

Digital Pathology: Into a New Era

Digital pathology, or whole-slide imaging, scans prepared glass microscope slides to generate digital images readily available for software-based, advanced analytics—e.g., automated diagnoses—storage, transfer, and sharing. This evolving digital technology ecosystem creates an image-based information platform best fit for oncology. Digital pathology is important to both research and diagnostic applications.

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1. Global Tissue Diagnostics Market, Forecast to 2022 (Frost & Sullivan, May 2018)
In cancer research, it enables a better understanding of the underlying mechanisms leading to disease, with automated diagnoses helping identify important physiological biomarkers, drug targets, and biochemical and cellular pathways. In clinical diagnoses, an application area with huge potential, digital pathology improves operational efficiencies and, most importantly, diagnostic speed and accuracy for timely, proper, cost-effective care. Through comparative tissue analysis, pathologists achieve an unparalleled understanding of the TME, critical for cancer subtype identification, target validation, and patient selection and stratification to optimize targeted therapeutics and, thus, enhance patient outcomes.

While 60% to 70% of the use cases for digital pathology are in research applications, the digital pathology diagnostic market looks promising. Notably, adoption rates in Nordic countries and the Netherlands are significant, with other countries now following suit.

Continued workflow automation coupled with developments in staining methodologies and digital enablers, like advanced imaging technologies, artificial intelligence (AI), and machine learning (ML), for real-world data assessment and IHC staining quantification will open new inroads for improved analysis and future market growth. Amidst stiff competition in this rapidly evolving technology landscape, software development and innovation, particularly image analysis and data management, take center stage. Frost & Sullivan estimates the global digital pathology software market will reach nearly $200 in 2021, with a compound annual growth rate of 18% from 2016 to 2021.

**Visionary Innovation & Performance and Customer Impact**

Founded in 2001 and headquartered in Hørsholm, Denmark, Visiopharm A/S (Visiopharm) is a global leader in quantitative image analysis software and end-to-end digital pathology solutions—over 900 installations with several licenses each and exceeding 1,500 peer-reviewed scientific publications since 2010.

In recent years, the company expanded its offerings to include CE-IVD algorithms for cancer diagnostics. Visiopharm’s cutting-edge image analysis software for tissue-based cancer diagnostics, Oncotopix®, leverages AI and ML integrating digitized high-throughput pathology lab workflows for improved diagnostic accuracy, speed, and confidence, increasing productivity while lowering costs.

Strategically located subsidiaries in Sweden, the United Kingdom (UK), the United States (US), and re-sellers in Asia, service company customers in three continents, Europe (EU), North America, and Asia—e.g., headquarters in Denmark and subsidiary in Sweden back its presence in the Scandinavian Peninsula. An authorized and growing global distributor network combined with top integration partners support Visiopharm’s expanding geographical footprint, including Philips and Akoya Biosciences, its latest addition.

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*2 Global Tissue Diagnostics Market, Forecast to 2022 (Frost & Sullivan, May 2018)*

*3 Ibid.*
A Radical Approach: End-to-End Quality Data

“The lack of interpretive accuracy challenges pathology’s usefulness as a diagnostic discipline and undermines precision medicine’s promise, questioning its reality.”

-Michael Grunkin, CEO, Founder, and Managing Director, Visiopharm

An early entrant to digital pathology, Visiopharm strives to mitigate and eliminate errors in the biopsy’s journey, from tissue sampling to pathological evaluation. The company conducted extensive research with key opinion leaders (KOLs) in the field across the value chain, pathology, in general, and digital pathology, in particular. Visiopharm uncovered and quantified two particularly important error sources in the diagnostic workflow. Aspects of both histological staining and manual image reading and interpretation result in high error rates, a significant roadblock in the path towards interpretive diagnostic accuracy.

Qualitopix™: Heralding Tissue Pathology Standardization

“According to leading providers of EQA services, Only about 70% of pathology labs achieve staining proficiency in the general IHC modules. Thus, 30% of pathology lab reports could lead to faulty conclusions, e.g., false-negative and false-positive, and either delay potentially life-saving therapies or result in unnecessary treatments with possibly very harmful side effects. Tissue pathology standardization is strategic to us [Visiopharm] and every stakeholder in this ecosystem—patient, physician, company, and organization.”

-Michael Grunkin

Staining sufficiency and proficiency is the cornerstone in interpretive accuracy of diagnostic biomarkers. In many countries, pathology labs using IHC/ISH stains rely on external quality assessment (EQA) programs to maintain staining quality and, in some countries, even accreditation.

