

## Proteomics: The Next Frontier in Life Science Tools and Diagnostics

September 28, 2021

- **Bottom Line: Proteomics represents a large \$75B market opportunity in life science tools and diagnostics, in our view, with \$20B in research today and \$55B emerging in diagnostics and personalized medicine.** We see multiple winners in this market over the next decade - from pure-play to profitable, providing a wide investable space and a fertile ground for potential acquisitions and exits as these technologies and platforms deliver. Appreciation that proteomics is significantly more complex than genomics has finally sunk in - but emerging technologies are differentiated and showing signs of rapid adoption despite the target of the human proteome still being elusive. In the following deep dive, we explore technologies ranging from the legacy mass specs over the last two decades, expansion in RUO antibodies and immunoassays, to the fast growing area of high-plex proteomics today and the emerging technologies that remain to be proven in the market. We leverage our own insights from our lab experience in proteomics (45+ papers) and key proteomics KOLs around the world (via MEDACorp) to provide a broad and relatively in-depth view on proteomics.
- **Next decade in proteomics poised to be significantly different vs the last two.** Proteomics is the identification and quantification of a large number of proteins (from 100s to 1000s) in a single experiment. Though the last two decades of innovation in proteomics was largely in mass spec (TMO's [OP] Orbitrap and more recently BRKR's [OP] timsTOF), the next decade is likely to see new technologies including high-plex proteomics (OLK [OP], SLGC [Not Rated]) making a meaningful dent in proteomics adoption over the next 5 years with routine detection of nearly ~10k proteins or more in an experiment. Beyond that, technologies that deliver PTMs (Post Translational Modifications) on a large scale will likely yield the ultimate winners in the space.
- **Identifying key drivers of success in the proteomics market in the long run and potential winners:** We see select key drivers of success that will define the next set of winners in proteomics: (1) **Accessibility** - technologies that drive democratization and enable access to proteomics within broader labs; (2) **Reproducibility** - mass spec proteomics is plagued with reproducibility challenges and technologies addressing the issue are poised to see success; (3) **faster turn-around time** - technologies and applications that produce results within hours to 1-2 days will gain more traction vs those delivering results in weeks; and (4) ultimately we believe, technologies that **reduce complexity** will be welcomed by proteomics. Based on these key drivers, we favor both TECH [OP] and ABCM [OP] among

Reason for report:

**INDUSTRY UPDATE**

S&P 500 Health Care Index:

1,517.58

### Companies Highlighted

A, ABCM, BRKR, EXAS, GH, ILMN, MASS, MYGN, NEO, NTRA, OLK, QTRX, TECH, TMO, WAT

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RUO antibodies; OLK in high-plex proteomics, though we recognize that SLGC is likely to remain a strong market participant. We also see ILMN [MP] providing the detection backbone to these high-plex platforms and among the mass spec (LC-MS) technologies we favor BRKR's timsTOF platform to drive the next leg of innovation.

- **Proteins are the ultimate analyte for diagnostics.** We expect proteomic markers/panels to enhance genomic diagnostic assays and believe such assays could potentially drive clinical actionability. Proteins are the ultimate analyte for diagnostics as proteins provide a real time picture of a patient's health and disease state. The enhanced insight proteins provide makes them more actionable than stand-alone genomics, and we see clinical applications in multiple indications beyond just cancer. With the introduction of high-plex proteomics technologies, we believe the bar for developing such proteomics assays is much lower, and we expect further innovation to yield multi-omics assays as a result. We estimate a \$55B market for proteomics-based diagnostics. Our \$55B diagnostic TAM is derived from a \$27B therapy management and monitoring market paired with a \$28B diagnostic screening market. Our market estimates assume \$300 ASPs, which we view as highly conservative given genomics assays currently are being routinely reimbursed at \$1,000+.

## Proteomics: The Next Frontier; \$75B Market in the Making

- **\$55B market in the making in Proteomics Dx:**

- **\$55B Proteomics Dx TAM:** We estimate the application of proteomics into diagnostics is likely to yield a market of \$55B with \$27B in therapy selection and monitoring being the most meaningful (see our disease and indication specific market build-up on page 29).
- **Conservative ASP:** We are assuming a conservative \$300 ASP for such a therapy management and monitoring test despite genomics assays routinely being reimbursed above \$1,000.
- **Proteins remain the best analyte:** Consistently, MEDACorp KOLs have emphasized that proteins remain the most real-time diagnostic markers representing more actionable insights than genes.

- **\$20B market in the making in Research/Discovery applications:**

- **Lab count and spend:** We collected data on both core and individual PI (Principal Investigator) led labs. We collected total NIH funding for research in various chronic diseases by academic institutions and assumed an extremely conservative 2.5% of funding allocation to proteomics despite the broad use of RUO antibodies and associated reagents, mass spec proteomics and fast growing high-plex proteomics. We took an average proteomic spend for the top 150 academic institutes and estimated a spend of \$0.3M at peak for individual labs and \$1.2M spend per core lab.

### \$55B Proteomics Dx TAM (US)

Therapy  
Management  
and Monitoring  
\$27B

Screening  
\$28B



### \$20B Proteomics Research TAM (US)

Research &  
Applied  
\$20B

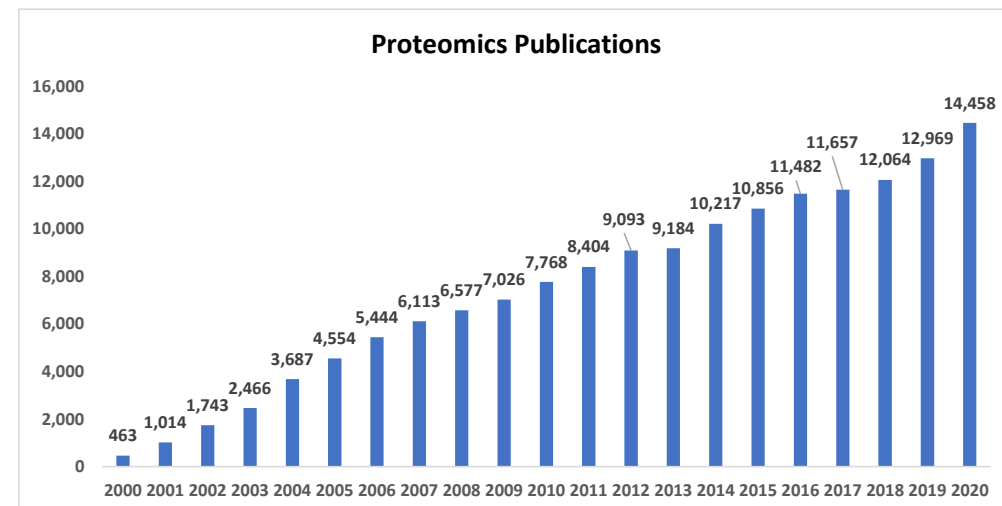
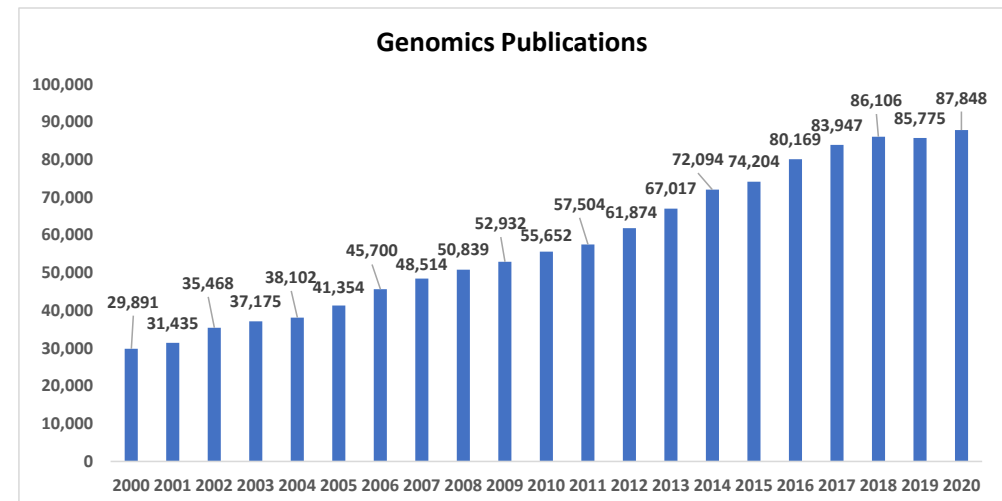
## Proteomics End-markets Poised to Grow; More Optionality Today vs Before

- **Expected growth rate in proteomics:** We expect the overall proteomics market to grow at a ~30% CAGR (2020-24E) with different segments of the proteomics market growing with respect to application growth in each segment.
- **High-plex market to see the most rapid grow in the near to mid term:** The fastest growing sub-market in proteomics is high-plex proteomics with both OLK and SLGC driving adoption and delivering on the needs of proteomics labs seeking a few hundred to few thousand proteins in a single experiment. For OLK, we see strong but still conservative revenue growth of 56% CAGR (2020-24E) that is bound to see significant upside as its Explore (3k proteins today, launching 4.5k next) line of proteomics panels drives adoption in the labs across biopharma and academia.
- **RUO (Research Use Only) antibodies** have historically grown mid-single digit to high-single digits annually at TECH and ABCM, and we expect RUO antibodies to grow at high-single digits despite 15% CAGR (2020-24E) given the backdrop of strong demand from biopharma and growing proteomics applications that will require validation via antibodies.
- **Mass spec (LC-MS):** We expect the mass spec market for proteomics to deliver high-single-digit to mid-teens growth given the legacy and long-standing position of TMO's Orbitrap with the now fast-growing BRKR timsTOF platform (see page 54 for timsTOF install numbers).

| Proteomics Technologies and Applications - Annual Revenue Growth |             |      |      |      |      |       |       |       |       |                 |
|--|-------------|------|------|------|------|-------|-------|-------|-------|-----------------|
| Name   | Ticker      | 2017 | 2018 | 2019 | 2020 | 2021E | 2022E | 2023E | 2024E | 2020-2024E CAGR |
| <b>Core Antibodies (RUO and Translational)</b>                   |             |      |      |      |      |       |       |       |       |                 |
| <b>Bio-Techne</b>  | <b>TECH</b> | N/A  | 14%  | 11%  | 4%   | 26%   | 19%   | 12%   | 12%   | <b>17%</b>      |
| <b>Abcam</b>   | <b>ABCM</b> | 8%   | 14%  | 7%   | -3%  | 20%   | 18%   | 11%   | 11%   | <b>15%</b>      |
| <b>Immunoassay/ELISA RUO Instruments</b>                         |             |      |      |      |      |       |       |       |       |                 |
| <b>Quanterix</b>   | <b>QTRX</b> | 30%  | 65%  | 51%  | 21%  | 43%   | 24%   | 27%   | 13%   | <b>26%</b>      |
| <b>High-Plex Proteomics</b>                                      |             |      |      |      |      |       |       |       |       |                 |
| <b>Olink Holding AB</b>  | <b>OLK</b>  | N/A  | N/A  | 36%  | 17%  | 71%   | 59%   | 52%   | 42%   | <b>56%</b>      |
| <b>SomaLogic</b>   | <b>SLGC</b> | N/A  | N/A  | N/A  | 25%  | 50%   | 33%   | 50%   | 43%   | <b>44%</b>      |
| <b>Mass Spectrometry (LC-MS)</b>                                 |             |      |      |      |      |       |       |       |       |                 |
| <b>Bruker timsTOF only</b>                                       | <b>BRKR</b> | N/A  | 100% | 100% | 38%  | 36%   | 39%   | 21%   | 11%   | <b>26%</b>      |
| <b>Average 2020-2024E CAGR</b>                                   |             |      |      |      |      |       |       |       |       | <b>31%</b>      |

## Proteomics: The Next Frontier; \$75B Market in the Making

- **Next decade in proteomics** - poised to be significantly different vs the last two:
  - Proteomics found its footing after the completion of the human genome project in 2003, and though the last two decades have seen significant growth in mass spec (LC-MS) and immunoassay technologies, a full human proteome still remains elusive.
  - We expect the next decade to bring **increasingly more innovation and technologies** to yield insights into the human proteome, driving increasing accessibility, faster turn-around times, higher reproducibility, and a broadening application base for developing therapies and diagnostics.
  - Proteomics has historically lagged behind genomics as evident by the publications in genomics vs proteomics. We see fundamental innovations including high-plex proteomics, technologies for large scale PTMs detections and reverse transcribing technologies or technologies that translate proteomics information into DNA to scale and multiplex as the most meaningful drivers of growth over the next decade.



# The Winning Formula: Key Drivers of Market Expansion in Proteomics

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We see the following as key drivers of success for fast growing proteomics technologies:

- **#1 Accessibility:**

- Large number of labs (both in pharma and academia) are interested in proteomics data and insights but find LC-MS still not directly accessible given significant capital equipment costs (mass specs and LCs) and the expertise required to operate, leading to high dependability on collaborators and core labs. Technologies that improve accessibility of proteomics into broader labs are bound to see growth.

- **#2 Reproducibility:**

- There is a strong need for reproducibility in proteomics experiments given the challenges faced with LC-MS technologies over the last two decades. Non-proteomics and proteomics researchers alike need experiments that can be repeated in any lab if the technologies are to scale and deliver on their promise. Reproducibility is also desired from antibody suppliers as more monoclonal vs polyclonals increase.

- **#3 Faster Turn-around times (TAT):**

- Faster turn-around of projects and experiments is highly valued vs legacy proteomics approaches and LC-MS projects that take weeks to months; essential for driving discovery to drug leads sooner and yielding high-quality publications and grants in academia. We see both non-MS (OLK, SLGC) and mass spec technologies (BRKR tims TOF) delivering faster turn around times. **Faster TAT are a key for diagnostics.**

- **#4 Price is not an objective if you can deliver value:**

- Labs and investigators are willing to spend for high-value experiments, suggesting cost is of limited concern if research is delivering value. Leading systems labs and non-proteomics core labs are already spending \$1M - \$2M (\$300-\$600/sample) annually on consumables (OLK and SLGC) matching the spending for mid-to-high volume ILMN customers today. We see this trend increasing to broader labs and cores as the awareness of these differentiated products grow.

## Proteomics: Our Experience, Background and Insights

- We believe our background and experience in the proteomics market should provide us with a clear line of sight to technologies, applications and themes that are poised to drive the market. These insights aid our investment thesis on proteomics, and we believe this should act as an excellent resource for investors seeking to understand the outlook of Proteomics over the next decade.

### Puneet Souda - Proteomics Background and Experience

- **Extensive background in proteomics**
- **Co-authored 45 scientific publications, with most in proteomics**
- Collaborated with academic investigators and biopharma companies
- Customer and collaborator of many Life Science Tools companies serving the broader proteomics, genomics and molecular analysis markets

### Puneet Souda - Select Peer-reviewed Scientific Publications in Proteomics

|   |   |
|---|---|
| mzML – a community std for mass spectrometry data   | Molecular and Cellular Proteomics, 2011 |
| Profiling of integral membrane proteins and their post translational modifications using high-resolution mass spectrometry  | Methods, 2011                           |
| A novel EF-hand protein, CRACR2A, is a cytosolic Ca <sup>2+</sup> sensor that stabilizes CRAC channels in T cells   | Nature Cell Biology, 2010               |
| Post-translational modifications of integral membrane proteins resolved by top-down Fourier transform mass spectrometry with collisionally activated dissociation | Molecular and Cellular Proteomics, 2010 |
| Minimum information about a proteomics experiment (MIAPE)   | Nature Biotechnology, 2007              |
| Top-down mass spectrometry of integral membrane proteins  | Expert Reviews in Proteomics, 2006      |

## Proteomics: Investable

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- **Proteomics is an investable theme and space for both public and private investors:**
  - A number of publicly traded companies including pure-play (high growth) proteomics, small to mid-cap and profitable mid to large caps with sizable exposure to proteomics exist today.
  - Pure-play: OLK, SLGC, QSI [Not Rated], NAUT [Not Rated], SEER [Not Rated] with meaningful proteomics exposures including TECH, ABCM, QTRX, BRKR, TMO.
- **Further technology innovations**
  - Technologies needed to fully realize the potential of PTMs and protein sequencing are yet to arrive on the market: Expect new market entrants; new company creation in proteomics ongoing currently in venture and early-stage private markets.
- **A Multi-omics world is emerging:**
  - We expect genomics to augment proteomics, additions of more “omics” from transcriptomics to metabolomics to yield biological insights not available before. Tools that enable such insights are poised to see strong growth.
- In the following slides, we review the various proteomics sub-markets and applications that are driving growth.



