

DOE

MARKET RESEARCH STUDY

TRANSITIONING QUANTUM IMAGING AND SENSING TECHNOLOGIES TO BIOIMAGING MARKETS

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1.0 Introduction

In March 2022, the Subcommittee on Quantum Information Science released a report entitled **Bringing Quantum Sensors to Fruition**. One of the four recommendations of the Subcommittee was that "Agencies leading QIST R&D¹ should accelerate the development of new quantum sensing approaches to prioritize appropriate partnerships with end users to elevate the technology readiness of new quantum sensors." The purpose of this report is to provide an introductory perspective on the market opportunities within biological sciences that could hypothetically use quantum sensors. The primary objective of this report is to help small businesses and researchers working with quantum sensor technology to understand the potential size of various market opportunities and how to best address some of the challenges that must be faced in order to commercialize their technologies. The report also provides insight into the direction of manufacturers who currently use conventional technologies.

This report starts with an overview of recent initiatives that have fostered accelerated research and development in quantum technologies. This introduction is included for small businesses which may be unfamiliar with the growing infrastructure. The focus then shifts to quantum sensors and potential commercial applications in the biological sciences. The emphasis in this report is on market drivers, the size of the market for conventional approaches, as well as those stakeholders in the commercial market that are looking at potential commercial applications of quantum sensing. Additional market applications of quantum sensing beyond biological sciences will be briefly touched upon.

1.1 Methodology

Both secondary and primary market research were conducted to generate this report. Secondary information came from both public (such as company press releases, investor presentation slide decks and annual reports) and subscription databases. Market size and growth and projections for quantum sensors and quantum communications are based on secondary sources of information. Primary market research was conducted with a limited number of individuals with strong backgrounds in microscopy and/or the QIST (Quantum Information Science and Technology) initiatives. Throughout this report, information from both primary and secondary sources are interspersed to provide more insight on given topics.

2.0 Background

On December 13, 2018, the U.S. Senate unanimously passed the National Quantum Initiative Act¹ which was signed into law by President Donald Trump on December 21, 2018.² Passage of this Act followed a public-private summit³ with industry representatives including Microsoft and Google, as well as numerous government agencies including the Department of Energy (DOE), the National Science Foundation (NSF), and the National Institute of Standards and Technology (NIST). The purpose of the Act was to support continued advancements in Quantum Information Science (QIS), especially in data encryption, a field in which China was making great advances. A report prepared by the Harvard Belfer Center for Science and International Affairs in December 2021⁴ highlighted the acceleration in the

¹ QIST: Quantum Information Science and Technology

great tech rivalry between China and the U.S. on many fronts including quantum information science, semiconductors, biotechnology and green energy.

The **NQI Act**, often referred to as the National Quantum Initiative Act, resulted in a coordinated and significant effort among numerous federal agencies. Specifically, the act:

- Established a **Subcommittee on Quantum Information Science** including membership from the National Institute of Standards and Technology (NIST) and the National Aeronautics and Space Administration (NASA)
- Indicated that the President must establish a **National Quantum Initiative Advisory** committee to provide advice to the President and the Subcommittee
- Articulated specific responsibilities for the National Institute of Standards and Technology (NIST), the National Science Foundation (NSF) and the Department of Energy (DOE)
- NIST was directed to conduct specified quantum science activities and <u>convene a consortium</u>⁵ to identify the future measurement, standards, cybersecurity and other needs to support the development of a quantum information science and technology industry.
- NSF was directed to carry out basic research and education programs on quantum information science and engineering and award grants for the establishment of <u>Multidisciplinary Centers for</u> <u>Quantum Research and Education.</u>⁶
- DOE was directed to conduct a basic research program on quantum information science. In addition, the Office of Science of DOE was directed to establish and operate <u>National Quantum information</u> <u>Science Research Centers</u>⁷ to conduct basic research to accelerate scientific breakthroughs.

Today, much of the new infrastructure needed to execute the NQI Act is in place.

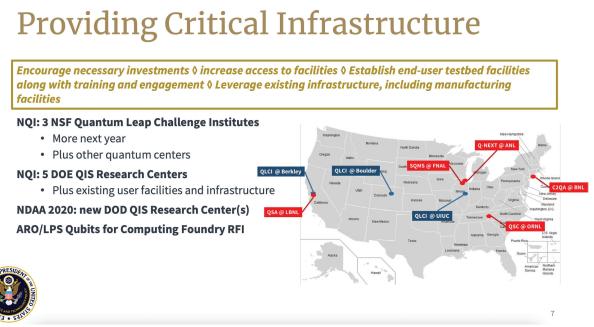


Figure 1: Critical Infrastructure for QIS Source: National Strategy⁸

Figure 1 represents the location of the three NSF Quantum Leap Challenge Institutes (QLCI), as well as the five Department of Energy QIS research centers (in red). The three QLCIs are at the following Universities:⁹

- **University of Colorado Boulder** has a QLCI focused on Enhanced Sensing and Distribution Using Correlated Quantum States
- University of Illinois Urbana-Champaign has a QLCI focused on Hybrid Quantum Architectures and Networks
- University of California, Berkeley has a QLCI for Present and Future Quantum computing

The five Department of Energy QIS Research Centers are listed below with the Lead Laboratory noted:¹⁰

- **Q-NEXT- Next Generation Quantum Science and Engineering** (Argonne National Laboratory)
- C²QA Co-design Center for Quantum Advantage (Brookhaven National Laboratory)
- SQMS Superconducting Quantum Materials and Systems Center (Fermilab)
- QSA Quantum Systems Accelerator (Lawrence Berkeley National Laboratory)
- **QSC Quantum Science Center** (Oak Ridge National Laboratory)

The **Quantum Economic Development Consortium** has engaged an active community. Membership is available to corporations, academic institutions and other entities involved with the quantum industry and supply chain. Entities interested in becoming a member should consult the **QED-C membership page**. The list of existing members is also available from this site. The

Established markets could be significantly impacted by advances in quantum sensing technologies including the Live Cell Imaging market, the Microscopy market and the Cryo-electron market.

site also has a **Quantum Marketplace** for bringing together suppliers, customers and partners. In the next section we will begin to explore the market opportunities for quantum sensors.

2.1 Quantum Sensors

Scientists working in the field of quantum information science (QIS) work at a level of understanding that is not shared by many commercial entities. Indeed, part of the challenge with the recommendation to "prioritize appropriate partnerships with end users" is to understand the gap between how QIS researchers understand quantum sensing and the knowledge of various end users. It is important to also understand that the decision makers on the commercial side of the equation approach business from a cost-benefit perspective. Even though the physicists in industry may share an understanding of the technology, many decision makers will not. In looking for clear definitions of these terms, it became apparent that more often than not, the terms "quantum sensing" and "quantum sensor" are not defined – but instead examples are provided of how they can be of benefit. It is beneficial to provide both operational definition of any phenomena, as well as discuss the benefit of what it can do.

The following are included as examples of descriptions of "quantum sensors" and "quantum sensing," keeping in mind that many times these terms are not defined.

BAE Systems, Inc.

"Quantum sensing is an advanced sensor technology that vastly improves the accuracy of how we measure, navigate, study, explore, see and interact with the world around us by sensing changes in motion, and electric and magnetic fields. The analyzed data is collected at the atomic level. Its called quantum sensing because it uses quantum resources – delicate phenomena that are apparent only on an atom-sized scale – to achieve this extreme accuracy. Collecting these "delicate" data at the atomic level often means extracting information from individual atoms instead of from the huge collections of atoms, as happens in classical physics...Devices that use quantum sensing are also not subject to the same physical constraints as conventional sensors allowing for exceptional

reliability with less vulnerability to the signal jamming and other electromagnetic interference that is increasingly common with today's light and sound-based data sensors."