Typically, EQA organizations create multi-blocks with well-characterized tumor samples of positive, negative, and positive intermediaries, concerning the biomarker in question. They send test sections from this block to participating pathology labs for proficiency testing. The participating labs stain the test sections and then send them back to the EQA for review. Several external assessors, in some cases as much as 10, then review the stained test sections; based on a consensus score, the EQA organization provides laboratories with a report indicating if the staining quality falls within the acceptance criteria. EQAs typically cannot offer participants more than one or two quality runs per year per biomarker. Nonetheless, quality fluctuations are common, which is not enough to sustain staining quality and consistency over time.
Visiopharm is currently the first and only solution provider supporting the EQA organization with a software platform allowing them to improve the efficiency and scalability of their activities. The company engaged EQA program leaders around the world to build its upcoming product, Qualitopix™—a scalable method for repeated staining performance monitoring—with development and validation undertaken along partners including the Canadian Immunohistochemistry Quality Control (CIQC) program, UK National External Quality Assessment Service (UKNEQAS), and Nordic Immunohistochemical Quality Control (NordiQC). Today, the Qualitopix™ administration platform is in practical use by UKNEQAS for quality runs.

Qualitopix™, a novel patented platform technology, enables both administering quality runs and scalability through computer-assisted stain quality assessment using digital image analysis and AI for objective, standardized results. Digitization and workflow automation combined with computer-assisted proficiency testing enable scalability for the EQA's. The digitized slides facilitate interactions with pathology labs through the platform, allowing cost-efficient resource utilization. Moreover, the administration platform supports and facilitates protocol review with participating labs that fail the proficiency testing. Contributing to the standardization and quality of staining with diagnostic tissue-biomarkers, is central to achieving precision pathology and sustainable cancer healthcare, and ultimately achieve Visiopharm’s vision of improving patient outcomes.

Image analysis applications (APPs) running on Visiopharm's image analysis platform enable computer-assisted proficiency testing. The image analysis APPs can provide a quantitative quality grading of IHC staining, allowing objective, frequent, and low-cost stain quality readings. High quality, optimal staining is the basis for a more precise diagnostic assessment, and the company anticipates that these APPs, once widely deployed, will standardize testing for patients. Visiopharm anticipates full roll-out of both the Qualitopix™ administration platform and its patented Qualitopix APPs during 2019.

**Oncotopix®: Ushering a New Era in Pathology**

It is well-known that significant inter- and intra-reader variability is a problem in diagnostic tissue pathology. The magnitude of the problem depends on the indication, biomarker, or the special stain in question. Scientific studies have demonstrated that the sources of variability and errors associated with manual reading and interpretation of tissue biomarkers include the inability to reliably identify invasive tumor cells, and discriminate them from pre-invasive tumor cells and stromal cells. Also, manual identification of hot-spots of biomarker expressions has proved a significant challenge in practice. These problems will grow exponentially as understanding and characterizing the TME require more complex and even multiplexed biomarkers. Improving interpretive accuracy will be critical to patient and societies benefiting from promising new targeted immunotherapies, reaching the market over the next few years.
"Biomarkers today are very simple compared to the new biomarkers intended to identify responders to immunotherapies. PD-L1 testing is just one example. New multiplexed assays are also entering the market. We have developed methods that arm scientists, pathologists, and, ultimately diagnostic pathologists to work efficiently with these very complex assays."

-Michael Grunkin

Visiopharm’s industry-leading cross-platform modular software solution for cancer diagnostics and research, Oncotopix®, combines image analysis, ML, and AI with workflows supporting the analysis of massive data sets, data management, reporting, connectivity to LIMS and PACS systems, and compatibility with all image/slide formats.

An industry pioneer, Visiopharm started developing ML- and AI-based image analysis and workflow tools since inception, over the last 17 years. Fully-automated, the software suite offers reproducible, quantifiable, precise data, helping pathologists’ read and interpret regions inside and outside of the tumor as well as tumor heterogeneity, cellular and molecular characteristics, at the invasive tumor front with multiple biomarkers correctly—essential for both precision pathology and high-throughput digital pathology. Currently, Visiopharm has more than 100 APPs published for biomarker quantification and region identification for the Oncotopix® platform. An advanced Author module allows scientists to write their APPs, to answer just about any new scientific question that emerges as their research and insight evolves. Infinitely configurable, with a comprehensive "language" for image analysis, the Oncotopix® research platform is future-proof, ensuring users will not hit the wall of limited capabilities.