## Proteomics Is Investable: From Pure Play to Profitable

- **Core Antibodies companies - Least risky way to participate in proteomics:** Smid to large cap companies could be considered the most conservative way to gain exposure to proteomics. With strong growth in biopharma/academic end markets, best-in-class gross margins, strong operating and profitability outlook, we view these companies as the least risky way to participate in proteomics. Important to note that as the proteomics ecosystem grows, the need for validation via antibodies will only grow higher.
- We see **3 investable names in core RUO antibody providers:** Bio-Techne (TECH), Abcam (ABCM) and Thermo Fisher (TMO). We prefer TECH and ABCM given the exposure to proteomics.
- **TECH:** Bio-Techne is the global leader in proteins with its >425k antibodies, cytokine, and reagents. The company has 76% exposure to proteomics.
- **ABCM:** We view Abcam's in-house catalogue of 26k antibodies as having unmatched quality and data validation. ABCM has a large exposure to proteins and proteomics given its leading position in RUO antibodies.
- **TMO:** TMO has a strong global position in antibody production through their Invitrogen/LIFE businesses, though the overall proteomics exposure of TMO is limited given its diversity of revenue base.

| Name   | Ticker      | Rating    | YTD Return | 2020-2023E CAGR | Mkt Cap (\$M) | EV (\$M)  | Price 9/27/21 | PT           | Metric    | 2021E Cons | 2022E Cons | 2023E Cons |
|--|-------------|-----------|------------|-----------------|---------------|-----------|---------------|--------------|-----------|------------|------------|------------|
| <b>Core Antibodies (RUO and Translational)</b> |             |           |            |                 |               |           |               |              |           |            |            |            |
| <b>Bio-Techne</b>                              | <b>TECH</b> | <b>OP</b> |            |                 | \$22,570      | \$22,688  | \$511         | <b>\$575</b> | EV/Sales  | 24x        | 21x        | 18x        |
|  |             |           | 61%        | 14%             |               |           |               |              | EV/EBITDA | 62x        | 53x        | 46x        |
|  |             |           |            |                 |               |           |               |              | P/E       | 76x        | 66x        | 57x        |
| <b>Abcam</b>                                   | <b>ABCM</b> | <b>OP</b> |            |                 | \$4,743       | \$4,439   | \$21          | <b>\$25</b>  | EV/Sales  | 11x        | 9x         | 8x         |
|  |             |           | -4%        | 21%             |               |           |               |              | EV/EBITDA | 46x        | 29x        | 23x        |
|  |             |           |            |                 |               |           |               |              | P/E       | 111x       | 55x        | 42x        |
| <b>Thermo Fisher (Invitrogen/LIFE)</b>         | <b>TMO</b>  | <b>OP</b> |            |                 | \$242,680     | \$254,780 | \$595         | <b>\$675</b> | EV/Sales  | 7x         | 7x         | 6x         |
|  |             |           | 28%        |                 |               |           |               |              | EV/EBITDA | 22x        | 24x        | 22x        |
|  |             |           |            |                 |               |           |               |              | P/E       | 27x        | 29x        | 26x        |
| <b>Perkin-Elmer (BioLegend)</b>                | <b>PKI</b>  | <b>NC</b> |            |                 | \$20,679      | \$22,721  | \$177         |              | EV/Sales  | 5x         | 6x         | 5x         |
|  |             |           | 23%        |                 |               |           |               | EV/EBITDA    | 15x       | 22x        | 20x        |            |
|  |             |           |            |                 |               |           |               | P/E          | 18x       | 28x        | 26x        |            |

Source: SVB Leerink Research

## Proteomics Is Investable: From Pure Play to Profitable

- **High-plex proteomics technologies** to have the most meaningful impact in the next 5 years, in our view, as they drive democratization, increase accessibility, deliver faster turn-around times, higher reproducibility, and broaden the application base.
- We see **3 investable names in high-plex proteomics**: Olink (OLK), Somalogic (SLGC) and Illumina (ILMN). We prefer OLK within our coverage universe given its growth profile, product segmentation and growing adoption of its kits vs service.
- **OLK**: Product segmentation across both Target and Explore panels is the key differentiator for OLK. Recently expanding to a 3k panel, we expect 4.5k panel next and high-plex proteomics to deliver nearly 10k proteins with KOLs estimating that blood plasma has 10k -15k proteins.
- **SLGC**: Ultra-high-plex capabilities with its aptamer-based approach differentiates Somalogic. Its SomaScan assay can detect 7k protein analytes today.
- **ILMN**: Provides the backbone for OLK, as OLK's PEA assay for the larger Explore kits are read using ILMN instruments. ILMN invested in SLGC, and we believe SLGC holds potential to transition microarrays to ILMN instruments in the longer term to drive scale.

| Name                        | Ticker      | Rating    | YTD Return | 2020-2023E CAGR | Mkt Cap (\$M) | EV (\$M) | Price 9/27/21 | PT           | Metric    | 2021E Cons | 2022E Cons | 2023E Cons |
|-----------------------------|-------------|-----------|------------|-----------------|---------------|----------|---------------|--------------|-----------|------------|------------|------------|
| <b>High-Plex Proteomics</b> |             |           |            |                 |               |          |               |              |           |            |            |            |
| <b>Olink Holding AB</b>     | <b>OLK</b>  | <b>OP</b> |            |                 | \$2,935       | \$2,779  | \$24          | <b>\$50</b>  | EV/Sales  | 30x        | 19x        | 13x        |
|                             |             |           | -34%       | 41%             |               |          |               |              | EV/EBITDA | -          | 517x       | 79x        |
|                             |             |           |            |                 |               |          |               |              | P/E       | -          | -          | 328x       |
| <b>SomaLogic</b>            | <b>SLGC</b> | <b>NC</b> |            |                 | \$2,327       | \$428    | \$12          |              | EV/Sales  | -          | -          | -          |
|                             |             |           | -10%       | 35%             |               |          |               | EV/EBITDA    | -         | -          | -          |            |
|                             |             |           |            |                 |               |          |               | P/E          | -         | -          | -          |            |
| <b>Illumina</b>             | <b>ILMN</b> | <b>MP</b> |            |                 | \$65,197      | \$61,955 | \$426         | <b>\$425</b> | EV/Sales  | 14x        | 13x        | 11x        |
|                             |             |           | 15%        |                 |               |          |               |              | EV/EBITDA | 45x        | 41x        | 35x        |
|                             |             |           |            |                 |               |          |               |              | P/E       | 66x        | 72x        | 61x        |

Source: SVB Leerink Research

## Proteomics Is Investable: From Pure Play to Profitable

- **Mass Spectrometry (LC-MS)** Mass spectrometry (LC-MS) is widely regarded as the “gold standard” in proteomics for protein and peptide analysis.
- We see 6 **investable names in Mass Spectrometry (LC-MS)**: Bruker (BRKR), Thermo Fisher (TMO), Agilent (A, OP), Waters (WAT, MP), Danaher (DHR, Not Rated), and 908 Devices (MASS, OP) with varying degree of exposures to proteomics. **We prefer BRKR** among these names given its innovative timsTOF platform.
- **BRKR**: BRKR’s timsTOF is an innovative mass spec launched in 2017 and upgraded in 2021 that offers differentiated speed of analysis (50-200 samples per day and > 100 Hz speed) and is the first MS system to meaningfully challenge TMO’s Orbitrap’s position in proteomics applications.
- **TMO: Instrumentation**: TMO offers a wide range of mass spec and chromatography systems including Triple Quad MS, single quads, UHPLCs, GCs and sample prep solutions. The Orbitrap suite of instruments is regarded as market leader in mass spec due to historically unmatched performance characteristics.

| Name                             | Ticker      | Rating    | YTD Return | 2020-2023E CAGR | Mkt Cap (\$M) | EV (\$M)  | Price 9/27/21 | PT           | Metric                       | 2021E Cons       | 2022E Cons       | 2023E Cons       |
|----------------------------------|-------------|-----------|------------|-----------------|---------------|-----------|---------------|--------------|------------------------------|------------------|------------------|------------------|
| <b>Mass Spectrometry (LC-MS)</b> |             |           |            |                 |               |           |               |              |                              |                  |                  |                  |
| <b>Bruker Corporation</b>        | <b>BRKR</b> | <b>OP</b> | 47%        | TimsTOF<br>23%  | \$12,940      | \$13,202  | \$80          | <b>\$100</b> | EV/Sales<br>EV/EBITDA<br>P/E | 6x<br>27x<br>41x | 5x<br>24x<br>36x | 5x<br>22x<br>31x |
| <b>Thermo Fisher Scientific</b>  | <b>TMO</b>  | <b>OP</b> | 28%        |                 | \$242,680     | \$254,780 | \$595         | <b>\$675</b> | EV/Sales<br>EV/EBITDA<br>P/E | 7x<br>22x<br>27x | 7x<br>24x<br>29x | 6x<br>22x<br>26x |
| <b>Agilent</b>                   | <b>A</b>    | <b>OP</b> | 40%        |                 | \$52,793      | \$54,443  | \$166         | <b>\$170</b> | EV/Sales<br>EV/EBITDA<br>P/E | 9x<br>31x<br>39x | 8x<br>28x<br>35x | 8x<br>26x<br>31x |
| <b>Waters</b>                    | <b>WAT</b>  | <b>MP</b> | 54%        |                 | \$24,444      | \$25,410  | \$381         | <b>\$385</b> | EV/Sales<br>EV/EBITDA<br>P/E | 9x<br>27x<br>36x | 9x<br>26x<br>33x | 8x<br>24x<br>30x |
| <b>Danaher</b>                   | <b>DHR</b>  | <b>NC</b> | 42%        |                 | \$242,680     | \$257,210 | \$316         |              | EV/Sales<br>EV/EBITDA<br>P/E | 9x<br>26x<br>33x | 8x<br>25x<br>32x | 8x<br>25x<br>31x |
| <b>908 Devices</b>               | <b>MASS</b> | <b>OP</b> | -41%       | 25%             | \$1,119       | \$992     | \$33          | <b>\$65</b>  | EV/Sales<br>EV/EBITDA<br>P/E | 24x<br>-         | 19x<br>-         | 15x<br>-         |

Source: SVB Leerink Research

## Proteomics Is Investable: From Pure Play to Profitable

- **Emerging proteomics technologies** are still in early innings and have to “prove themselves” before broader appreciation and adoption of the technologies. Key indicator should be published data (posters or papers) for these companies as the data could make emerging instruments more appealing (or less appealing) to early adopters and customers.
- **Emerging proteomics**, in our view, should democratize access to the proteome and transform research, identification, and development of new therapeutics.
- We see **3 investable names in emerging proteomics technologies**: Nautilus (NAUT), Quantum-Si (QSI) and Seer (SEER). With limited data on these platforms, it is challenging to assess the long-term success just yet, but we believe that emerging data and new customer will be most insightful.
- **NAUT**: Nautilus is working towards a large-scale, single-molecule platform that can achieve quantification of >95% of the proteome while also identifying PTMs globally in an experiment.
- **QSI**: The company plans to launch their Carbon, Platinum, and QSI Cloud powered by their proprietary single-molecule detection semi-conductor.
- **SEER**: The company’s product suite includes a sample prep instrument and reagents designed to reduce the complexity of samples upfront prior to LC-MS.

| Name                                    | Ticker      | Rating    | YTD Return | 2020-2023E CAGR | Mkt Cap (\$M) | EV (\$M) | Price 9/27/21 | PT | Metric    | 2021E Cons | 2022E Cons | 2023E Cons |
|---|-------------|-----------|------------|-----------------|---------------|----------|---------------|----|-----------|------------|------------|------------|
| <b>Emerging Proteomics Technologies</b> |             |           |            |                 |               |          |               |    |           |            |            |            |
| <b>Nautilus Biotechnology</b>           | <b>NAUT</b> | <b>NC</b> | -65%       |                 | \$842         | \$469    | \$7           |    | EV/Sales  | -          | 120x       | 30x        |
|   |             |           |            |                 |               |          |               |    | EV/EBITDA | -          | -          | -          |
|   |             |           |            |                 |               |          |               |    | P/E       | -          | -          | -          |
| <b>Quantum-Si</b>                       | <b>QSI</b>  | <b>NC</b> | -10%       |                 | \$1,278       | \$756    | \$9           |    | EV/Sales  | -          | -          | -          |
|   |             |           |            |                 |               |          |               |    | EV/EBITDA | -          | -          | -          |
|   |             |           |            |                 |               |          |               |    | P/E       | -          | -          | -          |
| <b>Seer</b>                             | <b>SEER</b> | <b>NC</b> | -35%       |                 | \$2,489       | \$1,971  | \$37          |    | EV/Sales  | 432x       | 134x       | 59x        |
|   |             |           |            |                 |               |          |               |    | EV/EBITDA | -          | -          | -          |
|   |             |           |            |                 |               |          |               |    | P/E       | -          | -          | -          |

Source: SVB Leerink Research

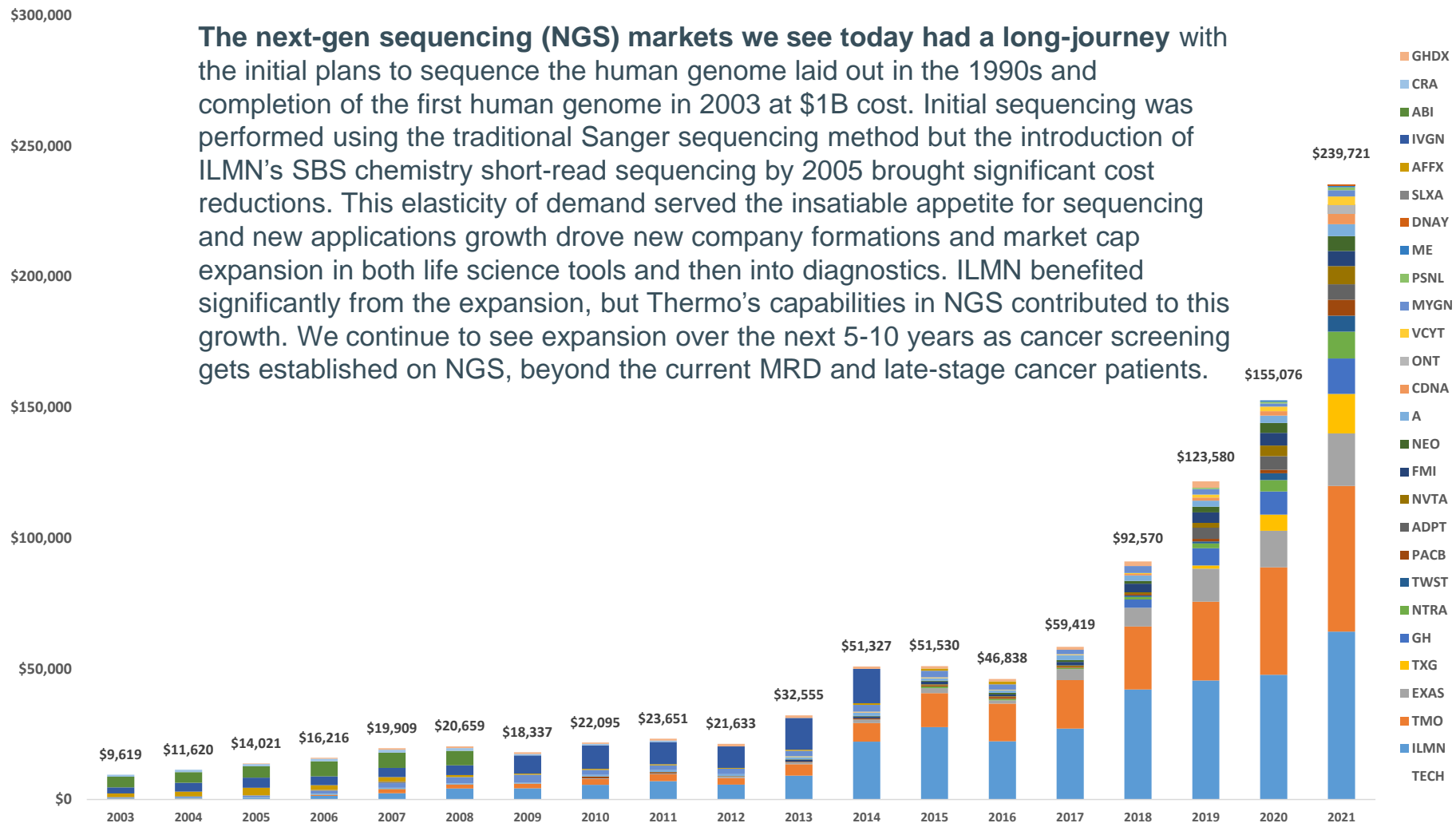
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# Background