Massachusetts Institute of Technology

"Quantum sensors, which detect the most minute variations in magnetic or electrical fields have enabled precision measurements in materials science and fundamental physics...Quantum sensors can take many forms; they're essentially systems in which some particles are in such delicately balanced state that they are affected by even tiny variations in the fields they are exposed to. These can take the form of neutral atoms, trapped ions and solid-state spins."¹¹

Northwestern University

"The requirements for quantum sensors are similar to those for quantum bits, or qubits. Much like qubits, quantum sensors must (1) have discrete, well-defined quantum states, such as polarization of photons, quantized currents in superconducting circuits, and electronic or nuclear spin states; (2) be initialized into a single, well-known state such that the desired stimulus produces a specific, predictable, and measurable signal; (3) be addressable for manipulation, for example, via optical, microwave, or radiofrequency excitation; and (4) incorporate a sensor read-out pathway to measure the signal response. However, unlike qubits that interact minimally with the surrounding environment, quantum sensors must (5) interact strongly with their sensing target. This interaction needs to induce changes in the quantum state of the sensor or transition rates between states or modulate the quantum coherence of the sensor. Judicious selection of the quantum system is imperative to maximize sensitivity to the desired physical quantity while mitigating background noise."¹²

3.0 Quantum Sensors in Imaging Applications

Market analysts have been actively reviewing the potential applications of quantum sensing and quantum sensors in various markets. Mentioned throughout this section is information from an April 2020 report by Frost & Sullivan entitled **Opportunities for Quantum Technologies in Chemical Sensors**, **Biosensors and Imaging Sensors**. This report is available through a subscription with Frost & Sullivan. Key insights from this report are presented, due to their specificity.

- Manipulation and sensing of individual atoms and sub-atomic particles will enable supersensitive chemical sensors and biosensors with improved selectivity and response time.
- These same properties will enable vastly improved resolution and range in imaging devices, as well as the ability to see through obscurants and around corners.
- As quantum devices become miniaturized and more fully functionalized, they could potentially impact and disrupt healthcare diagnostics, environmental monitoring, food quality monitoring, security and defense and other industries.
- Quantum imaging with more efficient single-photon sources and detectors will find increasing opportunity in medical imaging, defense and security and gas leak detection.

Examples of specific targets highlighted by Frost & Sullivan are listed below. In addition, Figure 2 provides more details on opportunities.

"... quantum plasmonic sensors with considerably less noise have opportunities in areas such as blood protein analysis, chemical detection, and atmospheric sensing. Quantum sensors with

nitrogen-vacancy (NV) diamonds have key potential in chemical analysis, NMR spectroscopy, and materials characterization. Quantum sensors, including NV-diamond sensors, also have the potential to detect Covid-19. Quantum imaging has significant opportunities in areas such as environmental monitoring (for example, methane detection), healthcare (for example, biomedical imaging), security/defense (for example, ghost imaging, which creates correlated photon pairs to imaging using light that has never physically interacted with the object to be imaged, for applications such as covert imaging for security)."¹³

"Quantum-enhanced plasmonic sensors that are probed using squeezed light have opportunities in medical diagnostics, environmental monitoring, food safety, and chemical detection. Squeezed light,² a non-classical state of light, can boost the sensitivity by reducing the noise of such sensors."¹⁴

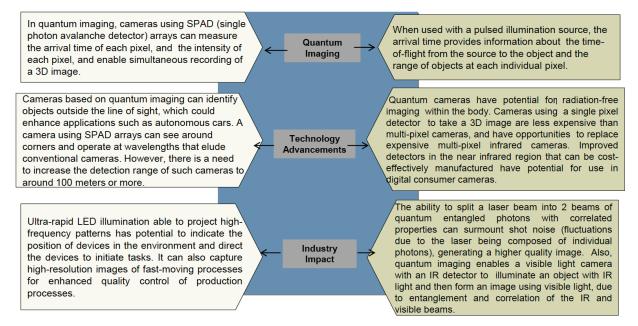


Figure 2: Quantum Technology Generates, New Enhanced Forms of Imaging Source: Reprinted with permission from Frost & Sullivan¹⁵

Other conclusions drawn are based on meeting cost and performance goals that compete with conventional technologies on multiple metrics. Analysts predict that quantum imaging has the potential to ultimately replace conventional consumer digital cameras, improved 3D cameras, ghost imaging,³ range-finding and gas leak imaging. In addition, quantum sensors based on nanomaterials could hypothetically enable early disease detection, as well as improved environmental and food monitoring.¹⁶ Challenges to adoption include miniaturization, reduced noise vulnerability, sensitivity, scalability and range.

² Squeezed light is used to reduce photon counting noise in optical high precision measurements, most notably in laser inter ferometers.

³ Ghost imaging is also referred to as "two-photon imaging" and "correlated-photon imaging." It is a technique that produces an image of an object by combining information from two light detectors.

Medical Diagnostics to Detect Pathogens and Biomarkers Biosensors that leverage quantum technology are attracting keen interest to create extremely sensitive sensors for medical diagnostics or therapy. Quantum biosensors able to detect tiny amounts of pathogens in blood or other biological fluids and to rapidly identify challenging-to-diagnose diseases will greatly increase the reliability and efficiency of medical diagnosis. Fluorescing biological nanomaterials in the form of DNA-stabilized metal quantum clusters can enable cost-effectively produced quantum biosensors able to detect specific biomarkers.

 Quantum technology that allows for developing much more sensitive and faster tunnel field-effect transistor (FET) sensors able to detect biomarkers at very low concentrations have potential as more cost-effective (can be integrated in siliconbased semiconductor technology), scalable biosensors for point-of-care disease diagnostics and can detect trace substances for forensics and security.

Blood Protein Analysis; Vital Sign Monitoring; Detection of Bacterial Infection

- Quantum plasmonic sensors that generate photon pairs and detect single photons can provide enhanced sensitivity and significantly reduced noise below the shot noise limit to benefit applications, such as analyzing blood proteins in an aqueous solution with different concentrations.
- There is interest in using sensors that exploit light-matter interactions at the quantum level and extract information via fluorescence measurement to provide non-invasive sensing of blood glucose bio-molecule levels or address other healthcare applications.
- Moreover, key opportunities exist for more rapid and accurate diagnosis of bacterial infections based on detecting fluorescence emissions at the photon level.

Figure 3: Quantum Chemical Sensors and Biosensors Have Opportunities to Disrupt Healthcare and Chemical Analysis **Source:** Reprinted with permission from Frost & Sullivan¹⁷

This report calls out a large number of specific biosensor and chemical challenges that researchers interested in quantum sensing technology can address. In the following sections of this report, three markets will be reviewed: the Live Cell Imaging market, the Microscopy market and the Cryo-electron Microscopy market. As noted in the Frost & Sullivan report, each of these markets could be significantly impacted by advances in quantum biosensing technologies during the next 10 to 15 years.