Aspirational Leadership: Augmented Pathology

While the co-evolutionary development of digital pathology and tissue image analysis continues, Visiopharm’s quest to optimize workflows and mitigate or eliminate error sources in the quantitative assessment of biomarker response or tissue morphology is fundamental to unlocking the full potential of digital pathology. First-generation digital pathology software solutions do not meet the emerging high-data quality requirements to bring pathology’s usefulness to the next level of precision pathology for sustainable healthcare.
"We realized 17 years ago that tissue pathology is a highly complex area, with many indications, biomarkers, staining techniques, and imaging methodologies, setting a high bar for any image analysis platform to stay scalable and future-proof—both for Visiopharm and for our customers. We decided to develop a high-level language allowing us and our customers to configure new apps, even non-programmers, easily. This approach allows scientists to grow and advance with their research in a rapidly evolving field in a scalable, timely, and cost-efficient way. It has been one of the best decisions we ever made. We never hit a capability wall with the software."

-Michael Grunkin

With its Qualitopix™ and Oncotopix® platforms, Visiopharm offers a comprehensive end-to-end data quality solution for tissue-based cancer research and diagnostics. There is an open and configurable platform for researchers, a closed platform for diagnostics, and a technically simple translation from research APPs to the diagnostics platform, subject to validation and regulatory clearance. In an era of targeted therapies, these platforms combined address the varied and complex needs of drug and biomarker development, tissue diagnostics, and the concomitant needs for companion diagnostic biomarkers with the ability to deploy both in a sustainable way within healthcare systems.

The company understands the pain points in modern pathology and aligns with technological trends to push forward developments in the industry. Its flexible technology architectures allow for fast, agile AI-based APP development cycles, growing at pace with evolving market needs. For instance, Visiopharm can configure a specific cancer diagnostics or research APP within an hour. With the AI and deep learning capabilities, pathologists themselves can easily develop new APPs through a simple teach-by-example interface. The company’s APP center boasts the largest number of APPs in the industry, with over 100 published APPs.

Furthermore, the company validated its diagnostic APPs for different slide scanners and reagent manufacturers so that customers can choose best-of-breed technologies. By systematically integrating to advanced workflow and data management systems, such as LIMS and PACS, Visiopharm’s product portfolio plugs seamlessly into existing digital workflows.

Automated, agnostic to every component in the entire pathology value chain, and fully configurable, Oncotopix® takes tissue analysis for diagnosis and cancer research to a higher echelon.
What the Future Holds

Visiopharm’s end-to-end digital data quality and diagnostics workflow approach resonates with existing customers. A 2018 Frost & Sullivan global end-user survey—including qualified respondents from academic medical centers, biopharmaceutical companies, contract research organizations, and private and public pathology labs—identifies Visiopharm as a top innovative digital pathology company and provider, garnering the most mentions for preferred clinical decision support provider. Visiopharm’s ML and AI algorithms also bode extremely well, gaining end-users’ recognition as a leading provider.4

In August 2018, Visiopharm raised around €13.5 million to accelerate growth over the next few years, building the infrastructure to support its very ambitious expansion goals. The company plans to broaden its global reach to fulfill the increasing digital pathology needs in the marketplace. While expensive and time-consuming, Visiopharm is setting up direct sales channels to get out in front of customers, which is extremely important in an emerging high-technology market such as digital pathology. The company subspecializes within its sales force to ensure that people with situational knowledge are always available for engaging customers at the right time in their buying journey to consult in the many aspects of research- or diagnostic digital pathology solutions.

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Conclusion

While subjective, inconsistent, and semi-quantitative, tissue-based diagnostics is still the gold standard in cancer diagnosis. Nonetheless, image analyses and digital pathology software solutions continue to evolve, progressively becoming an integral factor in advancing both cancer diagnostics and research.

Frost & Sullivan recognizes Visiopharm’s technology foresight and strategic role in promoting anatomic pathology’s digital transformation through its best-in-class end-to-end digital pathology software solutions. The company’s Qualitopix™ and Oncotopix® platforms bolster quality data combined with simplified and quantifiable results for accurate, efficient, and rapid histopathological evaluation. Visiopharm’s quantitative image analysis software suite uniquely offers a secure, scalable, high-quality, agnostic platform, helping pathologists’ worldwide face the quality and cost challenges in care delivery. At the technological forefront, Frost & Sullivan believes that Visiopharm’s software solutions will shape tomorrow’s pathology as it turns to its digital future. The company will continue to report strong growth and capture market share, leveraging its first-mover advantage and strong brand recognition.