# NGS Drove Significant Market Cap Expansion Across The Sector

- Market cap for genomics companies has expanded from nearly \$10B in 2003 to \$240B in 2021

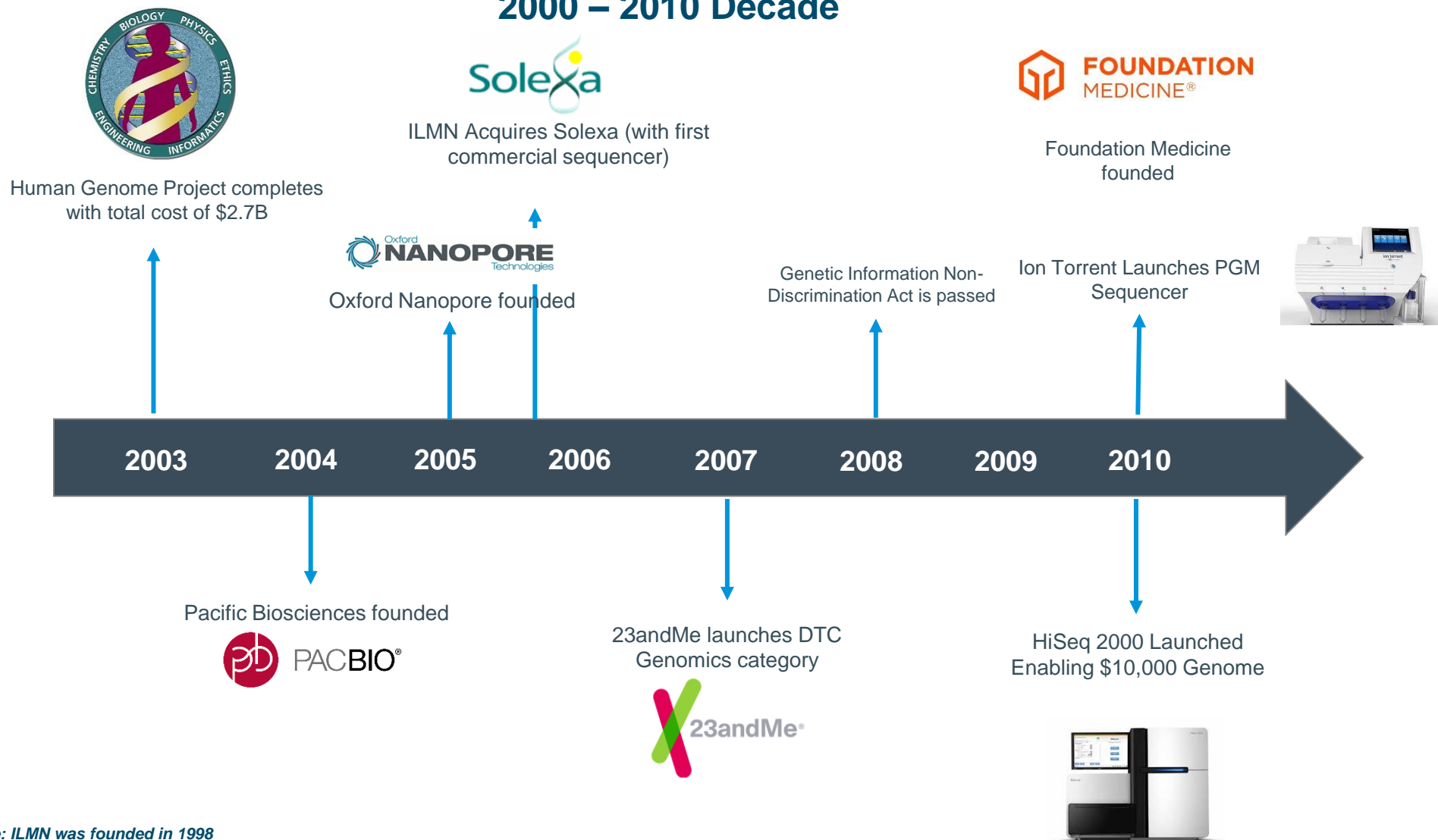
Genomics Market Expansion in Research and Diagnostics (2003 - 2021)



# Looking to History to Understand the Future

- Next-Gen Sequencing (NGS) market we see today had a long journey

## 2000 – 2010 Decade

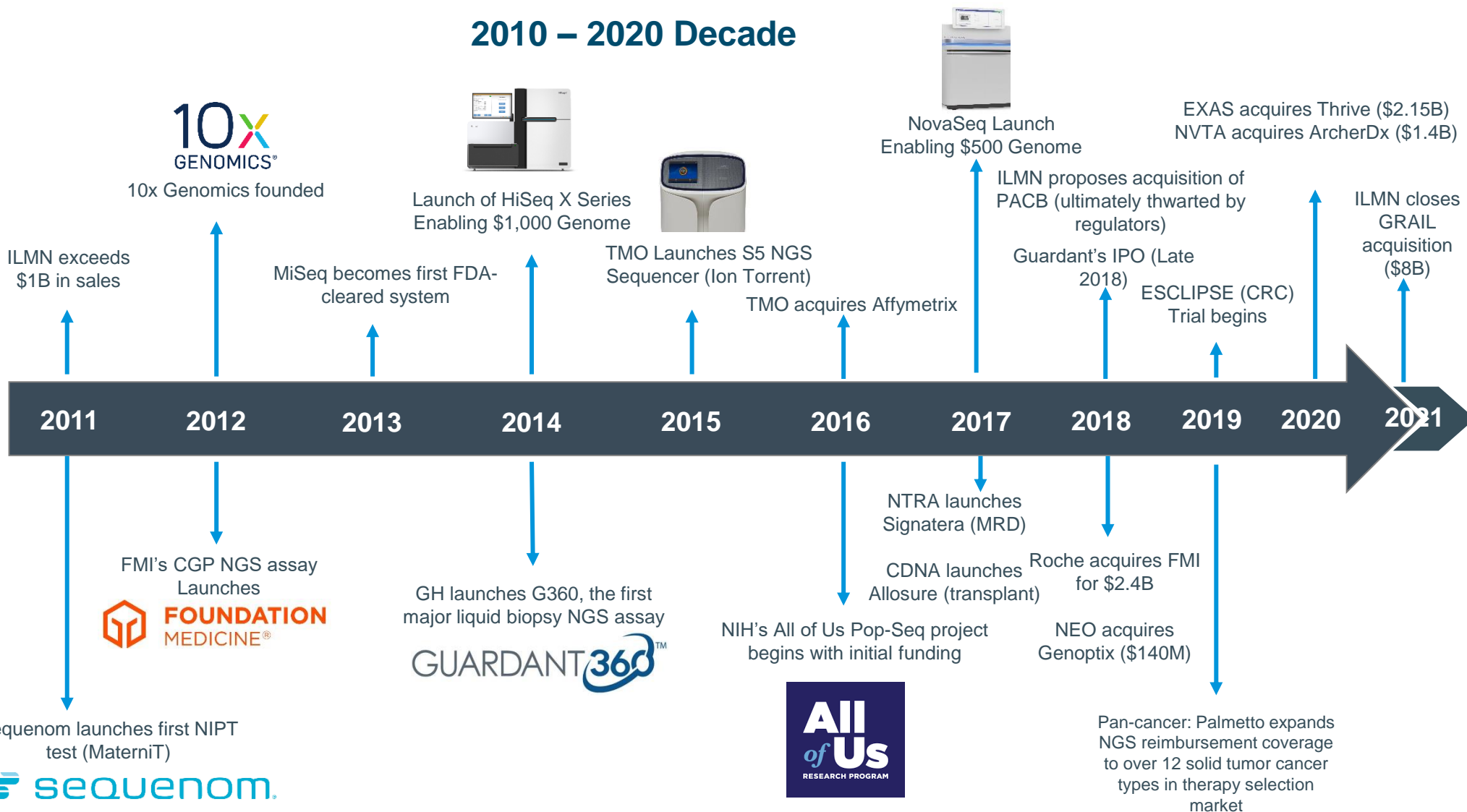


Note: ILMN was founded in 1998

Source: Company Filings, Journals, SVB Leerink Research

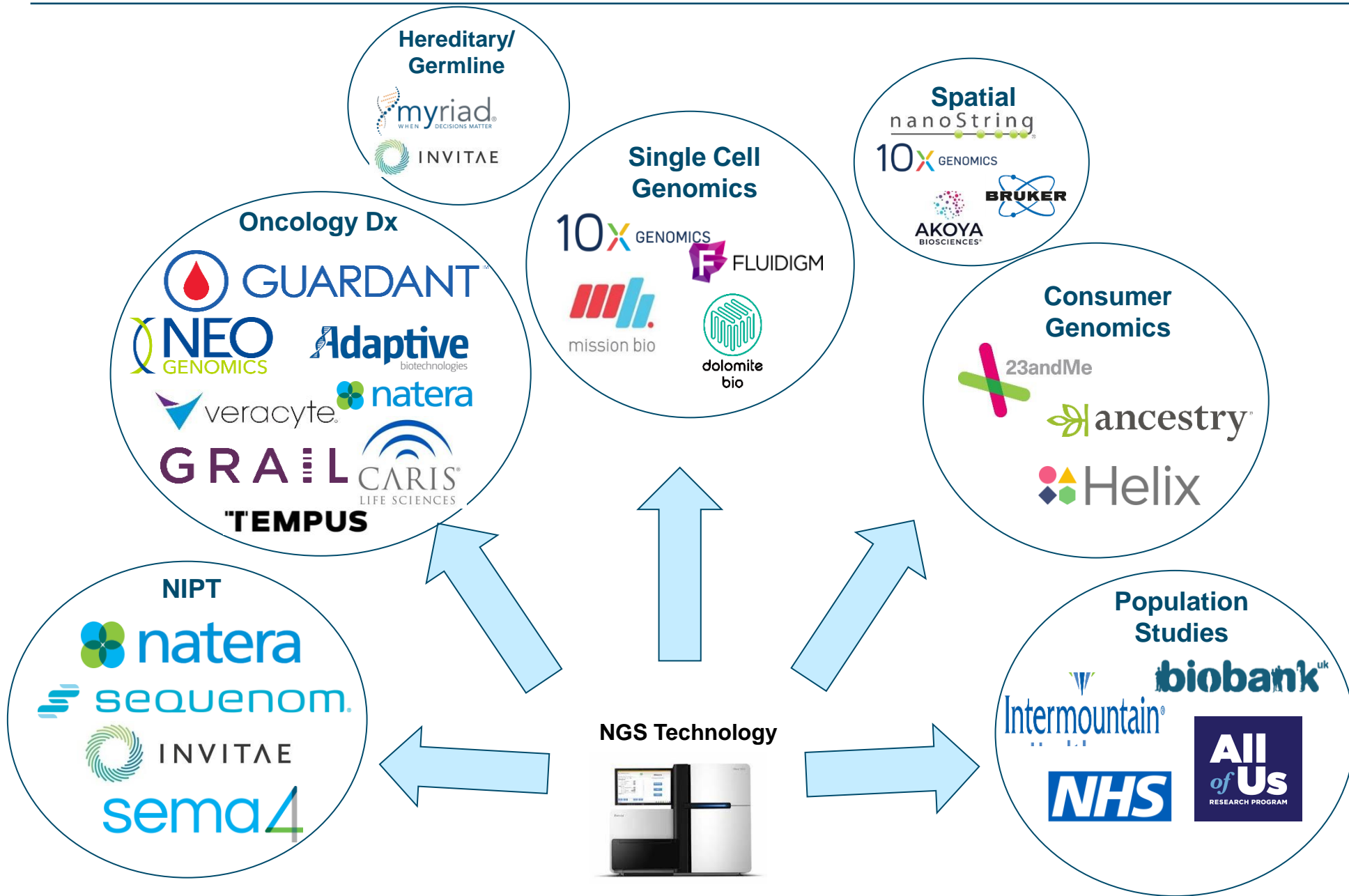
# The Next-Gen Sequencing (NGS) Market Had a Long Journey

## 2010 – 2020 Decade





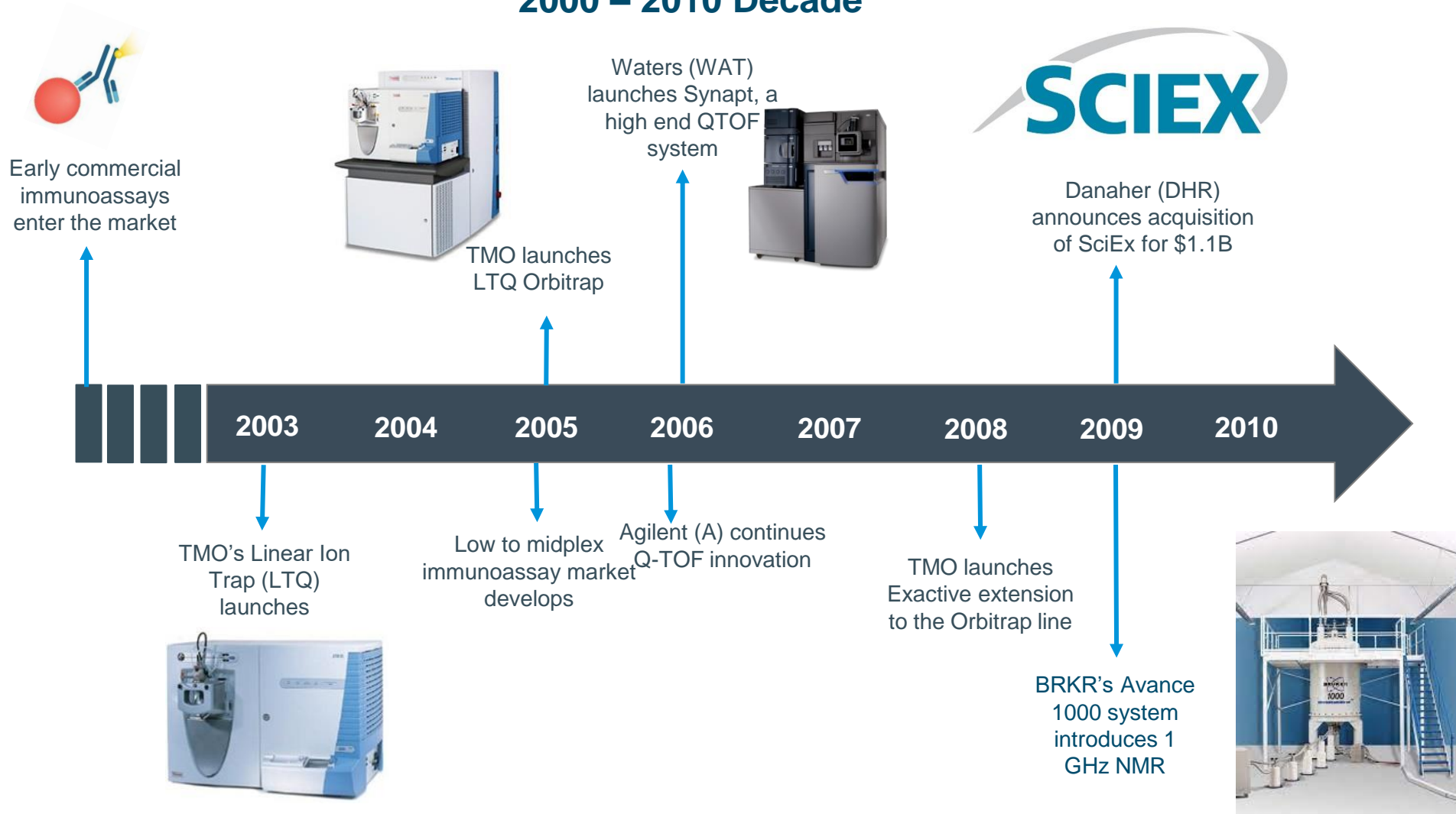
# The Impact of NGS



# Proteins: The Next Stop on the Personalized Medicine Journey

- **The proteomics journey** – not as eventful or rapid as genomics; mostly driven by mass spec and immunoassays but the complexity of proteomics was underappreciated