4.0 Live Cell Imaging Market

Markets for imaging technologies can be classified and defined in many different ways. One market which seems highly appropriate given the preceding discussion is referred to as the Live Cell Imaging market. Live cell imaging is a microscopy technique which enables in vivo imaging of cells over a period of time. These techniques allow researchers to gather information on biological behavior in vivo. A recent study using novel quantum sensors resulted in the ability to detect "oxidative stress" non-invasively using fluorescent imaging and MRI. This condition is seen in affected organs during the early stages of difficult-to-treat diseases like cancer and kidney dysfunction.¹⁸

Live cell microscopy is a specialized segment within microcopy applications. As this is a market that could potentially be severely challenged by advances in quantum sensing, it is useful to look at the

current size of that market. Published in October 2020, a report from consulting firm MarketsandMarkets projects the global live cell imaging market to reach \$2.8 billion by 2025 from an estimated value of \$1.8 billion in 2020, growing at a CAGR of 8.8% during the 2020-2025 time span.¹⁹

Instrumentation is considerably more expensive than software and/or consumables employed in live cell imaging. Therefore, it is not surprising that it is the instruments segment that leads the market by a considerable margin. To illustrate, in 2019 the instruments segment accounted for 51.3% share of the total product and services market with the remainder split between consumables (next in value), followed by software and then services. The introduction of more advanced instruments, higher disease rates, and the increase in government initiatives focused on cell-based research – have served as market drivers, positively influencing the demand for live cell imaging instruments.²⁰

Product & Service	2018	2019	2020	2025	CAGR (2020-2025)
Instruments	1,013.3	1,104.1	970.9	1,486.9	8.9%
Consumables	518.8	569.0	503.0	795.5	9.6%
Software	278.4	301.2	262.4	387.3	8.1%
Services	164.9	176.8	152.3	214.6	7.1%
Total	1,975.4	2,151.0	1,888.6	2,884.3	8.8%

Table 1: Global Live Cell Imaging Market, by Product & Service, 2018-2025 (USD Million)

Source: Reprinted with permission from MarketsandMarkets²¹

In 2019 the microscopes segment accounted for 54.5% of the live cell imaging instruments market. Market factors driving growth for the microscopes market include "increasing studies into cell behavior and the need to correlate multiple events and markers with cell morphology, favorable funding scenario for R&D in microscopy, rising focus on regenerative medicine, technological advancements in microscopes, and favorable regulatory procedures to launch new instruments in the market."²²

In 2019, the software segment accounted for 14% of the market. Most live cell imaging instrument providers include integrated imaging software. However, there are also several companies that provide stand-alone software solutions including **Perkin Elmer**, **Sartorius** and **Thermo Fisher Scientific**. Software

Software accounts for 14% of the global live cell imaging market.

falls into two major categories: (1) image analysis software; and (2) data management software – both of which are fueling the growth of this market. However, the paucity of trained personnel acts as a market restraint.

Table 2: Global Live Cell Imaging Market by Technologies, by Type, 2019-2025 (USD Million)

Туре	2018	2019	2020	2025	CAGR (2020-2025)
Microscopes	552.8	602.0	529.3	807.5	8.8%
Standalone Systems	258.2	284.0	251.8	403.2	9.9%
Cell Analyzers	120.3	130.3	113.7	168.4	8.2%
Accessories	81.9	87.9	76.1	107.8	7.2%
Total	1,013.3	1,104.1	970.9	1,486.9	8.9%

Source: Reprinted with permission from MarketsandMarkets²³

The accessories segment includes filter tubes, eyepieces, detectors, eyepiece tubes, holders, holder clamps, lenses, cameras and several other items. Examples of accessory products provided by companies in this space include: (1) a <u>Wide Field of View (FOV) Camera provided by BioTek Instruments</u> Inc.; (2) <u>EVOS Vessel Holders provided by Thermo Fisher Scientific</u>; as well as (3) <u>Manual XY stage</u>, <u>Accessible Deck and Optical Lenses provided by Etaluma, Inc</u>. In addition, Olympus Corporation, Leica Microsystems, Bruker Corporation and GE Healthcare all provide accessories.

When viewing the global value for live cell imaging microscopes, the U.S. leads this market by considerable proportion, as evidenced by the table below.

Country/Region	2018	2019	2020	2025	CAGR (2020-2025)
US	234.48	256.42	226.40	352.31	9.2%
Canada	12.40	13.53	11.92	18.30	9.0%
Germany	60.06	65.02	56.83	84.09	8.2%
UK	44.22	47.60	41.37	59.48	7.5%
France	27.54	29.69	25.84	37.41	7.7%
China	37.02	41.15	36.92	62.31	11.0%
Japan	32.40	34.82	30.20	43.05	7.3%
India	9.67	10.64	9.45	15.18	9.9%
Latin America	9.65	10.32	8.92	12.44	6.9%
Middle East & Africa	6.02	6.39	5.47	7.31	6.0%
Others	79.38	86.41	75.95	115.59	8.8%
Total	552.84	601.98	529.28	807.47	8.8%

 Table 3: Live Cell Imaging Microscopes Market, by Country, 2018-2025 (USD million)

Source: Reprinted with permission from MarketsandMarkets²⁴

Based on technology, the live cell imaging market is segmented into:

- Time-lapse microscopy, fluorescence resonance energy transfer (FRET)
- Fluorescence recovery after photobleaching (FRAP)
- High-content screening (HCS)
- Other technologies, such as:
 - Fluorescence in situ hybridization (FISH)
 - Total internal reflection fluorescence microscopes (TIRF)
 - Multiphoton excitation microscopy (MPE)

In 2019, it was the time-lapse microscopy segment that garnered the largest share, by technology, capturing 66.1% of the total live cell imaging market. Automation and the adoption of fluorescence imaging in cell-based research continue to advance the use of time-lapse microscopy.²⁵ Increased activity in cell-based research is a market driver for this segment.

Table 4: Global Cell Imaging Market, by	Technology, 2018-2025 (USD Million)

Technology	2018	2019	2020	2025	CAGR (2020-2025)
Time-lapse Microscopy	1,313.6	1,421.5	1,242.9	1,832.3	8.1%
Fluorescence Resonance Energy Transfer (FRET)	286.4	313.2	275.4	425.7	9.1%
Fluorescence Recovery after Photobleaching (FRAP)	177.8	193.3	168.7	253.0	8.4%
High-content Screening (HCS)	128.4	148.9	138.3	285.5	15.6%
Other Technologies	69.1	74.1	63.3	87.8	6.8%
Total	1,975.4	2,151.0	1,888.6	2,884.3	8.8%

Source: Reprinted with permission from MarketsandMarkets²⁶

By application, cell biology is the largest segment, followed by stem cells, developmental biology, and drug discovery.

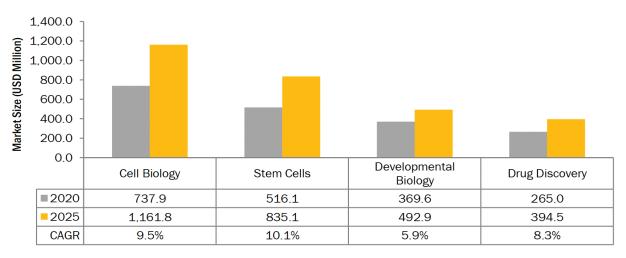


Figure 4: Live Cell Imaging Market by Application, 2020 vs 2025 (USD Million) Source: Reprinted with permission from MarketsandMarkets²⁷

Figure 5 represents the same data by end-users. Pharmaceutical and biotechnology companies are the largest users.