With its exceptional foresight and industry-leading cross-platform modular software solutions for cancer diagnostics, Visiopharm earns Frost & Sullivan’s 2019 Global Company of the Year Award in the digital pathology software solutions market.
Significance of Company of the Year
To receive the Company of the Year Award (i.e., to be recognized as a leader not only in your industry, but among your non-industry peers as well) requires a company to demonstrate excellence in growth, innovation, and leadership. This kind of excellence typically translates into superior performance in three key areas: demand generation, brand development, and competitive positioning. These areas serve as the foundation of a company’s future success and prepare it to deliver on the two criteria that define the Company of the Year Award (Visionary Innovation & Performance and Customer Impact).

Understanding Company of the Year
As discussed above, driving demand, brand strength, and competitive differentiation all play a critical role in delivering unique value to customers. This three-fold focus, however, must ideally be complemented by an equally rigorous focus on Visionary Innovation & Performance to enhance Customer Impact.
Key Benchmarking Criteria

For the Company of the Year Award, Frost & Sullivan analysts independently evaluated two key factors—Visionary Innovation & Performance and Customer Impact—according to the criteria identified below.

Visionary Innovation & Performance

Criterion 1: Addressing Unmet Needs
Requirement: Implementing a robust process to continuously unearth customers’ unmet or under-served needs, and creating the products or solutions to address them effectively.

Criterion 2: Visionary Scenarios through Mega Trends
Requirement: Incorporating long-range, macro-level scenarios into the innovation strategy, thereby enabling “first-to-market” growth opportunity solutions.

Criterion 3: Implementation of Best Practices
Requirement: Best-in-class strategy implementation characterized by processes, tools, or activities that generate a consistent and repeatable level of success.

Criterion 4: Blue Ocean Strategy
Requirement: Strategic focus on creating a leadership position in a potentially “uncontested” market space, manifested by stiff barriers to entry for competitors.

Criterion 5: Financial Performance
Requirement: Strong overall business performance in terms of revenues, revenue growth, operating margin, and other key financial metrics.

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.

<table>
<thead>
<tr>
<th>STEP</th>
<th>OBJECTIVE</th>
<th>KEY ACTIVITIES</th>
<th>OUTPUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Monitor, target, and screen</td>
<td>Identify Award recipient candidates from around the globe</td>
<td>Pipeline of candidates who potentially meet all best-practice criteria</td>
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<tr>
<td></td>
<td>Perform 360-degree research</td>
<td>Perform comprehensive, 360-degree research on all candidates in the pipeline</td>
<td>Matrix positioning of all candidates’ performance relative to one another</td>
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<tr>
<td>2</td>
<td>Invite thought leadership in best practices</td>
<td>Perform in-depth examination of all candidates</td>
<td>Detailed profiles of all ranked candidates</td>
</tr>
<tr>
<td>3</td>
<td>Initiate research director review</td>
<td>Conduct an unbiased evaluation of all candidate profiles</td>
<td>Final prioritization of all eligible candidates and companion best-practice positioning paper</td>
</tr>
<tr>
<td>4</td>
<td>Assemble panel of industry experts</td>
<td>Present findings to an expert panel of industry thought leaders</td>
<td>Refined list of prioritized Award candidates</td>
</tr>
<tr>
<td>5</td>
<td>Conduct global industry review</td>
<td>Build consensus on Award candidates’ eligibility</td>
<td>Final list of eligible Award candidates, representing success stories worldwide</td>
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<tr>
<td>6</td>
<td>Perform quality check</td>
<td>Develop official Award consideration materials</td>
<td>High-quality, accurate, and creative presentation of nominees’ successes</td>
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<tr>
<td>7</td>
<td>Reconnect with panel of industry experts</td>
<td>Finalize the selection of the best-practice Award recipient</td>
<td>Decision on which company performs best against all best-practice criteria</td>
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<tr>
<td>8</td>
<td>Communicate recognition</td>
<td>Inform Award recipient of Award recognition</td>
<td>Announcement of Award and plan for how recipient can use the Award to enhance the brand</td>
</tr>
<tr>
<td>9</td>
<td>Take strategic action</td>
<td>Upon licensing, company able to share Award news with stakeholders and customers</td>
<td>Widespread awareness of recipient’s Award status among investors, media personnel, and employees</td>
</tr>
</tbody>
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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-degree research methodology provides an evaluation platform for benchmarking industry participants and for identifying those performing at best-in-class levels.

About Frost & Sullivan

Frost & Sullivan, the Growth Partnership Company, enables clients to 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 practice models to drive the generation, evaluation, and implementation of powerful growth strategies. Frost & Sullivan leverages more than 50 years of experience in partnering with Global 1000 companies, emerging businesses, and the investment community from 45 offices on six continents. To join our Growth Partnership, please visit http://www.frost.com.