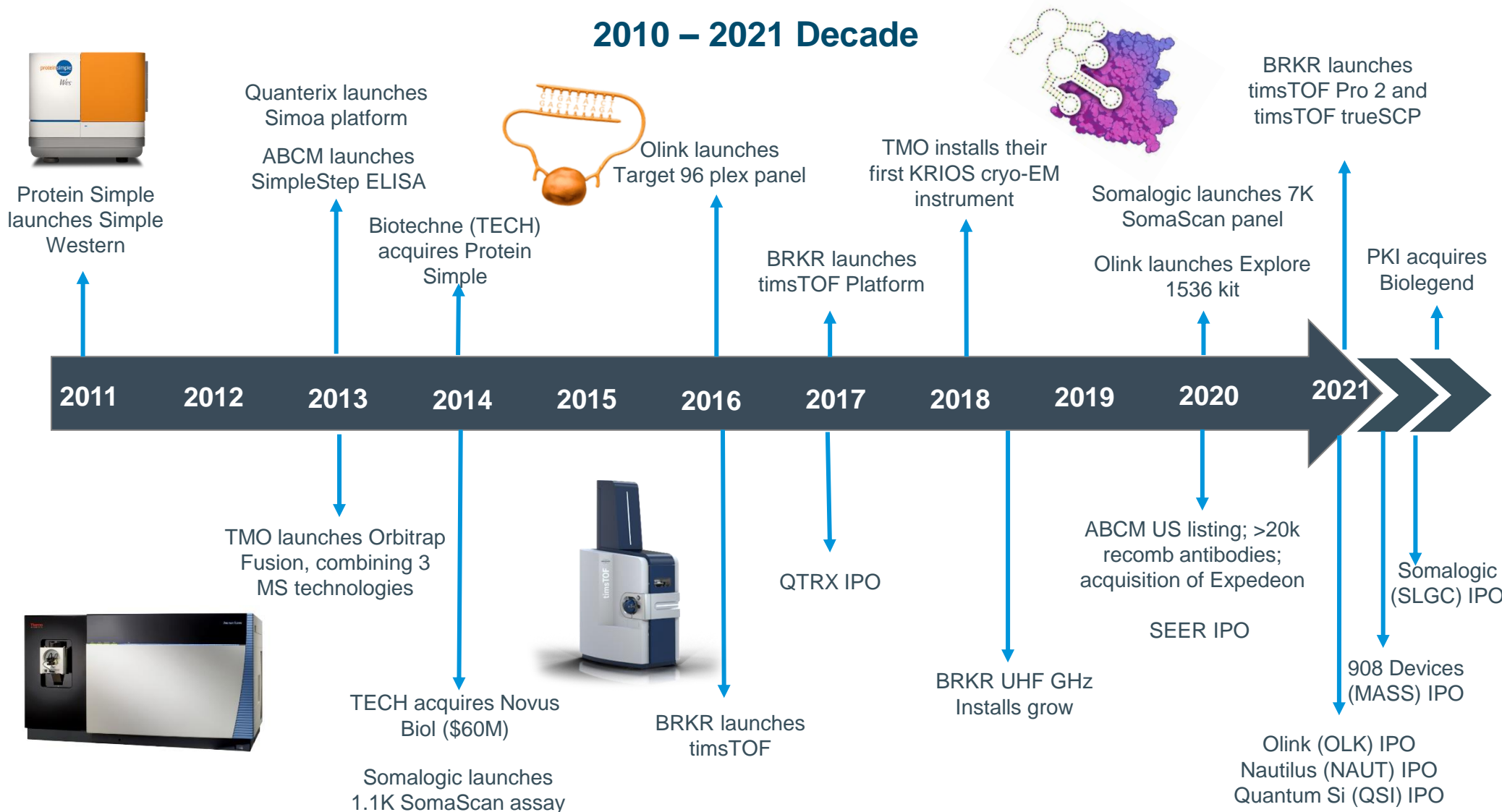
## 2000 – 2010 Decade



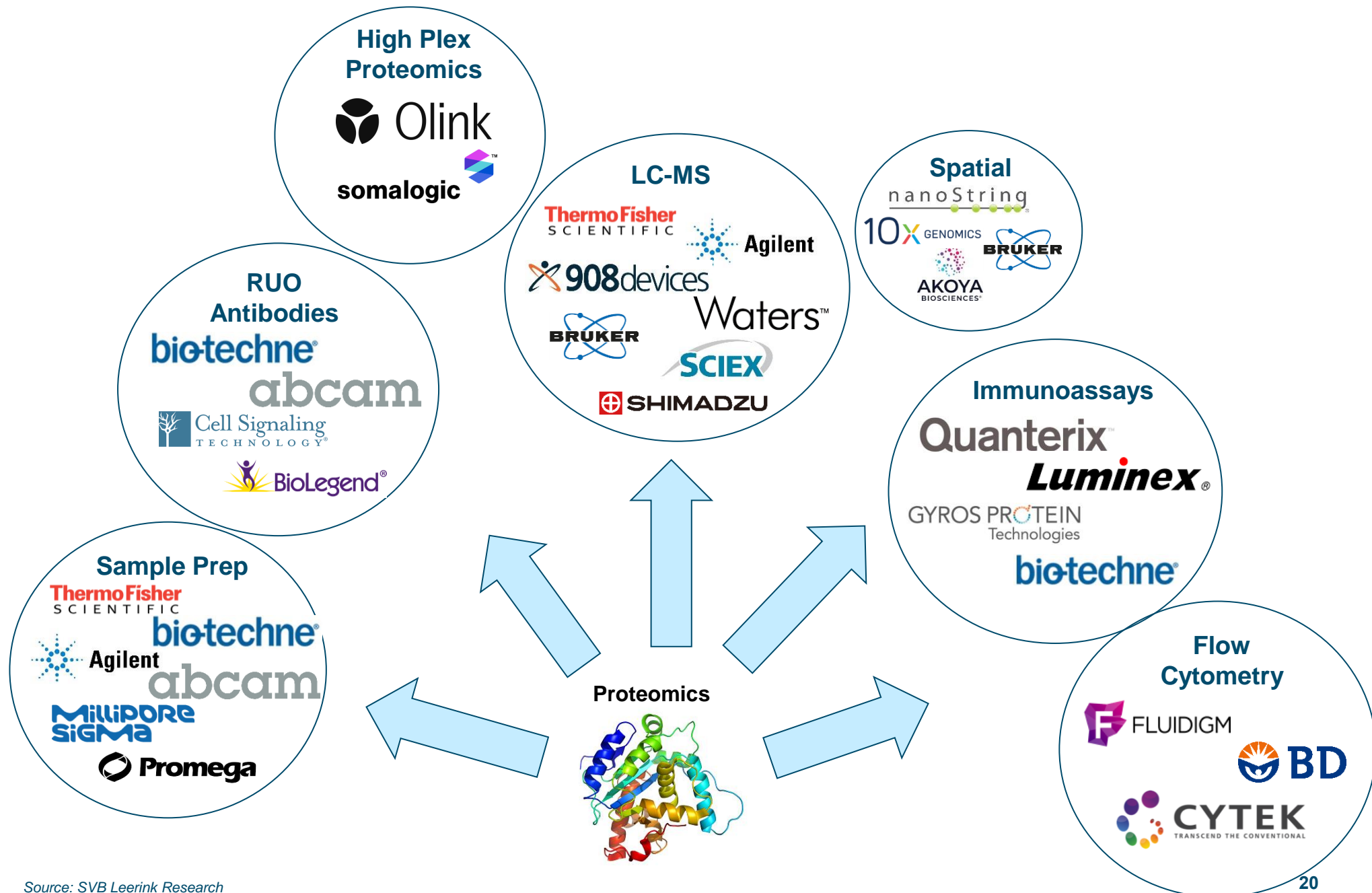
Source: Company Filings, Journals, SVB Leerink Research

# Proteins: The Next Stop on the Personalized Medicine Journey

## 2010 – 2021 Decade



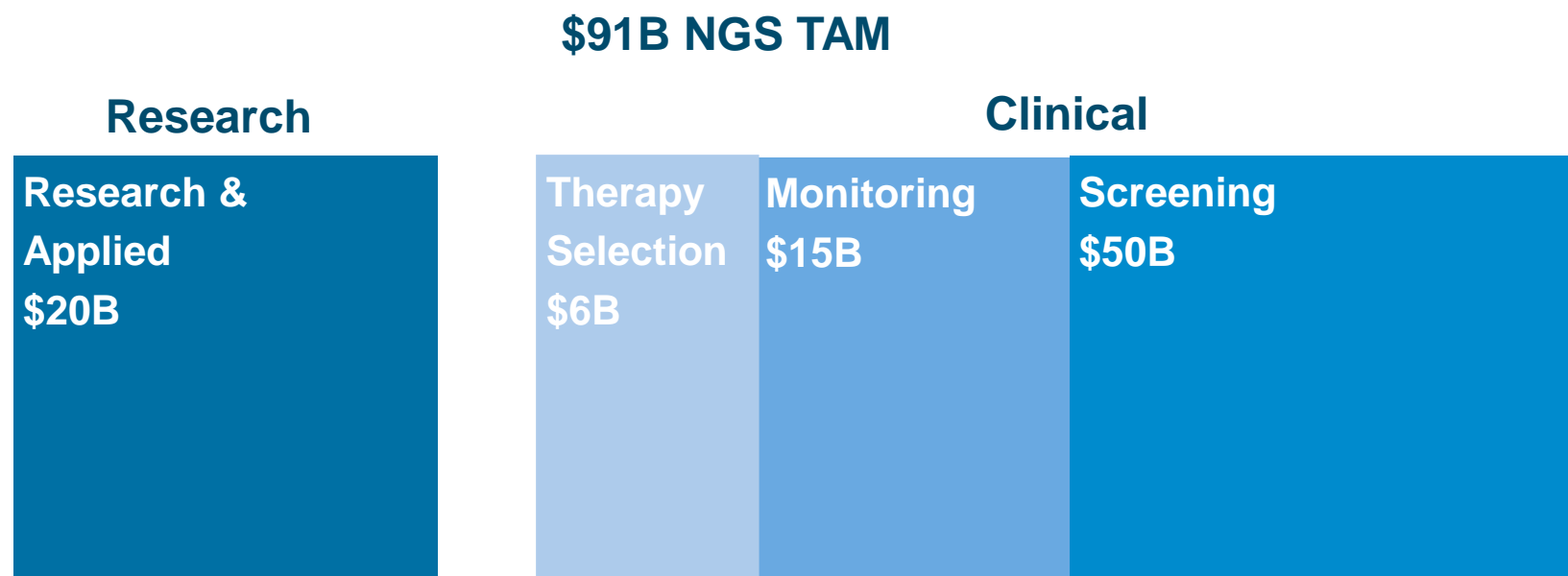
# The Diversified Exposure of Proteomics



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# Proteomics: A Massive Market Beyond Genomics

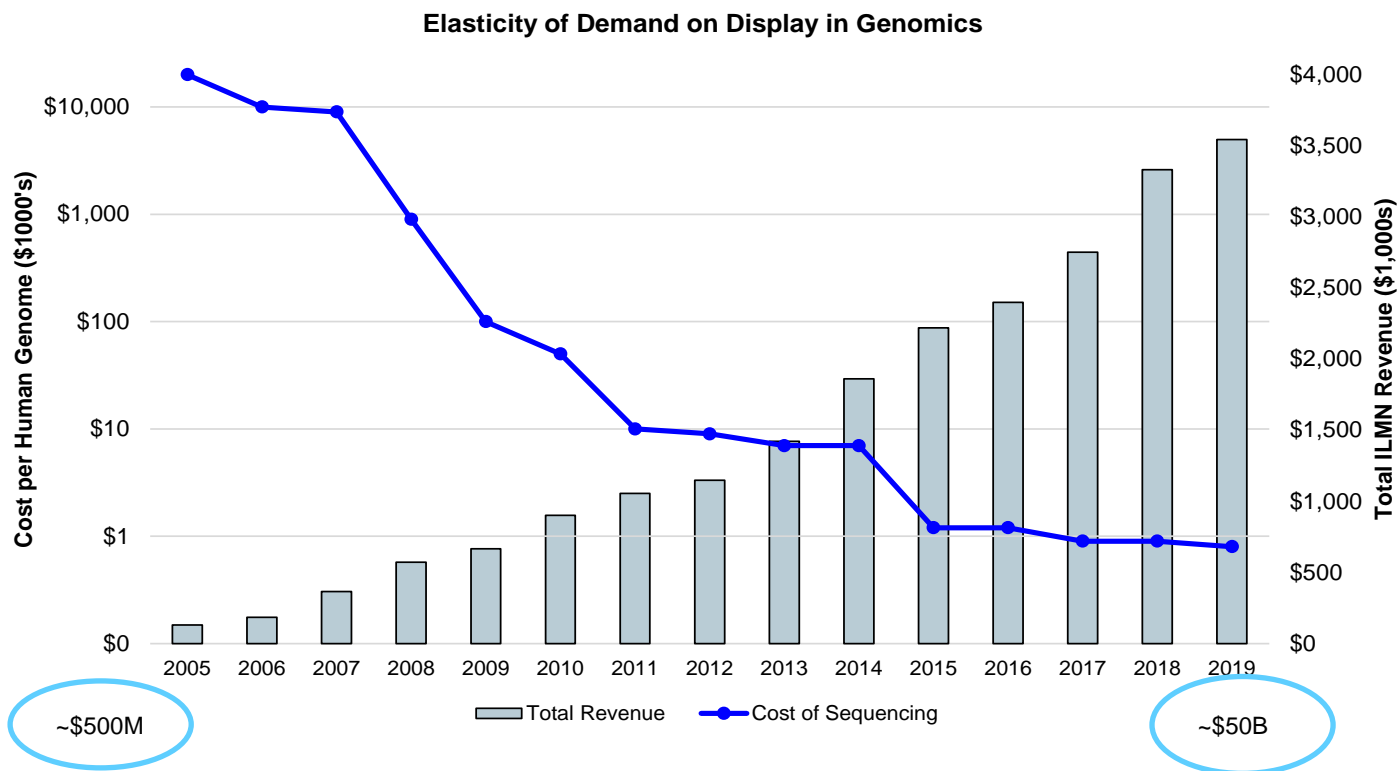
## NGS Market: Proven, with More to Come



- **To understand the market in proteomics, one has to look at the NGS market first.** NGS is already delivering on a ~\$90B TAM having started with early adoption in research applications (gene expression, WGS, Exomes) to now well-established markets in CGP (Comprehensive Genomic Profiling) for oncology patients using both tissue and liquid and is rapidly expanding to MRD and recurrence monitoring, with a clear line of sight to CRC screening and multi-cancer screening.
- With **CGP markets already penetrated nearly 35% - 40%**, further growth in genomics market is predicated on expansion into oncology diagnostics. Immediate opportunity for growth is in MRD or recurrence monitoring (a \$15B+ market with NTRA and GH in the lead), while screening with CRC (GH, EXAS, Freenome [Not Rated]) and ultimately multicancer screening (EXAS/Thrive; ILMN/GRAIL) is expected to drive the expansion into the \$50B screening market among healthy individuals.