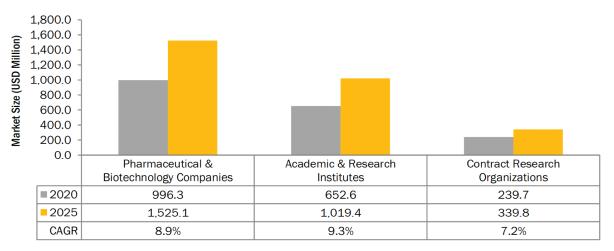
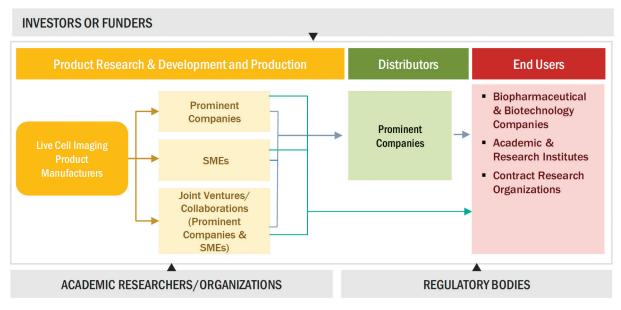
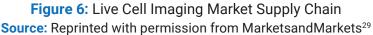


Figure 5: Live Cell Imaging market, by End-user, 2020 vs 2025 (USD Million) Source: Reprinted with permission from MarketsandMarkets²⁸

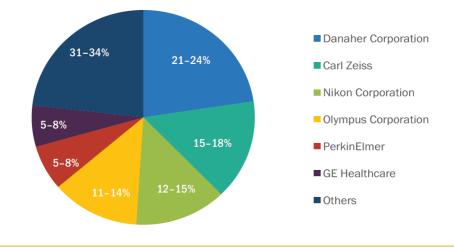
4.1 Supply Chain Analysis

As illustrated by the figure below, the supply chain for the live cell imaging market includes not only major players (i.e., prominent companies) but also small and medium size enterprises (SMEs) in its product R&D stage. Notably, this would not preclude partnerships between these same "prominent players" and SMEs also as a part of this stage. In addition to the groups in this stage, product manufacturers, distributors and end users complete the balance of the supply chain. While these groups, when combined, represent the key stakeholders in this market, its major market influencers are the investors and funders – as represented by the top grey bar of the following figure.





Some of the key players participating in the live cell imaging market include **Danaher Corporation**, **ZEISS AG (Germany)**, **Nikon Corporation (Japan)**, **Olympus Corporation (Japan)**, **PerkinElmer, Inc., GE Healthcare, Bruker Corporation, Thermo Fisher Scientific, Sartorius AG (Germany)**, **Oxford Instruments (UK)**, and **BioTek Instruments**. The top tier (i.e., Danaher, Carl ZEISS and Nikon) controls between 40-57% of the entire market.³⁰



Note: Others include Oxford Instruments (UK), BioTek Instruments (US), Etaluma, Inc. (US), CytoSMART Technologies (Netherlands), NanoEnTek Inc. (Korea), Phase Focus Limited (UK), Tomocube, Inc. (South Korea), Phase Holographic Imaging PHI AB (Sweden), BD Biosciences (US), Sony Biotechnology, Inc. (US), Merck KGaA (Germany), KEYENCE Corporation (Japan), ibidi GmbH (Germany), Bio-Rad Laboratories (US), Bruker Corporation (US), Thermo Fisher Scientific Inc. (US), Logos Biosystems (South Korea), and Nanolive SA (Switzerland).



One can note the absence of any mention of quantum sensing within coverage of the live cell imaging market. This absence is due to the fact that this field still is in its nascent stage. That said, it will be instructive to continue monitoring the live cell imaging market to see when various quantum sensing techniques realize the capability to serve as potential replacements for current approaches.

5.0 The Microscopy Market

As noted previously, markets can be defined in many ways. Markets may overlap and/or be subsets of other markets depending on how each is defined. As researchers in plant biology use many different analysis and imaging techniques – with live cell imaging being just one approach – an overview of the microscopy market is also included. If the ability of quantum sensing to provide superior performance at a reduced cost is achieved, this technology may also have a significant impact on the microscopy market. It is for this reason that coverage of the microscopy market is important.

The global microscopy market is forecast to reach a value of \$8.9 billion in 2026, as compared to a market value of \$6.5 billion in 2020, reflecting a 5.6% CAGR sustained through the 2019-2026 time frame. Market drivers for the overall microscopy market include factors such as increased funding targeting specific R&D efforts, technological improvements to microscopes, and a more pronounced focus on both nanotechnology and regenerative medicine.³² The three primary product types in the microscopy market include microscopes, software, and accessories.

			,	,				,	CAGR
Product	2019	2020	2021	2022	2023	2024	2025	2026	(2021-2026)
Microscopes	5,398.5	5,533.6	5,756.8	6,000.1	6,265.2	6,572.7	6,914.5	7,287.4	4.8%
Software	464.5	507.2	560.4	618.7	682.8	755.4	836.5	926.3	10.6%
Accessories	414.3	440.7	475.5	513.5	555.2	602.7	655.7	714.2	8.5%
Total	6,277.3	6,481.6	6,792.7	7,132.3	7,503.2	7,930.9	8,406.7	8,928.0	5.6%

MICROSCOPY MARKET, BY PRODUCT, 2019–2026 (USD MILLION)

Source: Reprinted with permission from MarketsandMarkets³³

Based on microscope type, the microscopy market can be further divided into the following segments: optical microscopes, electron microscopes, scanning probe microscopes, and other microscopes. "Other" microscopes include X-ray microscopes, Raman microscopes, and scanning acoustic microscopes. While in 2020, optical microscopes accounted for the largest share of the microscopy market, it is the electron microscopes segment that

The microscopy market is broadly divided into three segments: optical microscopes, electron microscopes and scanning probe microscopes.

is forecast to exhibit the highest growth rate (6.1%) during the 2019–2026-frame. Two factors account for this: first, the notable increased activity in life science and materials science research; and second, the emergence of correlative light and electron microscopy, which are forecast to influence a growing demand for electron microscopy.

Туре	2019	2020	2021	2022	2023	2024	2025	2026	CAGR (2021-2026)
Optical Microscopes	2,504.9	2,556.5	2,648.1	2,748.0	2,856.9	2,984.0	3,125.4	3,279.3	4.4%
Electron Microscopes	2,013.6	2,090.3	2,202.0	2,323.5	2,455.9	2,607.7	2,776.2	2,960.5	6.1%
Scanning Probe Microscopes	561.4	567.2	581.4	597.0	614.0	634.3	656.9	681.4	3.2%
Other Microscopes	318.5	319.6	325.3	331.5	338.3	346.7	356.1	366.2	2.4%
Total	5,398.5	5,533.6	5,756.8	6,000.1	6,265.2	6,572.7	6,914.5	7,287.4	4.8%

Table 6: Global Microscopy Market by Type, 2019-2026 (USD Million)

Source: Reprinted with permission from MarketsandMarkets³⁴

Information on optical, electron and scanning probe microscopes follows, with key players noted for each segment.

5.1 Optical Microscopes

In 2020, the optical microscopes segment accounted for 46.2% of the microscopy market. Based on type, the optical microscopes market is divided into confocal, stereo, digital, compound, and other. The "other" optical microscopes segment includes fluorescence, multi-photon, polarized, and phase-contrast microscopes.³⁵

Туре	2019	2020	2021	2022	2023	2024	2025	2026	CAGR (2021-2026)
Confocal Microscopes	726.4	746.5	778.6	813.4	851.4	895.2	943.9	996.9	5.1%
Stereo Microscopes	425.8	430.1	440.9	452.7	465.7	481.2	498.5	517.3	3.2%
Digital Microscopes	275.5	285.1	299.2	314.6	331.4	350.6	371.9	395.2	5.7%
Compound Microscopes	200.4	201.3	205.2	209.5	214.3	220.1	226.6	233.7	2.6%
Other Optical Microscopes	876.7	893.5	924.2	957.7	994.2	1,036.9	1,084.5	1,136.3	4.2%
Total	2,504.9	2,556.5	2,648.1	2,748.0	2,856.9	2,984.0	3,125.4	3,279.3	4.4%

Table 7: Optical Microscopes Market, by Type, 2019-2026 (USD Million)

Source: Reprinted with permission from MarketsandMarkets³⁶

5.1.1 Key Players

The key players providing optical microscopes include **Olympus Corporation**, **Nikon Corporation**, **Leica Microsystems**,⁴ and **Carl ZEISS**.