# NGS Adoption Was Driven by Elasticity of Demand; Declining Costs Led to Market Expansion

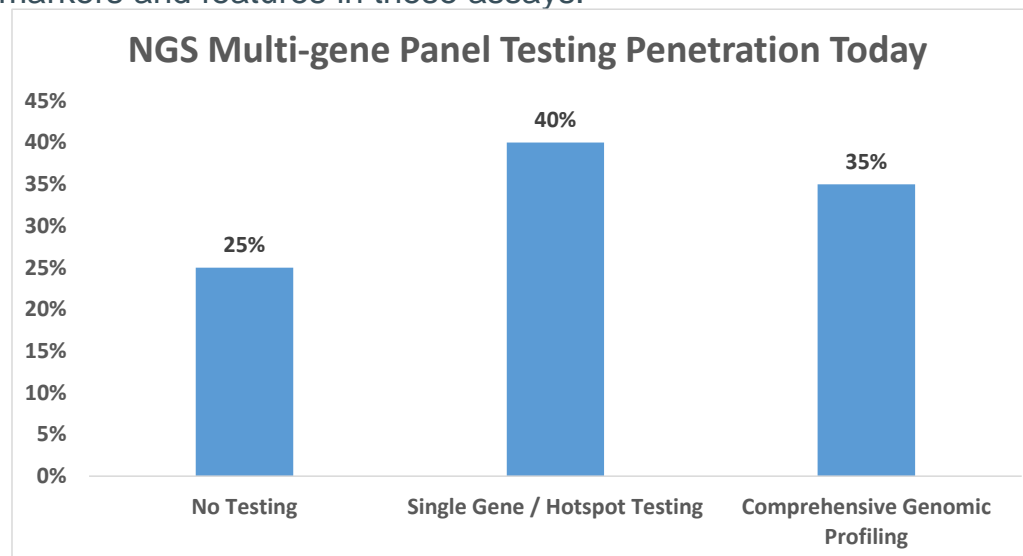
- **Elasticity of Demand:** Illumina, as the leading provider of sequencing instruments, drove elasticity of demand into the market by lowering of price of sequencing (\$/Gb), which, in turn, drove new applications that were not imagined before (Oncology Dx, NIPT, DTC and others). Volumes grew more than 2x as price of sequencing declined by half, driving ILMN's revenues higher. As a result, ILMN's market cap increased from **\$500M in 2005 to \$50B in 2019**.
- We see **NGS continuing to remain relevant to proteomics** for technologies where information is translated into DNA and read out via NGS. Multiple proteomics technologies, including Olink's PEA assay, utilize NGS to multiplex, scale and read-out proteomics data, and recall that ILMN has also invested into Somalogic. We believe ILMN's sequencers could remain relevant to proteomics in the longer term as more technologies including Encodia, Erisyon and others utilize NGS for detection.



Source: Company Filings, SVB Leerink Research

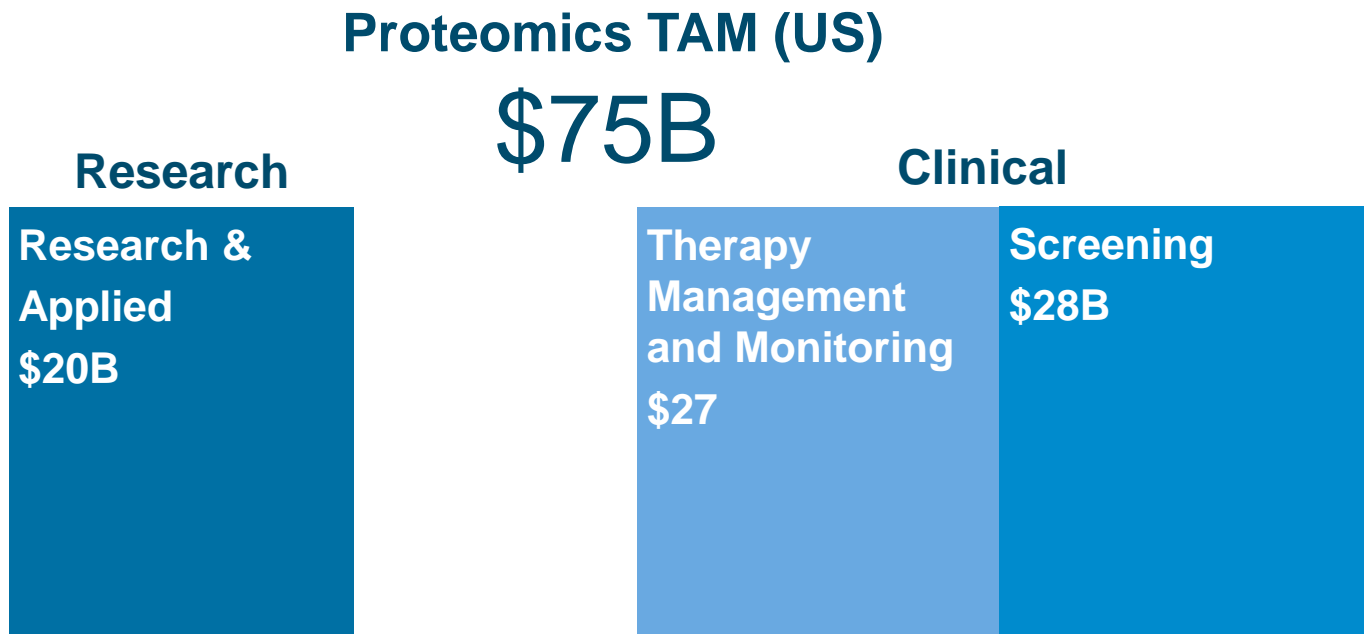
## The NGS Therapy Management Market Penetration

- **NGS Panels – emerging towards a standard of care:** Fast forwarding the growth of NGS from research to diagnostics, today, late-stage cancer patients are routinely being tested with multi-gene panels and comprehensive genomics profiling (CGP) tests to direct targeted therapies. The use of these tests is also increasing into earlier lines of therapies, thus expanding the market. As oncologists become increasingly comfortable with genetic testing (mostly in the community setting since academic is already penetrated), comprehensive genomic profiling (CGP) should see broader adoption in our view.
- **Further penetration for NGS and CGP is largely dependent on service levels, ease of ordering and more targeted therapies in earlier lines.** We spoke with a number of MEDACorp KOLs in both the community and the academic setting to identify drivers of further penetration from currently ~35% penetration in NGS. Most oncologists preferred one CGP test over the other with Roche(FMI) F1CDx being the mostly commonly cited in tissue and Guardant G360 mostly commonly in liquid biopsy. Based on the feedback, most oncologists expect volumes to continue to go higher annually with some projecting still 50% y/y growth at current levels. Preference for one test over the other was largely driven by duration of experience with a test, ease of electronic ordering, service levels from the Sales and the medical liaison team and ultimately the number of approved therapies for the growing number of markers and features in these assays.



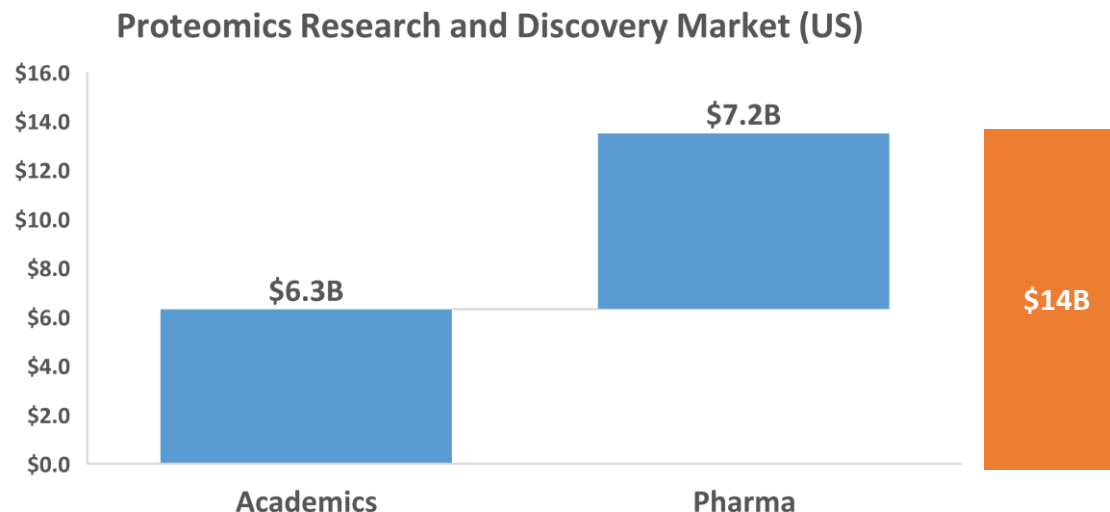


## Genomics Has Set the Stage for the Proteomics Market



- **The proteomics market is primed to expand beyond the limits of the genomics market in the coming years with a large number of diseases and indications beyond oncology.** Genomics has set the stage for adoption of personalized medicine with reimbursement being a key pillar that did not exist prior to the adoption of NGS assays. Proteins are still considered the best analytes by KOLs – providing the most real-time picture of the disease while providing more actionable insight than genes. We see significant potential for Proteomics Dx in diseases beyond oncology, though our ASP expectations are considerably lower vs genomics given a number of chronic diseases vs high ASPs for terminal cancer. We conducted a careful analysis for the current research labs in the US and the market for proteomics panels in therapy management, monitoring and screening diagnostics to arrive at our market estimates. Our proteomics market estimates are on the conservative side today, but we see potential for these markets to be even larger if ASPs or the indications and patient population turned out to be higher than what we are assuming in our models.

# Proteomics Research Opportunity in Biopharma and Academic Is Large



| US Academic and Applied Research Labs Proteomics Market |               |                  |              |
|---|---------------|------------------|--------------|
| Lab Type  | Count         | Spend (in \$M)   | TAM (in \$B) |
| Core Lab  | 1,500         | \$1.20           | \$1.8        |
| Individual Labs (PI led)                                | 15,000        | \$0.30           | \$4.5        |
| Pre-Clinical Pharma (Discovery)                         | 4,800         | \$0.5            | \$2.4        |
| Clinical Pharma (Developmental)                         | 4,800         | \$1.0            | \$4.8        |
| <b>Total Labs</b>                                       | <b>26,100</b> | <b>Total TAM</b> | <b>\$14</b>  |

- Lab count and spend:** We collected data on both core and individual PI (Principal Investigator) led labs. Our Core Lab count is based on ABRF members performing mass spec, genomics, and flow cytometry. We assume 10 individual labs per core lab based on a portion of the number of NIH awards per institute in 2020, though we recognize that core lab to PI led lab ratio could significantly vary depending on the institution. We collected total NIH funding for research in various chronic diseases by academic institutions and assumed an extremely conservative 2.5% of funding allocation to proteomics. We believe this is a conservative estimate given the broad use of RUO antibodies and associated reagents, mass spec proteomics and fast growing high-plex proteomics. We took an average proteomic spend for the top 150 academic institutes and estimated a spend of \$0.3M at peak for individual labs and \$1.2M spend per core lab.

\*Based on NIH funding for chronic diseases to get per lab spend. Number of labs based on NIH budget data and ABRF membership. US vs ex-US TAM split using R&D spend data from the OECD.  
Source: NIH funding, OECD, SVB Leerink Research

## Proteomics Dx: Precision Medicine Beyond Oncology

### \$55B Proteomics Dx TAM (US)

Therapy  
Management  
and Monitoring  
\$27B

Screening  
\$28B

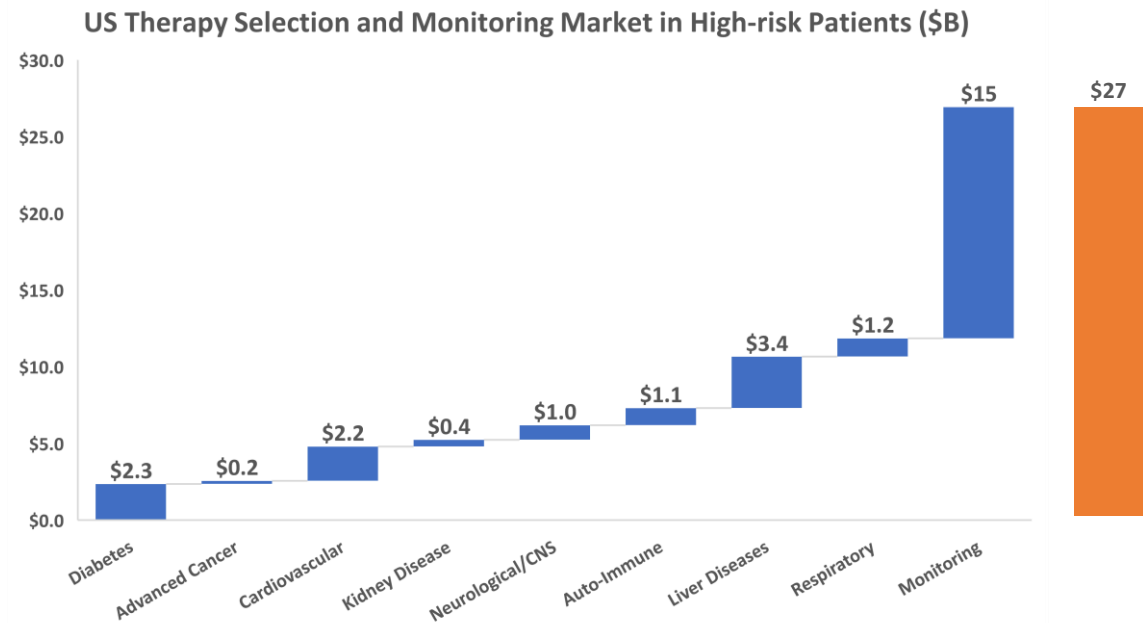
- **\$55B Proteomics Dx TAM:** We estimate the application of proteomics into diagnostics is likely to yield a market of \$55B with \$27B in therapy selection and monitoring being the most impactful. We see limited market in screening via proteomics assays given that a number of chronic disease have lower risk profile vs cancer and where some screening measures are already in place.
- **Conservative ASP:** We are assuming only a conservative \$300 ASP for such a therapy management test despite genomics assays routinely being paid above \$1,000. We remain optimistic that proteomics tests are likely to see upside with reimbursement, with strong clinical data being key in those evaluations. We expect that diagnostics companies utilizing genomic markers today would be the first ones to seek proteomics markers/panels to enhance their assays and drive clinical actionability.
- **Proteins remain the best analyte,** presenting the most real-time picture and more actionable insight than genes. Traditionally, building proteomics panels has been challenging given the significant groundwork and basic research (usually with LC-MS) required to build sophisticated multiplexed immunoassays. With the introduction of high-plex proteomics technologies, we believe the bar for building such assays is now lowered and further innovations and instruments not launched yet will only help cover the broader proteome.