Within the "other" category one will find the following types of microscopes. For each, a brief description is included as well as a list of key players providing these solutions:

- Fluorescence microscopes are essential tools in biomedical and materials science applications. ZEISS, Danaher, Nikon, Bruker, and Olympus are the major players.
- Multi-photon microscopes are an alternative to confocal and fluorescence microscopes. Bruker and Nikon are the key players offering multi-photon microscopes in the market.
- Phase-contrast microscopes are used to study the behavior of living cells. These microscopes have major applications in the life sciences industry. OPTIKA, Meiji Techno, and Labomed offer phase-contrast microscopes.
- Polarized microscopes use polarized light and generate information on absorption color and optical path boundaries between minerals of differing refractive indices. These microscopes provide high-quality images. Nikon, Danaher, and Olympus are the major players offering polarized microscopes in the market.
- Compound microscopes are widely used in academic & research institutes, hospitals, diagnostic centers, forensic laboratories, and blood banks. Olympus, Meiji Techno Co., Laborned, and ACCU-SCOPE are the major players offering compound microscopes.
- Digital microscopes are optical microscopes in which the eyepiece is replaced by a digital camera. Keyence, Danaher, and ZEISS are the major players offering digital microscopes in the market.
- Stereo microscopes are low-magnification microscopes often used to inspect electronic components, minerals, jewelry, coins, textiles, insects, and animal dissections. Major players offering stereo microscopes include ZEISS, Danaher, and Nikon.

Although still referred to as Leica Microsystems, since 2005 the company has been a wholly owned subsidiary of Danaher Corporation.

5.2 Electron Microscopes

Electron microscopes possess very high magnification capabilities, with the ability to reach ratios up to 5,000,000x. For this reason, these microscopes are employed in biology, materials science, nanotechnology, and semiconductor applications. A drawback is the high cost associated with electron microscopes. Based on electron microscope type, this market is further divided into scanning electron microscopes (SEM) and transmission electron microscopes (TEM).³⁷ Please note that cryo-electron microscopy is not called out as a specific subset in these data.

Туре	2019	2020	2021	2022	2023	2024	2025	2026	CAGR (2021-2026)
Scanning Electron Microscopes	1,582.7	1,648.3	1,742.0	1,844.1	1,955.4	2,082.9	2,224.6	2,379.8	6.4%
Transmission Electron Microscopes	430.9	442.0	460.0	479.5	500.5	524.8	551.6	580.7	4.8%
Total	2,013.6	2,090.3	2,202.0	2,323.5	2,455.9	2,607.7	2,776.2	2,960.5	6.1%

Table 8: Global Electron Microscopy Market, by Type, 2019-2026 (USD million)

Source: Reprinted with permission from MarketsandMarkets³⁸

5.2.1 Key Players

Major manufacturers of electron microscopy equipment are comprised of mostly large companies, including ZEISS,³⁹ Olympus,⁴⁰ Hitachi High-Technologies,⁴¹ Leica Microsystems (a division of Danaher),⁴² and FEI, after it was purchased by Thermo Fisher Scientific in 2016.⁴³ The market also includes medium-sized companies with less than \$1 billion in sales, such as JEOL⁴⁴ (and FEI, before its acquisition).

The electron microscope market is relatively mature with its industry concentrated primarily in Germany, Japan, and the United States. These companies maintain global distribution and service networks and very often sustain legacy reputations within various imaging markets.

5.3 Scanning Probe Microscopes

As its name implies, scanning probe microscopes (SPMs) employ physical probes that scan a specimen to produce an image. An advanced microscopy technique, SPMs are "widely used in semiconductors, materials science, electronics, and nanotechnology for topographic analysis."⁴⁵ A driver in the SPM market is the increased focus on nanotech R&D targeting the development of nano-sized particles. SPMs work by measuring deflections of different forces (e.g., mechanical, electrostatic, magnetic, etc.) and based on which force is how SPMs are classified into the following three subsets:

- Atomic force microscopes (AFMs)
- Scanning tunneling microscopes (STMs)
- Near-field scanning optical microscopes (NSOMs)

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Table 9: Scanning	Probe Microscopes	iviarket, by Type,	, 2019-2026	

Туре	2019	2020	2021	2022	2023	2024	2025	2026	CAGR (2021-2026)
Scanning Tunneling Microscopes	440.2	446.1	458.8	472.5	487.5	505.2	524.8	546.1	3.5%
Atomic Force Microscopes	71.3	71.3	72.4	73.6	74.9	76.6	78.5	80.6	2.2%
Near-field Scanning Optical Microscopes	50.0	49.8	50.3	50.9	51.6	52.5	53.5	54.7	1.7%
Total	561.4	567.2	581.4	597.0	614.0	634.3	656.9	681.4	3.2%

Source: Reprinted with permission from MarketsandMarkets⁴⁶

5.4 Microscopy Applications

The microscopy market spans many industries and is divided into semiconductor, life science, materials science, and other applications. In 2021, semiconductor applications accounted for the largest share of the market, followed by life science applications.

 Table 10: Microscopy Market, by Application, 2019-2026 (USD Million)

Application	2019	2020	2021	2022	2023	2024	2025	2026	CAGR (2021-2026)
Semiconductor Applications	2,131.0	2,183.4	2,270.5	2,365.4	2,468.9	2,589.0	2,722.4	2,868.0	4.8%
Life Science Applications	1,870.4	1,904.4	1,968.0	2,037.2	2,112.8	2,201.2	2,299.7	2,406.8	4.1%
Materials Science Applications	1,051.6	1,097.3	1,161.8	1,231.9	1,308.4	1,395.7	1,492.6	1,598.8	6.6%
Other Applications	345.5	348.4	356.6	365.5	375.2	386.8	399.8	413.8	3.0%
Total	5,398.5	5,533.6	5,756.8	6,000.1	6,265.2	6,572.7	6,914.5	7,287.4	4.8%

Source: Reprinted with permission from MarketsandMarkets⁴⁷

Microscopy is critical to areas such as pharmaceutical and biotechnology drug discovery and development. Further, within academic research groups, microscopes are pivotal to applications such as cell biology, neurobiology, cancer biology, marine biology, and more. Digitization, live-cell imaging, super-resolution, and high-throughput analysis are advanced techniques that have served to draw increased interest in microscopy technologies. Atomic force microscopes and electron microscopes are advanced microscopes typically employed in quality control. "SEM microscopes such as <u>EVO</u>, <u>Sigma</u>, and <u>MultiSEM 505/506</u> (ZEISS); <u>LV100N polarizing microscope</u>; <u>AZ100 MULTIZOOM</u> upright zoom microscope; and high zoom <u>SMZ25</u> and <u>SMZ18</u> stereomicroscopes (Nikon) are used in life science research."⁴⁸

5.5 Other Microscopes

The global market for "other" microscopes referenced in Table 6 was valued at \$318.5M in 2019 and is forecast to reach a market valued at \$366.2M in 2026, exhibiting a 2.4% CAGR during the 2019-2026 time frame. The other category includes X-ray, Raman, and scanning acoustic microscopes. Raman microscopes are laser-based, allowing for nondestructive analysis. Scanning acoustic microscopes also offer nondestructive analysis, differing in that these employ sound (via transducers) when imaging samples for analysis. Primary application areas include the semiconductor industry, materials research, and life sciences.

5.6 Changes in the Microscopy Market

Certain technology advancements such as digitization, live-cell imaging, super-resolution, and highthroughput methods are able to realize a reduction in product and test costs. "Owing to technological advancements, there has been a shift in the usage patterns of microscopes. Conventional microscopes are gradually losing their popularity to high-end microscopes such as electron microscopes, scanning probe microscopes, and digital microscopes due to their advanced features, higher resolution, and magnification power."⁴⁹ This preference shift comes with a price tag:

The cost of these systems rises exponentially with the addition of sample preparation & transfer systems and customized software for analyzing the generated images. While basic software is priced low, software with advanced features and specific applications, such as applied sciences and materials, is often costly. This still varies based on end user; academic and research institutes are offered lower prices than industrial end users, due to their budgets. An integrated corrective light-electron microscopy (CLEM) workflow includes light and electron microscopes, and its cost rises exponentially with the addition of sample preparation & transfer systems and customized software. For a CLEM workflow, the setup cost is very high—approximately USD 0.2–0.5 million.