\* Based on disease incidence for heart disease, diabetes, NAFLD, dementia, and kidney disease according to CDC and AHA

Source: NIH funding, OECD, AHA, CDC, SVB Leerink Research

# Proteomics Dx: Precision Medicine Beyond Oncology

Therapy  
Management  
and Monitoring  
\$27B

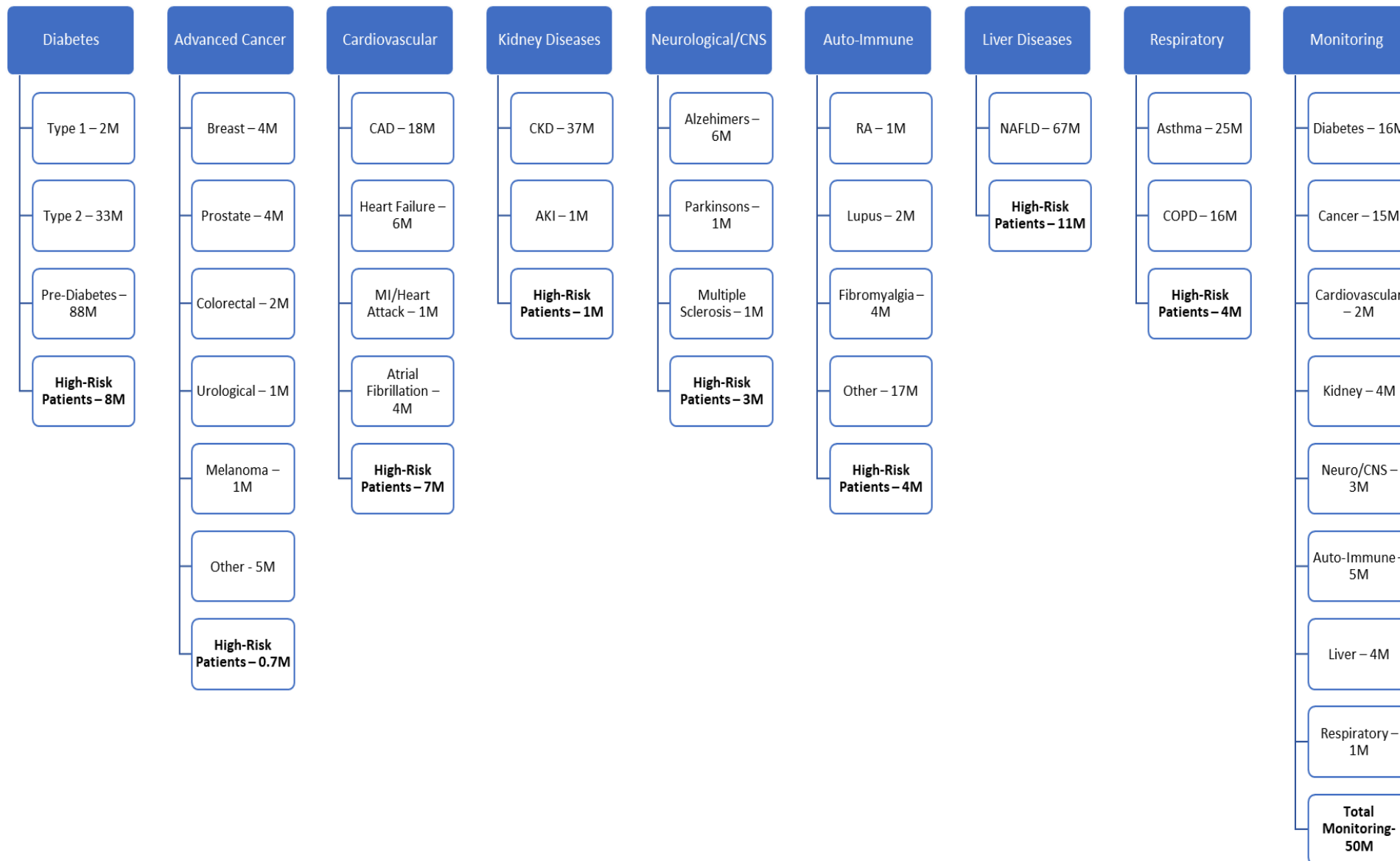


- Proteomics for therapy management and monitoring:** We see advanced proteomic tests/panels helping identify molecular drivers of disease and establish targeted therapy for indications beyond cancer where genomics might not be as actionable as it is in Oncology. Though no such high value assays exist on the market today, we see biopharma and drug developers pursuing these tests, much as they did with markers derived from CGP and are currently pursuing with MRD using liquid biopsy (ctDNA).
- For therapy management and monitoring market in proteomics, we are assuming **only the high-risk TAM and an ASP of \$300** (vs >\$1000 for NGS assays) given that majority of non-cancer indications are chronic diseases and not expected to be terminal. However, we expect CMS to closely look at the overall clinical evidence behind the assay before setting a Medicare price for the assay. Both CMS and MACs appreciate the growing role of personalized medicine, and we expect the LCDs for proteomics likely to be favorable.

\* Based on disease incidence for heart disease, diabetes, NAFLD, dementia, and kidney disease according to CDC and AHA and assuming test ASD of \$150 in US, \$15 in ex-US

Source: NIH funding, OECD, AHA, CDC, SVB Leerink Research

# Proteomics Dx: Therapy Management and Monitoring



\* Based on disease incidence for heart disease, diabetes, NAFLD, dementia, and kidney disease according to CDC and AHA

Source: NIH funding, OECD, AHA, CDC, SVB Leerink Research

# Proteomics Dx: Screening Holds Potential, but the Market Could Be Limited

Screening  
\$28B

| Proteomics Screening TAM Scenarios |                 |             |
|------------------------------------|-----------------|-------------|
| ASP                                | Eligible US Pop | TAM (\$B)   |
| \$200                              | 140             | <b>\$28</b> |
| \$300                              | 140             | \$42        |
| \$500                              | 140             | \$70        |
| \$700                              | 140             | \$98        |

- **Screening via proteomics holds promise but could be limited to diseases with no existing screening modalities:** We expect proteomics to enable standalone assays or multiomics assays that incorporate multiple proteins or peptides into existing genomics/NGS assays to enhance the performance (boosting sensitivity, specificity) by adding an orthogonal detection of proteins/peptides much in line with how methylation has emerged as a high quality marker for improving detection in early stage CRC and multi-cancer screening assays. Given that majority of the widespread and lifestyle driven diseases including cardiovascular, diabetes and hypertension associated disorders are chronic vs cancer that could be terminal, screening via proteomics assay could have limited applicability. A number of cardiovascular and diabetic screening factors including age, weight, cholesterol and tryglycerides and hemoglobin (HbA1C) assays are already measured annually and benefits of early detection via proteomics assays is likely to be limited to certain specific indications. We spoke with MEDACorp KOLs on this topic and their feedback appears to be in line as well.
- **Multiomics screening assays likely hold the most potential:** We believe that multi-omics assays hold the most potential in screening and oncology, where protein and peptide biomarkers that elevate performance could be used in conjunction with genomic and methylation signatures.
- **A conservative estimate:** Given the already existing screening algorithm in place and the uncertainty associated with the value of additional proteomics information, we are assuming a conservative \$28B market with 140M individuals (40-75 years) at a very conservative ASP of \$200 proteomics/multiomics assay that could be used for early detection in cancer, neurology, immunology, liver, cardiovascular and other chronic diseases. We recognize that the screening market in genomics for early detection of cancer is significantly higher (\$50B+), but based on our analysis, we believe that proteomics technologies will only augment the rapidly building screening assays for cancer.

\* Based on disease incidence for heart disease, diabetes, NAFLD, dementia, and kidney disease according to CDC and AHA and assuming test ASD of \$150 in US, \$15 in ex-US

# NGS Paved the Road to Reimbursement in Personalized Medicine; Proteomics Dx Should Benefit from It

- **For diagnostics, reimbursement remains the #1 driver with Medicare rates being an anchor.** Reimbursement established by CMS' MACs via LCDs or ADLTs remains the most important driver for market growth in diagnostics over the last 5 years and remains a key supporting pillar of growth in the years to come. Proteomics Dx should very likely benefit from the paved road of reimbursement for personalized medicine.
- **Investing into diagnostics companies was not attractive prior to 2016:** Majority of single-site LDTs and single-company-developed lab tests faced significant challenges prior to 2016 with CLFS (Clinical Lab Fee Schedule) dictating pricing that was highly unpredictable as it was set annually on unclear gapfill and crosswalk rules – creating both uncertainty for specialty labs whose entire revenue was dependent on a select few tests and the investors who invested in those companies and the sector.
- **Key events over the last few years** created the attractive Medicare reimbursement and robust diagnostics market we see today :
- (1) **Introduction of PAMA** (Protecting Access to Medicare Act) of 2014 that was fully implemented by 2018 was the most important driver in our view for specialty diagnostics tests, a majority of which were NGS, or gene expression based.
- (2) **Joint FDA and CMS NCD pathway** - FDA approval of Foundation Medicine's F1CDx assay and its CMS NCD (National Coverage Determination) which also included a pathway to improve the assay progressively as new markers were identified - was another key event in early 2018 that helped establish the pathway for NGS assays seeking robust reimbursement. Other tests including Guardant G360 have pursued the same pathway to obtain FDA approval, strong reimbursement and now ADLT rate at \$5k (for G360 CDx).
- (3) **Discovery of new driver mutations** and the use of targeted therapy drove the demand for NGS panels where multiple mutations can be identified vs a single ALK or EGFR antibody-based assay. We see the potential for proteomics to enhance the targeted therapy offering in cancer and more importantly well beyond cancer, but given the established reimbursed pathway or NGS, we feel more confident about proteomics Dx reimbursement as those assays emerge on the market.

## Reimbursement of Genomics and NGS Tests Has Emerged Strong

- **ADLT (Advanced Diagnostics Laboratory Test)** status was established as part of the CLFS final rule in 2016 (implementation of the Section 1834A of the Social Security Act). ADLTs is a subcategory of CDLT with separate reporting and payment requirements and includes tests that are covered under Medicare Part B, offered by a single laboratory (company) and involve multiple biomarkers in DNA, RNA or Proteins. Otherwise, these tests have to be FDA approved to be considered as an ADLT. Simple speaking, these tests gain ADLT status based on their “unique” or differentiated ability in a market that is lacking such a test or are FDA approved to be considered for the ADLT status.
- **Some of the highest reimbursed tests today are ADLTs and a few CDLTs(see below).** ASPs have risen as clinical utility for molecular diagnostics has never been higher. Roche’s F1CDx and Guardant’s G360 are already becoming the standard of care in late-stage cancer therapy selection. The rapid adoption and improved reimbursement environment are reflections of improved survival and also the reduction of unnecessary expensive therapies in earlier stages. As innovative targeted therapies, immunotherapies, and cell & gene therapies are approved, and as indications expand - the clinical utility of these tests should continue to rise. We expect commercial payor reimbursement to be lower vs Medicare (by 20% - 30%) but having a higher anchored Medicare payment is bound to yield solid commercial reimbursement as well.

| Company             | Genomics Test Name         | Medicare ADLT / LCD Reimbursement |
|---------------------|----------------------------|-----------------------------------|
| Castle Biosciences  | DecisionDx-Melanoma        | \$7,193                           |
| Veracyte            | Envisia Genomic Classifier | \$5,500                           |
| Guardant Health     | Guardant360 CDx            | \$5,000                           |
| Myriad              | myChoice CDx               | \$4,040                           |
| Biodesix            | BDX-XL2                    | \$3,520                           |
| Natera              | Signatera                  | \$3,500                           |
| Foundation Medicine | FoundationOne Liquid CDx   | \$3,500                           |
| Foundation Medicine | FoundationOne CDx          | \$3,500                           |
| CareDx              | Allosure                   | \$2,753                           |
| Myriad              | myPath Melanoma            | \$1,950                           |



## Recent MRD Reimbursement Provides Insights into Upside for Dx

- Recent ADLT reimbursement for NTRA’s Signatera assay highlights CMS’ increasing comfort with reimbursing tests at a meaningfully higher rates.** Signatera reimbursement stood at \$794 as established by the initial LCD which covered Stage 2 and 3 CRC patients, with expectations that indications will only expand to reach pan-cancer one day. Under the new ADLT designation, the test will now be reimbursed at \$3,500 by Medicare. The reimbursement is nearly 5x higher vs before – which we believe is significant considering the recurring nature of the assay over the first 3 years after cancer. The reimbursement includes the initial Medicare "bundle" of ~\$6,000 that covers the exome, assay construction and the 6-month adjuvant window, where test volumes average ~2 liquid tests given the duration of the window. Following this 6-month window, NTRA was previously being reimbursed at \$794 for all additional tests which will now be reimbursed at \$3500 by the ADLT designation. Management also reiterated their expectations to remain active appealing commercial payments that are in line with the ADLT in order to maintain the \$3,500 reimbursement rate. Additionally, NTRA is taking many “zeros” on non-covered indications at this time, which we expect to offer further tailwinds to ASPs once CMS approves for coverage and the indications are reimbursed under this ADLT.
- Clinical evidence is building with large-scale trials** such as NTRA’s BESPOKE and GH’s ECLIPSE aiming to deliver practice-changing results. Additionally, Signatera is expected to be meaningful in the adjuvant and neo-adjuvant setting and clinical trials leading to reduction of the time and the cost of clinical trial expense by 80% - a significant improvement vs current standards. The MRD and recurrence monitoring market is estimated at \$15B and remains barely penetrated today with NTRA and GH in the early lead. Increasing reimbursement has expanded this TAM, with NTRA now estimating the MRD liquid biopsy setting could be 4-5x the \$6B late-stage therapy selection opportunity, or \$24B - \$30B.

| Test Option | From DEX    | Calculated Pricing |                |                           |
|-------------|-------------|--------------------|----------------|---------------------------|
|             | MOLDx Price | Exome              | Plasma 1       | Plasma 2-4                |
| Full Bundle | \$5,898     | \$2,720            | \$1,158        | \$2020 (3 tests at \$673) |
| Exome+1     | \$3,878     | \$2,720            | \$1,158        |                           |
| Plasma 1-4  | \$3,178     |                    | \$1,158        | \$2020 (3 tests at \$673) |
|             |             | <b>\$2,720</b>     | <b>\$1,158</b> | <b>\$2,020</b>            |
| Per test    |             | \$2,720            | \$1,158        | \$673                     |

|                                   |              |
|-----------------------------------|--------------|
| <b>Additional Individual Test</b> | <b>\$794</b> |
|-----------------------------------|--------------|



| Patient flow (average) | Prior Medicare Pricing |                 | Pricing Under New ADLT |            |                 |
|------------------------|------------------------|-----------------|------------------------|------------|-----------------|
|                        | Price (Prior)          | Total (Prior)   | Price                  | Frequency* | Total           |
| Bundle (1H Year 1)     | \$5,898                | \$5,898         | \$5,898                | 2          | \$5,898         |
| 2H Year 1 - Year 3     | \$794                  | \$5,558         | \$3,500                | 7          | \$24,500        |
| <b>Total</b>           |                        | <b>\$11,456</b> |                        | <b>9</b>   | <b>\$30,398</b> |

|              |                |                |
|--------------|----------------|----------------|
| ASP per Test | <b>\$1,273</b> | <b>\$3,378</b> |
| Medicare Mix | 50%            | 50%            |
| Net ASP      | <b>\$636</b>   | <b>\$1,689</b> |

|                                       |             |
|---------------------------------------|-------------|
| <b>ASP Upside From Signatera ADLT</b> | <b>165%</b> |
|---------------------------------------|-------------|

Source: Diagnostics Exchange (DEX), SVB Leerink  
 Two tests assumed in full bundle, with 3 tests/yr

Source: Diagnostics Exchange (DEX), SVB Leerink  
 Source: MolDx, SVB Leerink Research

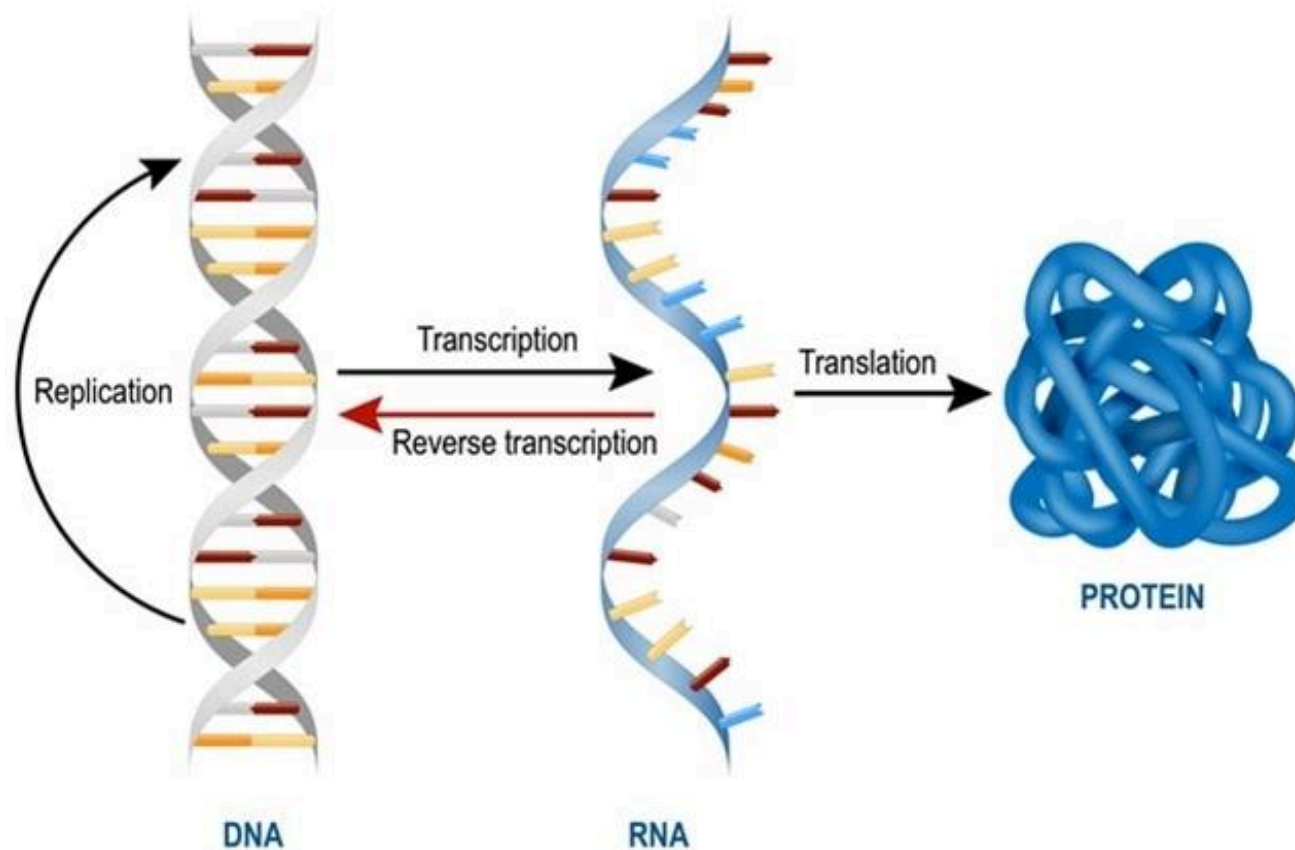
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# Proteomics: Background, Challenges and Complexity

## Proteins: Highly Complex but Most Actionable and Real-time

- **Fundamental Tenet to Human Biology:** A central dogma of biology is that the genetic code contains the instructions to produce 3D molecules called proteins, which carry out the important biological functions in our body. Proteins are significantly complex vs the genes and are responsible for most biochemical functions and regulation within and in-between cells.
- The process of turning a gene sequence into a protein is highly regulated within a cell and contains several steps including **transcription** into RNA and **translation** into peptides and proteins.

A chain of amino acids is called a **peptide** while long chains of amino acids are called **polypeptides**



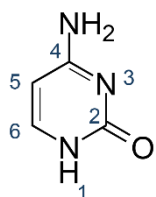
A complex of one or more polypeptides is called **proteins**

## Proteomics: Significantly Higher Complexity

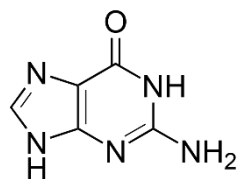
- Proteins consist of **20 amino acids** compared to 5 nucleic acids in DNA / RNA.
- The chemical properties of the amino acids meaningfully differ from each other, while the chemical properties of DNA / RNA nucleic acids are similar. A genome is generally linear in abundance whereas a few proteins can account for majority of the mass of proteins in blood plasma or cells.

### DNA / RNA

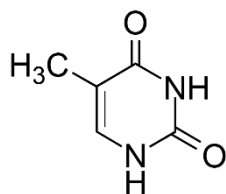
#### 5 Nucleic Acids



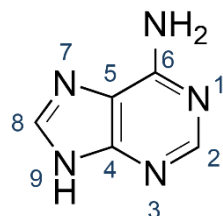
cytosine (C)



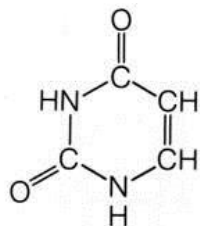
guanine (G)



thymine (T)  
(in DNA)



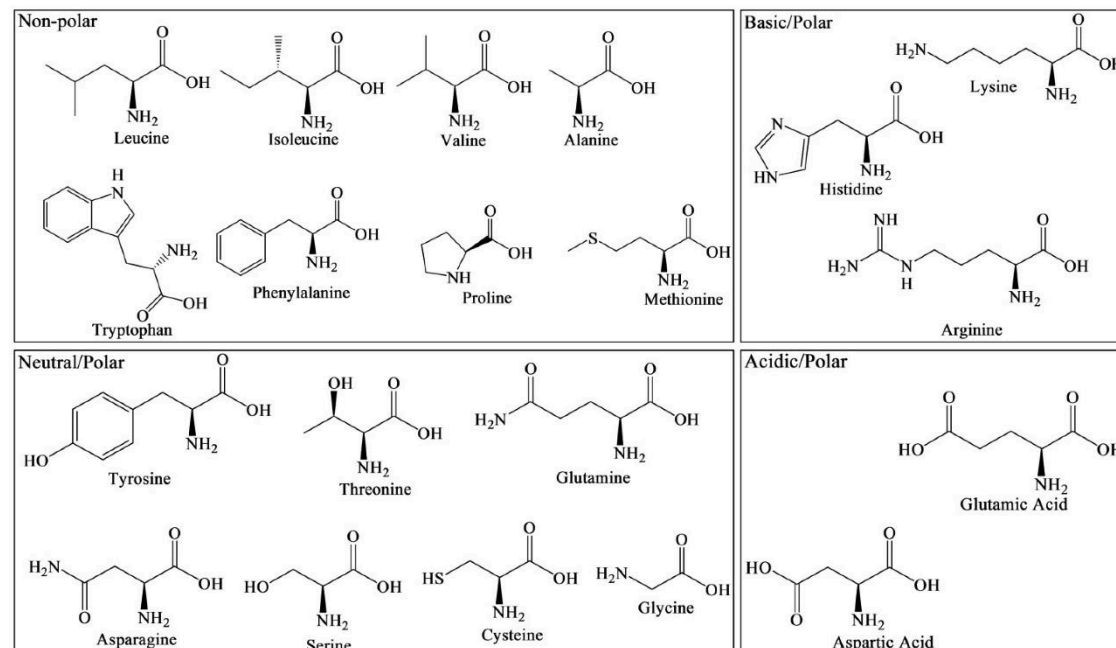
adenine (A)



Uracil (U)  
(in RNA)

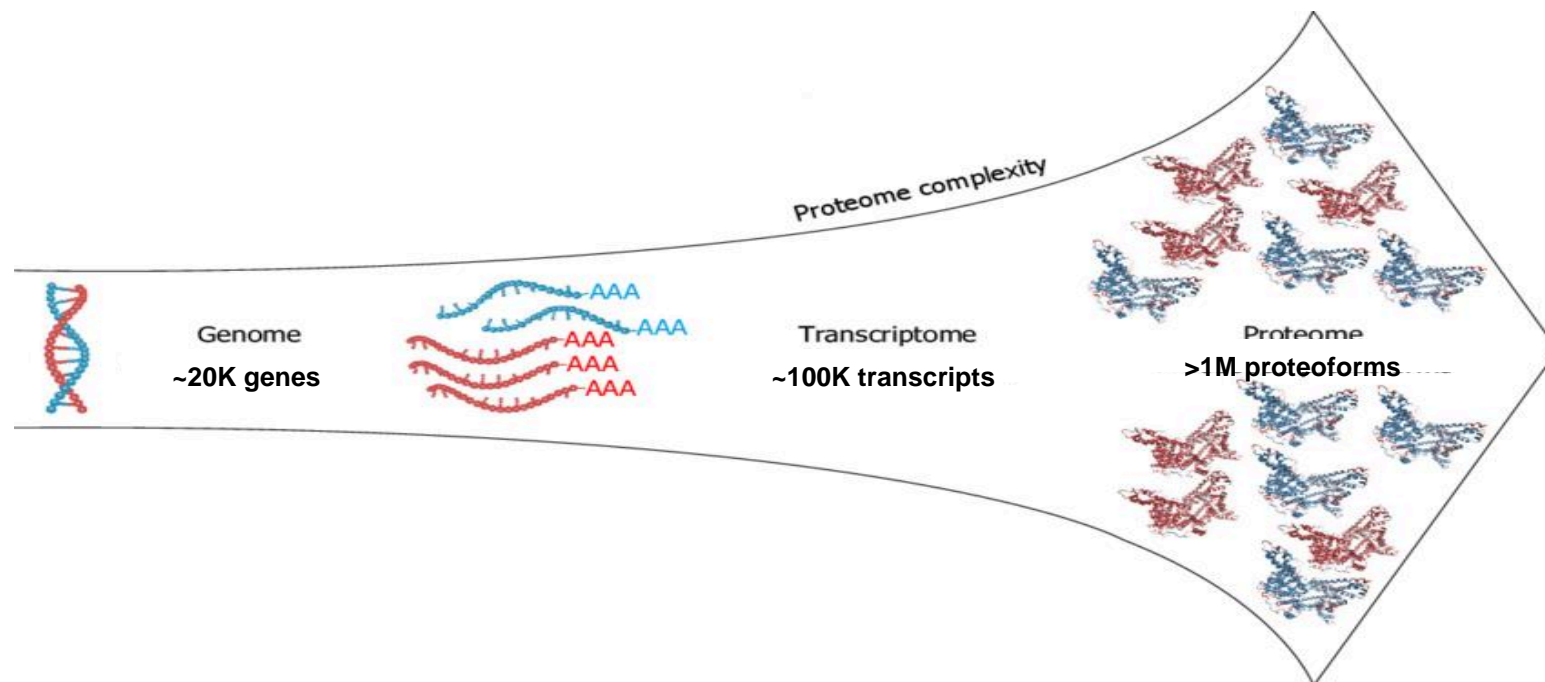
### Protein

#### 20 Amino Acids

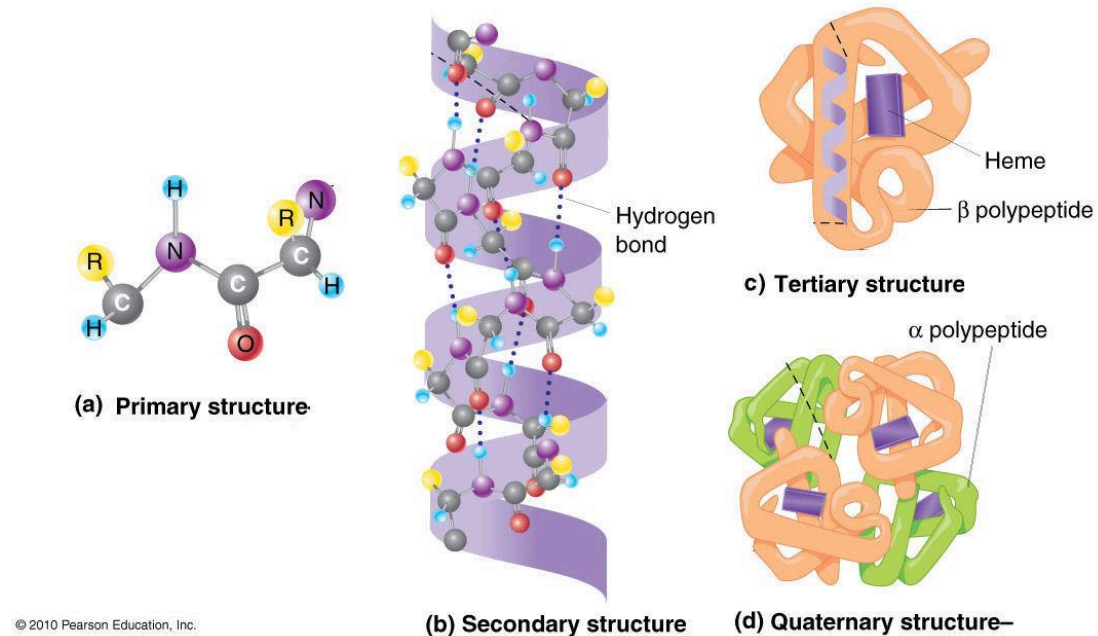


## Proteomics: Orders of Magnitude Higher Complexity

- Due to the **combinatorial nature of protein formation**, a relatively small number of genes can translate into several fold more different proteins known as proteoforms.
  - **Increased diversity:** Estimates for proteins blood plasma range from 10,000 – 15,000, with tissues having 20,000 – 30,000 proteins and potentially more than 1M proteoforms.
  - **Proteoform complexity:** Proteoforms are different forms of a protein emerging from a single gene. These proteoforms, or isoforms, are a result of the traditional transcription and translation of a protein from a gene being modified by genetic variations, alternatively spliced RNA transcripts, and post-translational modifications. Proteoforms, as a result, are a collection of proteins that behave functionally different – which highlights the level of complexity simply not seen in genomics.



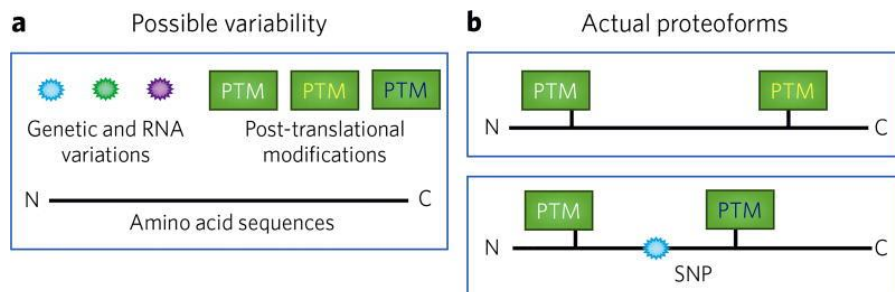
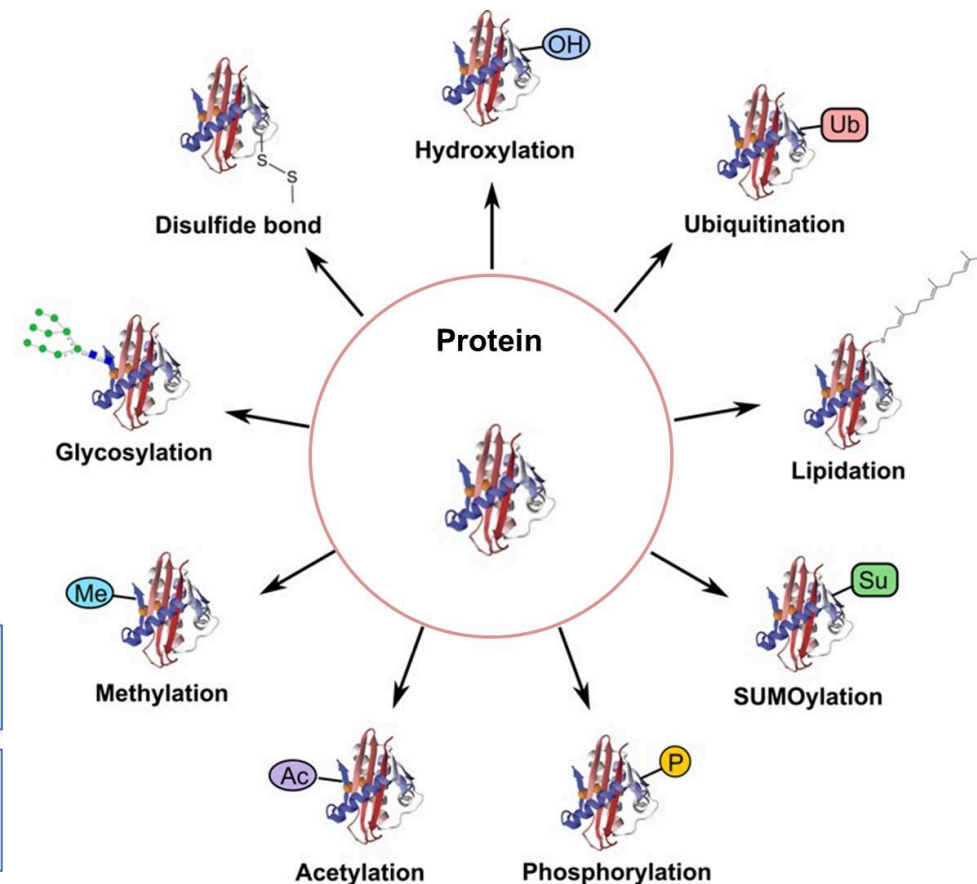
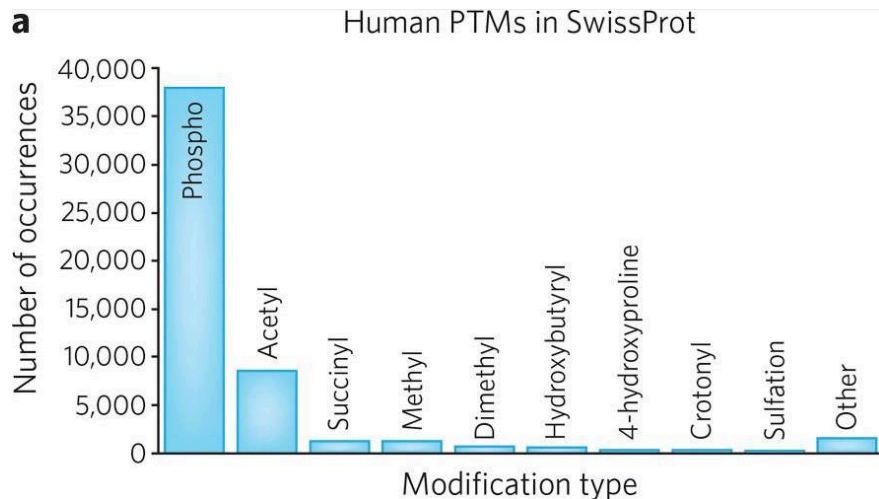
## Protein Folding and 3D Structure Only Adds to the Level of Complexity



- The amino acid sequence (primary structure) has limited information about the functionality of the protein.
  - The secondary and tertiary structure describe how a protein is oriented in 3D space. The quaternary structure describes how a protein links with others to form a functional unit. This 3D structure is essential to drive the functionality or form the pockets that might bind a receptor and activate downstream pathways and events.
  - Even when accounting for this level of complexity in the structure, there is still another layer of complexity with **post-translational modifications** that add to the protein's structure and its functions. Thus, the attempts to understand proteomics of a biological system get challenging – especially when looking at several thousand proteins that you could yield more than 1 million proteoforms.