In addition to this, there are recurrent expenses in the form of maintenance costs, which ultimately drive up the overall cost of ownership. The maintenance cost of a transmission electron microscope is between USD 15,000–USD 100,000 per year. This high cost has left users reliant on government and private research funding, which restricts market growth to a certain extent.

Digital microscopy offerings from key players include the <u>ShuttlePix P-400R</u> (Nikon), <u>Leica DVM6</u> (Danaher), and <u>Celldiscoverer 7</u> (ZEISS).⁵⁰ However, these microscopes are more expensive and cost between \$25,000 to \$2 million, which is a major factor limiting their widespread adoption.⁵¹

Recently introduced are microscopes with combination techniques. An example of this is the FIB-SEM technique that combines an electron beam and an ion beam, and with this combination, the instrument targets the same area of a specific sample. Microscopes with this combination technique offer advantages that include "super-resolution, multi-user functionality, and dynamic photo-manipulation capabilities."⁵² ZEISS, as an example of a major manufacturer, offers its <u>ELYRA Superresolution</u> <u>Combination Systems</u>. Another example of a combination instrument is the Thermo Fisher <u>DXR2</u> <u>Raman Imaging Microscope</u>.

The integration of microscopy with spectroscopy is expected to present major opportunities to research communities due to its wide variety of applications.⁵³ For instance, combining Raman spectroscopy with atomic force microscopy or optical microscopy provides detailed information about nanoscale properties and composition.⁵⁴ Other benefits of these combined techniques include precise alignment of the sample, optical signal transfer from the microscope to the spectrometer, and precise focus of the excitation light at the detection point.

Another advancement is the use of artificial Intelligence (AI) based on deep learning in what is termed AI-based microscopy. Key players are found entering this space. For example, in 2020, Nikon released its <u>NIS-A Clarify.ai</u> offering, which is an AI-based module for microscopes that uses artificial intelligence to remove signals emitted from out-of-focus image planes from fluorescence images.⁵⁵

5.7 Key Players

This section provides a brief introduction to the four largest microscope manufacturers.

5.7.1 Danaher Corporation | Leica Microsystems

Leica Microsystems was purchased by <u>Danaher Corporation</u> in 2005. Danaher is a publicly-traded company with headquarters in Washington, DC. According to its 2021 <u>presentation to investors</u>, revenues in that year were \$28B with Life Sciences being its largest segment. Other life science companies owned by Danaher include <u>Aldevron</u>, <u>Beckman Coulter</u>, <u>Cytiva</u>, <u>Pall</u>, <u>SCIEX</u>, <u>XXIDT</u>.

<u>Leica Microsystems</u>, with headquarters in Wetzlar, Germany develops and manufactures microscopes and scientific instruments for structural analysis at microstructure and nanostructure levels. Leica is a key participant in microscopy and instrumentation areas that include:

- compound and stereo microscopy
- digital microscopy
- confocal laser scanning and super-resolution microscopy with related imaging systems, electron microscopy sample preparation, and surgical microscopy.

In addition, Leica offers an extensive collection of imaging software for microscopes. New products introduced recently include:

- In June 2021, Leica launched their <u>Leica Nano</u> workflow, which is a new live-cell correlative light and electron microscopy (CLEM) workflow solution designed to increase experimental success rates, improve reproducibility, and simplify light and electron microscopy integration.⁵⁶
- April 2020, the company launched a confocal microscopy platform called <u>STELLARIS</u>. The platform will significantly improve how scientists are able to capture three-dimensional images of living cells and tissues.⁵⁷
- In 2019, the company launched the <u>SP8 confocal microscope platform</u>, now with built-in LIGHTNING detection technology. SP8 LIGHTNING confocal microscopes offer five highly sensitive detection channels for super-resolution live cell imaging in multicolor. As all channels operate in parallel, there is no trade-off between speed and resolution. This allows for simultaneous observation of fast biological processes in living cells.⁵⁸

Leica is actively involved with acquisitions and partnerships. In 2021, Acquired <u>Aivia</u>, a company that provides AI-enabled innovative visualization, analysis and interpretation software solutions. In 2011, Leica Microsystems has signed an agreement with the <u>Max Planck Society</u> and the German Cancer Research Center for the development of the next generation of super-resolution Stimulated Emission Depletion (STED) microscopy. This gives Leica Microsystems the license to develop STED into a commercial product.⁵⁹

5.7.2 Nikon Corporation

Founded in 1917 and headquartered in Tokyo, Japan, Nikon is a leading manufacturer and supplier of optical instruments. The company operates through four business segments: Imaging Products,

Precision Equipment, Healthcare, and Industrial Metrology. Nikon microscopy products are available through its Healthcare business segment. The company operates in the United States, Japan, Europe, China, and other countries with subsidiaries named geographically such as Nikon Americas, Inc. (U.S.), Nikon Precision Europe GmbH (Germany), Nikon UK Ltd. (UK), Nikon France S.A.S. (France), Nikon Instruments S.p.A. (Italy), Nikon Singapore Pte. Ltd. (Singapore), and Nikon Australia Pty Ltd. (Australia).

Nikon is well established in the live cell imaging market, offering microscopes to a diverse array of applications involving advanced R&D.⁶⁰ In 2018, <u>Nikon and Yumanity Therapeutics</u> entered into an agreement to develop drug discovery assay systems in the field of neurodegenerative disease by using Nikon's BioStation CT, which is a cell culture system that employs live cell imaging technology.⁶¹

Examples of recent product introductions involving microscopes and life science imaging include:

- In November 2021, Nikon Instruments released the <u>AX RMP multiphoton confocal microscope</u>, which can acquire high resolution, large field of view images, deep within living organisms at high speed. The AX R MP multiphoton confocal microscope enables high speed acquisition of high resolution, wide-field images. It supports a wide range of experiments and acquisition of images from various angles. The AX R MP efficiently acquires large amounts of data on ultrastructure in the deep regions of living organisms.⁶²
- In 2019, the company launched four add-on modules dedicated to the <u>CL-Quant cell imaging</u> analysis software.⁶³
- In 2019, the company introduced two silicone immersion objective lenses, the <u>CFI Plan</u> <u>Apochromat Lambda S 25XC Sil</u> and the CFI Plan Apochromat Lambda S 40XC Sil, for confocal laser microscope systems and Ti2 inverted research microscopes. These lenses combine high numerical apertures with large fields-of-view (FOV). The use of silicone oil for liquid immersion observation enables ultimate clarity when imaging live, thick specimens.⁶⁴
- In 2018, the company introduced <u>CFI S Plan Fluor LWD 20XC</u> and CFI S Plan Fluor LWD ADM 20XC objectives for biological microscopes. These objectives are effective in research utilizing stem cells and drug design research. They are capable of a long working distance and provide a high numerical aperture. These objectives provide clear images even in observation with plastic cell-culture dishes, which are frequently used in various types of research.⁶⁵
- In 2018, the company introduced the <u>A1 HD25/A1R HD25 confocal microscope</u>, which enables high-speed, high-resolution image acquisition of large areas utilizing the world's largest FOV (25 mm).⁶⁶

Examples of partnerships, collaborative efforts, licensing and patent agreements include:

- In August 2021, Nikon partnered with sensing and perception systems company <u>Aeva</u>, in an effort to deliver micron-level measurement capabilities to industrial automation and metrology markets.⁶⁷
- In 2017, Leica Microsystems "co-exclusively licensed to <u>Abberior Instruments</u>, developer and manufacturer of high-resolution STED and RESOLFT research microscopes, IP rights regarding its light microscopy product portfolio. In return, Abberior Instruments will also

co-exclusively license IP rights to Leica Microsystems. The licensing agreement is only applicable for the Licensor and Licensee."68

- In June 2015, Advanced Microscopy Inc. (a WiLAN subsidiary) entered into a patent license agreement with Leica Microsystems. "The license relates to technology that provides enhanced image processing capabilities. Potential applications relate to the life sciences, material sciences, and semiconductor research."⁶⁹
- As far back as 2014, Nikon partnered with JOEL in an effort to develop solutions involving correlative light and electron microscopy.⁷⁰

5.7.3 Olympus Corporation

Founded in 1919 and headquartered in Tokyo, Japan, Olympus is a leading player in the global microscopy market. The company operates primarily through four business segments: Endoscopic Solutions, Scientific Solutions, Imaging, and Others (which includes IT and Industrial Systems). It is the Scientific Solutions segment that is responsible for microscopes specific to various applications such as life science and medical research. Olympus offers an extensive line of inverted microscopes, confocal microscopes, as well as software. The company maintains operations in the U.S., Canada, Mexico, Brazil, Germany, the UK, France, Singapore, China, and India.⁷¹

Recent product launches include:

- In April 2020, Olympus upgraded the <u>cellSens</u> imaging software for microscopy with deep learning technology.⁷²
- In October 2019, the company launched the <u>SLIDEVIEW VS200</u> Research Slide Scanner to capture high-quality virtual slide images. This scanner enables advanced quantitative image analysis for cancer and stem cell research, as well as drug discovery.⁷³
- In 2018, the company upgraded the high-sensitivity model of the <u>SpinSR10 Super-Resolution</u> <u>Imaging System</u> that delivers clearer images and 3x the brightness of the standard model.⁷⁴

5.7.4 ZEISS AG

The ZEISS Group is involved in imaging areas that span microscopes, medical technologies, measuring technologies, semiconductor manufacturing equipment and more. Founded in 1846 in Jena, the company is headquartered in Oberkochen, Germany. ZEISS AG is the strategic management holding company that manages the ZEISS Group.⁷⁵ The ZEISS Group encompasses six business groups and various strategic business units that are involved with various optical systems that include microscopes, surgical microscopes, and more.⁷⁶

ZEISS has a long history with microscopes and is a leader in the field of surgical microscopes.⁷⁷ The company maintains an extensive portfolio of microscopy products.

At the 2018 ZEISS Symposium "Optics in the Quantum World," Dr. Ulrich Simon, Head of Research & Technology at the ZEISS Group noted ZEISS is committed to quantum imaging and they expect products

to be launched within the next ten years:78

Up until now, people have tended to underestimate the opportunities afforded by quantum technology. The first specific product launches are expected in several areas in the next five to ten years. The innovation cycles are becoming shorter, and it is important that companies like ZEISS commit to this technology. This will affect us more quickly than we thought a few years ago. In particular quantum sensors will prove important for ZEISS Medical Technology, Measuring Technology and Microscopy areas. Quantum sensors are enhanced sensors that are many times more precise than their predecessors.

Prof. Dr. Michael Kaschke, President & CEO of the ZEISS Group explained the ZEISS Symposium focused on quantum technology since close cooperation between science and industry is a key success factor. The ZEISS Symposium "Optics in the Quantum World" has helped foster this.

Along the lines of collaboration with scientists and industry, it is interesting that ZEISS is funding efforts in this space. ZEISS is to launch a competition, the "ZEISS Quantum Challenge" dedicated to the use of quantum technology in sensor and imaging applications in a real-life environment. The ZEISS Quantum Challenge is to advance the scientific application from lab to market-ready products in quantum technology. ZEISS ran a competition in three categories: medical, microscopy and industrial.⁷⁹ The Quantum Challenge winners were Prof. Dr. Friedemann Reinhard, Professor of Quantum Technology at the University of Rostock, and Dr. Gabriel Puebla-Hellmann, CEO of QZabre AG in Zurich.⁸⁰

The ZEISS group enters into collaborations with third parties as a critical part of its business strategy. Below are examples of past licensing agreements:

- ZEISS signed a license agreement with University of California in San Francisco (UCSF) to commercialize UCSF's Multidirectional Selective Plane Illumination Microscopy (mSPIN), which is an illumination technique for light sheet fluorescence microscopy. "By alternating illumination of the sample from multiple sides, mSPIM overcomes two common problems in light sheet imaging techniques: shadowing effects in the excitation path and spreading of the light sheet by scattering in the sample. The agreement grants Carl ZEISS the right to integrate the mSPIM technology in its microscopy systems."⁸¹
- In 2012, ZEISS Microscopy entered into an agreement with Gatan, Inc. (a manufacturer of instruments and software for electron microscopes) for the development and sales of a 3D cell and tissue imaging system. This imaging system provides high-resolution 3D data of resin embedded cell and tissue samples. The 3View system consists of an ultramicrotome directly integrated into the vacuum chamber of the ZEISS Merlin and Sigma VP field emission scanning electron microscopes.⁸²

6.0 Cryo-electron Microscopy Market

A technique increasingly used in the life sciences requires the use of cryo-electron microscopy. As this segment was not included in the Microscope market, a brief introduction to the Cryo-electron Microscopy market is presented here.^{83,84} Cryo-electron microscopy enables the structures of interest in a sample to be visualized in their native cellular or tissue environment at near atomic resolution. To accomplish this a transmission electron microscope is used at cryogenic temperatures. According to FIORMARKETS, in this approach "Specimens persist in their natural state without the need for colors or fixatives, [allowing] the study of acceptable cellular structures, viruses, and protein complexes at

molecular resolution."85

"Some of the notable players in the Cryo-electron Microscopy market are Thermo Fisher Scientific, JEOL Ltd, Hitachi High-Technologies Corporation, ZEISS, Delong America Inc, Cordouan Technologies, Nvidia Corporation, Cray Inc, Structura Biotechnology Inc, Gatan, Creative Bio Structure, Spider, Eman2, Frealign, Sparx, Sphire, Xmipp, Relion, Image Science Software GmbH, Drvision Tecnologies LLC, Eyen SE, OmicX, CsiTem, Aspire, C-CINA, The Gorgon Project, The Mechanical Rossmann laboratory, Tempy among others...Major players are continuously focused on new developments, strategic partnerships, acquisitions, and venture capital investments to obtain high growth in the market."⁸⁶

The cryo-electron microscopy market can be segmented by type (electron crystallography, single particle analysis, cryo-electron tomography and others); applications (semiconductors, life sciences, materials sciences, nanotechnology and other applications) and by geographic region. The global cryo-electron market is expected to grow by 8.14% between 2019 when the global market was \$ 540.1 million to \$1,010.66 million by 2027. Software tools have facilitated this burgeoning growth with special mention made of various ZEISS software products including ZEISS ZEN Core, ZEISS ZEN Intelleis software, ZEISS ZEN Connect, and arivis Vision4D and patent-pending arivis inViewR.

Within the electron microscope market segment, cryogenic electron microscopy (cryo-EM) is a vibrant subspeciality advancing biological sciences. Currently, optimized 300 kV TEMs equipped with direct electron detectors can be used to collect data on macromolecules and their complexes at a resolution sufficient to yield atomic level structure characterization. Lower-end (120 kV and 200 kV) cryogenic instruments are complementary microscopes necessary to screen and evaluate samples for suitability before collection of full data sets on the 300 kV instruments. There is a drive toward optimizing samples and instrument parameters to be able to collect high resolution on lower-cost 100 kV instruments, which could change the market by enabling independent research laboratories to purchase these lower cost microscopes. The same 300 kV TEMs are also used for cryo-electron tomography (cryo-ET) data collection, a technique to 3-dimensionally image parts of frozen biological cells. Instruments offered by some microscope companies that facilitate biological cryo-ET are focused ion beam scanning electron microscopes (FIB-SEMs), which are used to prepare lamella thin enough for effective electron transmission. Other accessories that enable and enhance biological cryo-EM and cryo-ET include direct electron detectors (as mentioned earlier), cryogenic sample stages, contrast phase plate optics and specialized sample freezing apparatus, among others. These facilitative elements, along with sample preparation and introduction, and various automation tools, are elements that may offer opportunity for development by small business concerns.87

6.1 Key players

In this section a brief introduction is made to three of the key players in the cryo-electron microscopy market, highlighting those not already mentioned in previous sections of this report including Thermo Fisher Scientific, JEOL Ltd. and Hitachi High-Technologies Corporation.

6.1.1 Thermo Fisher Scientific

<u>Thermo Fisher Scientific</u> was founded in 1956 and is headquartered in Massachusetts, US. A key player in the life science industry, a company with over 80,000 employees, maintains a market presence that

spans 80+ countries. Their Analytical Instruments segment is the division involved with microscopes. Microscopy products include transmission electron microscopes (TEM), scanning electron microscopes (SEM) and ion-beam workstations. In 2017, Thermo Fisher Scientific strategically acquired FEI, a manufacturer of high-performance electron microscopy solutions for life science and material science research.⁸⁸

Thermo Fisher Scientific has invested in multiple sectors such as life sciences platforms and tools, genomics, life sciences tech and more.⁸⁹ The latest acquisitions all are in life sciences: PPD (acquired for \$ 17.40B in April 2021);⁹⁰ PeproTech (acquired for \$1.8B in 2022);⁹¹ and Mesa Biotech (acquired for \$450M in February 2021).⁹²

Thermo Fisher is open to licensing and partnerships with companies and researchers. On their website, they have a web page dedicated to "Business Development & In-Licensing Model & Process."

In 2020, Thermo Fisher Scientific signed an exclusive license agreement with MSAID, a German software company transforming proteomics with deep learning, to develop and commercialize deep learning tools for proteomics, making MSAID's Prosit-derived framework widely accessible to proteomics laboratories. The algorithm allows gains in confidence and reproducibility and will be released as part of Thermo Fisher's newest Thermo Scientific Proteome Discoverer 2.5 software release.⁹³

6.1.2 JEOL Ltd.

With headquarters in Tokyo, Japan, <u>JEOL Ltd.</u> is often listed among the top ten analytical laboratory instrument manufacturing firms in the world. Among its products are electron microscopes, X-ray diffractometers, spectrometers and thermographs. According to GlobalData, in 2022 the company has approximately 3,200 employees with estimated revenue of \$1.2B.

<u>JEOL USA</u>, located in Peabody, MA, is a wholly-owned subsidiary of JEOL Ltd. and was incorporated in 1962. Its primary purpose is to support the sale of new instruments and peripherals in the United States, Canada, Mexico and South America. JEOL's newest Cryo-EM product is the <u>CRYO ARMTM 200 (JEM-Z200FSC) Field Emission Cryo-Electron Microscope</u>.

6.1.3 Hitachi High-Technologies Corporation

With its headquarters in Tokyo, Japan – Hitachi High-Technologies Corporation employees over 12,000 – and specializes in process equipment, electron microscopes, industrial solutions and industrial components and materials. The company has over 8,140 patents and revenues of \$5 billion in 2021. Hitachi also has a cryo-electron microscope and a cryo-transfer holder.⁹⁴

7.0 The Quantum Technologies Market

In previous sections of this report, we introduced two markets: (1) the live cell imaging market; and (2) the microscope market. In each section, the range of technologies used to address the needs of different industries were presented. To the extent that quantum sensing technologies in biotech fields

are able to address not only the technical challenges but also the price imperative, these markets will become the markets for quantum sensing applications in imaging and optics, as they begin to erode the current position of competing technologies. What we haven't addressed is the size of the market opportunities for the numerous and varied applications of quantum information science (QIS).

McKinsey & Company see the "overall, development and commercialization timelines for quantum sensors and quantum communications products as being **difficult to predict because progress depends on scientific breakthroughs**. For instance, some quantum sensors have difficulty functioning outside the protected lab environment because they are so sensitive. Broad adoption also depends on device optimization, especially for size and weight. Reducing cost is also critical, since potential buyers may not want to pay a higher price for quantum technologies, despite their greater accuracy, if alternative solutions are available. While many hurdles lie ahead, quantum solutions could generate substantial revenue over the next decade."⁹⁵

In the report, "<u>Shaping the long race in quantum communication and quantum sensing</u>," McKinsey & Company see that in addition to quantum computing, other interesting areas where quantum technologies are expected to make headway are quantum sensing and quantum communication, which McKinsey & Company expect could reach the market earlier and potentially transform multiple industries.⁹⁶ McKinsey & Company identify eight applications that quantum sensing has a competitive edge, shown in table 11 on the next page.

Application	Description					
Bioimaging	Neural sensing and heart imaging					
Spectroscopy	Imaging of molecular structures, such as proteins					
Communication	Signal receiving and amplification for radar; calibrating electrical standards to support 5G/6G					
Navigation	High accuracy GPS; assisting with navigation inside buildings and underground					
Environmental monitoring	Predicting volcano eruptions; measuring CO ₂ emissions					
Infrastructure monitoring	Monitoring mechanical stability and detecting leaks					
Geographical surveying	Location of oil and gas					
Fundamental Science	Accessing high energy physics beyond the standard model.					

Table 11: Applications in which Quantum Sensing has Advantages

Source: McKinsey & Company (December 2021)97

8.0 Preparing to Partner

The "valley of death" ... the road from concept to commercialization is filled with countless challenges. In order to provide guidance to small businesses working in QIS, interviews were conducted with a number of subject matter experts to garner recommendations to assist small business on their journey. To successfully bring technology to market, some form of collaboration with a large corporation or venture capital firm will be required. The following are recommended tips to help bridge the valley of death.

- The small business must develop a sound value proposition, a Minimally Viable Product intended to create value for the end user.
- It is valuable to publish in relevant journals, attend relevant meetings, and pursue intellectual property protection.
- Before approaching a large company, the small business must demonstrate a level of integration and have results that demonstrate a solution to a particular microscopy issue of interest to the large firm.
- The small business must have knowledge of the microscope commercialization value chain.
- It is useful for a small business to know what other attempts to solve the problem have failed or been successful and what improvements their technology brings over competitors' efforts.
- It is important to be open-minded to alternative applications.
- The technology should be readily integratable to existing platforms/systems.
- Have a thorough understanding of the voice of the customer (SBE should participate in I-Corps or NSF Bootcamp to get this knowledge.)
- Hire industry experts early, to help temper unrealistic expectations regarding timelines.
- Quantum sensing is very promising but be careful in comparing your quantum sensing solution to classical sensing capabilities. Be fair and honest in your assessments benchmark against the best classical systems.

For small, advanced technology firms, as your research results begins to emerge, it is important to continue refining your commercialization strategy. As suggested by subject matter experts actively involved in the microscopy market, listen to the voice of the customer and be able to articulate your value proposition.

8.1 Conclusion

This is an exciting and challenging time to be involved with quantum technologies. In a very short period of time the federal government has put an infrastructure in place that provides opportunities at all levels of the QIS ecosystem. An important organization to help small businesses "plug in" to this growing community is the <u>Quantum Economic Development Consortium</u>. Sizing market opportunities is a challenge with any technology, but particularly with emerging and revolutionary technologies. However, to realize the challenge of bringing new quantum technologies to market, it is important to start the process of reaching out to end-user communities, and learning what makes a viable, commercial product to those that manufacture products, as well as those who use them.

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