# The Challenge Is Enormous: PTMs Explode the Level of Complexity in Proteomics

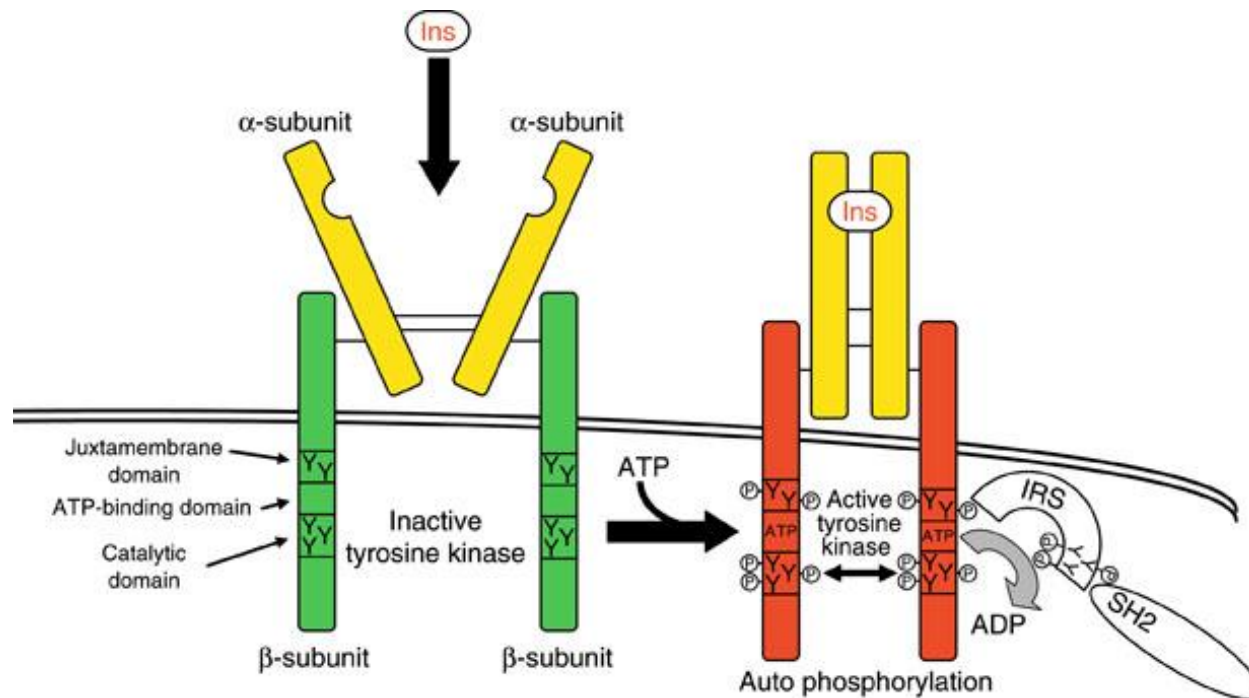
- Proteoforms are a major challenge in proteomic analysis. After a mRNA is translated into a protein, there are several **post-translational modifications (PTMs)** that may occur with the molecule. Though the estimated protein coding regions are only ~20,000, the splice variants itself increase that number to a diversity of 70,000. PTMs then increase that complexity even further as these modifications fundamentally change the protein leading to different functions. As a result, estimates suggest there are more than 1M PTMs in the human proteome. **These PTMs can mean the difference between a functional and non-functional protein.** The image below demonstrates how one protein becomes nine distinct proteoforms.



## PTMs: Appreciating the Complexity

### Significance of PTMs: Phosphorylation has a key role to play

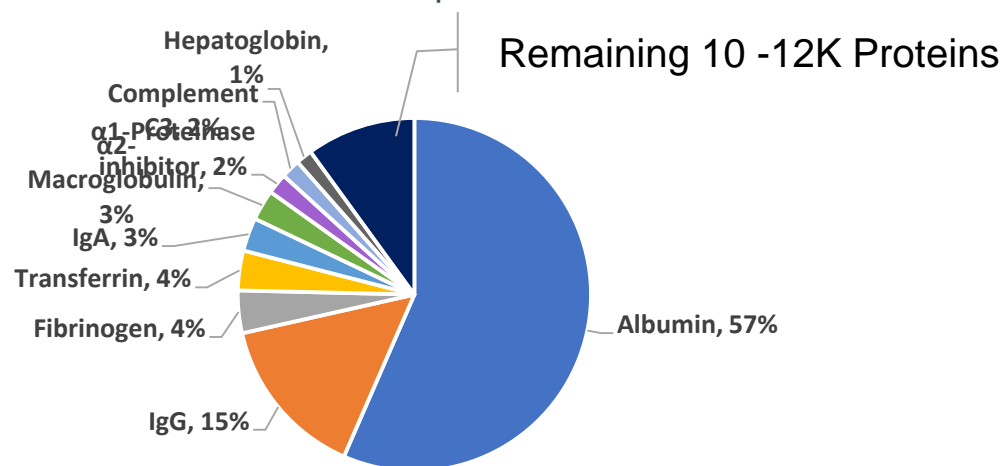
- Insulin is a protein that signals the cells for uptake of glucose from the blood stream. To start this process, insulin must bind to the insulin receptor (IR). In its inactive state, the downstream proteins have no phosphorylation. When insulin binds to the IR, it leads to protein to change shape and become phosphorylated. This phosphorylation activates IRS and other proteins, which signal the uptake of glucose into the cell. Type 2 Diabetes occurs when fats and cell stress disrupt the phosphorylation of IRs, resulting in insulin resistance and high blood sugar





## Core Challenge in Proteomics: Dynamic Range

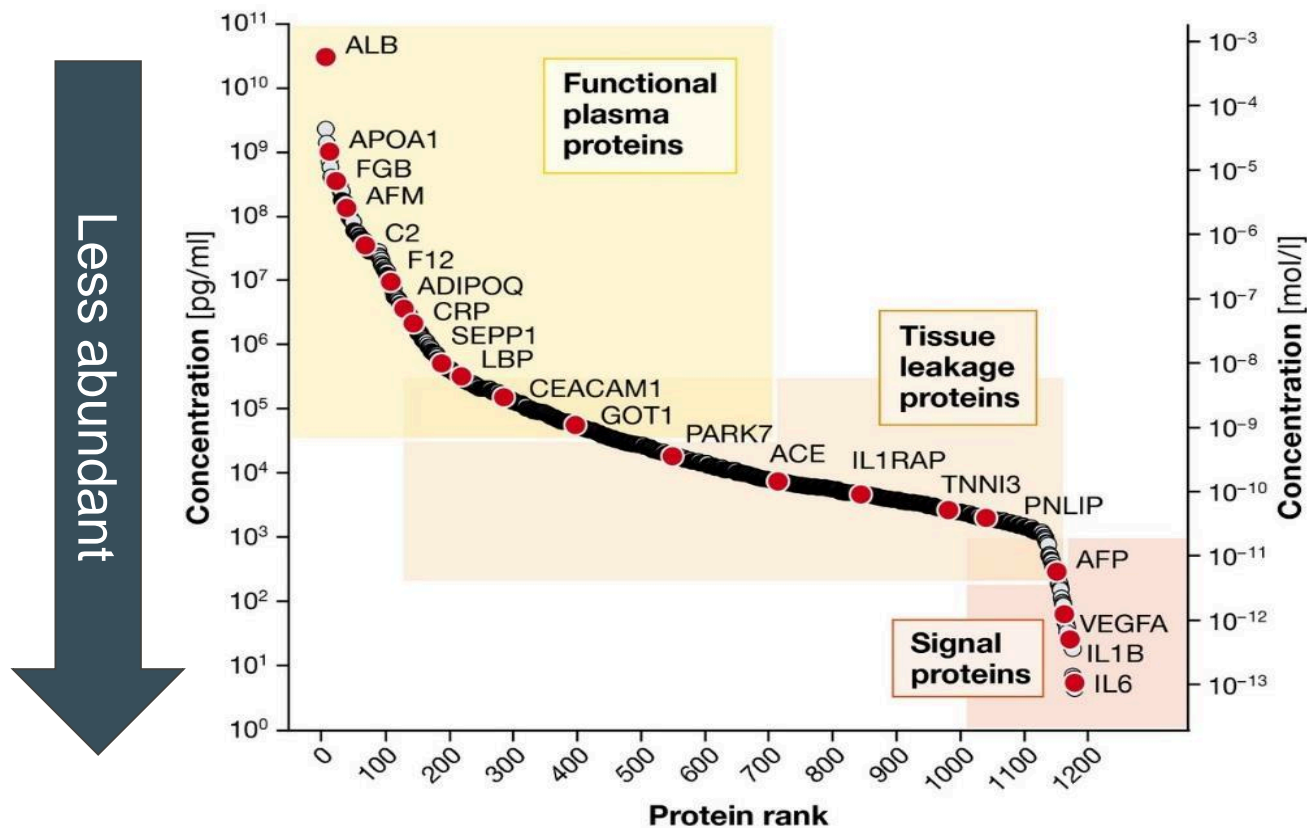
- **The Dynamic Range Problem:** A key obstacle in surveying the entire plasma proteome are large differences in concentration levels from the highest abundant proteins vs the least abundant ones. This challenge is worse in plasma vs the tissues and remains a key hurdle in proteomics given the potential for diagnostics from plasma.
  - Estimates range from 10-12 orders of magnitude between the highest and the lowest protein concentration levels.
  - The **top 10** most abundant proteins **comprise 90% of total proteins** in plasma. Albumin alone accounts for more than 50% of total proteins abundance in plasma.



- This can make it very difficult to sift through the higher abundant proteins that may be less clinically relevant and reach the very low concentration proteins including cytokines.
- Important to note that unlike **PCR for genes, no such amplification techniques exist for proteins.**
- **Current techniques** such as mass spectrometry can transverse 4 logs of dynamic range, while there are immunoassays specifically designed to measure proteins that are more difficult to detect but a comprehensive proteomics solution is still elusive. Leading MEDACorp Proteomic KOLs indicate **mass spec can reproducibly detect up to 1k – 1.5k** as compared to the 10k+ total proteins theorized to be in the plasma proteome.

## Plasma Proteins Have a Wide Dynamic Range

- The Dynamic Range Problem:** A key obstacle in surveying the entire plasma proteome is the large differences in concentration levels from the highest abundant proteins vs the least abundant ones. Dynamic range remains the single largest challenge in proteomics. Technologies that reduce the complexity upfront with sample prep have been utilized before and more innovation is emerging in the market, but getting the least abundant proteins continues to remain a big challenge. One MEDACorp KOL overseeing a growing clinical and translational lab has argued that low abundant proteins might not be as valuable as we think, but that is unlikely to reduce the desire to mine the lower end of the proteome among the researchers. Unfortunately, there is no amplification technique like PCR for proteins.



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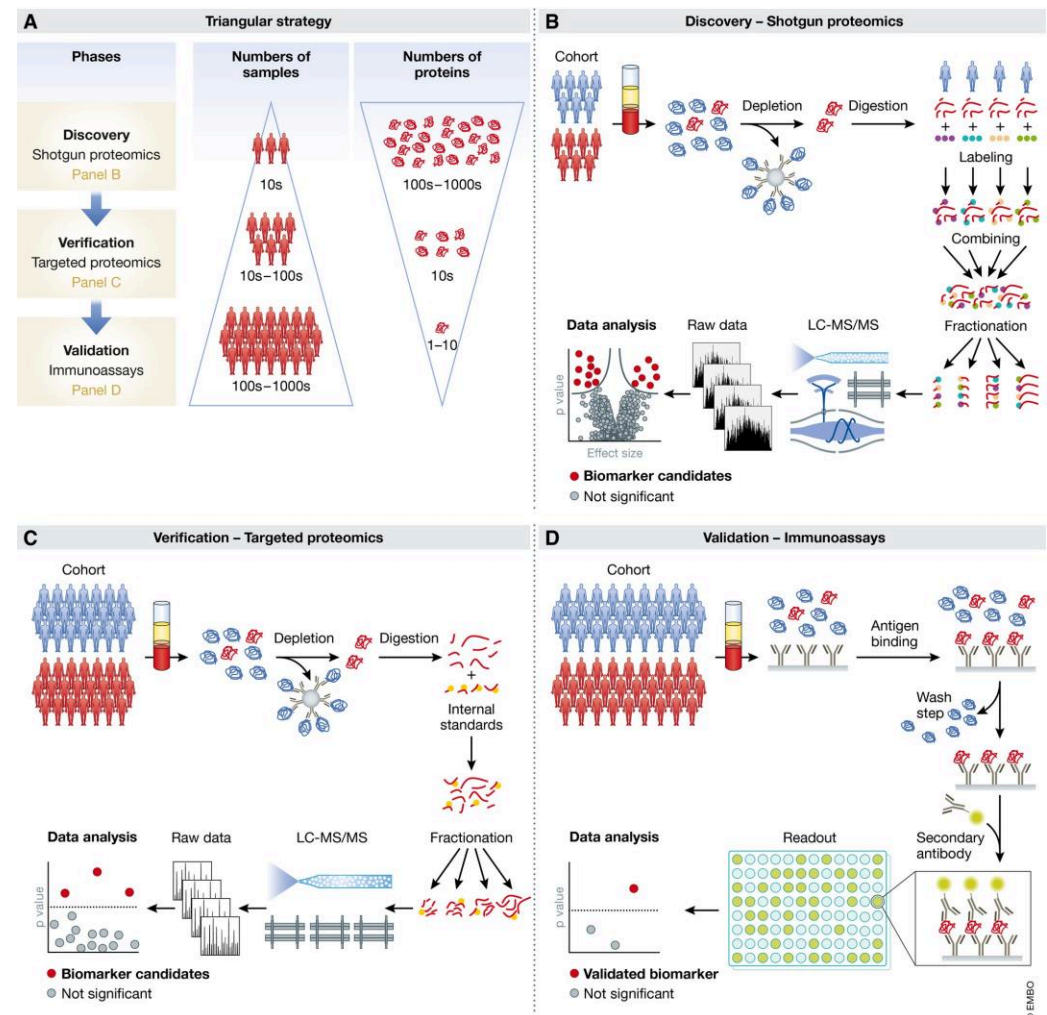
# Current Methods in Proteomics

## Established Approaches in Proteomics

- Established approaches:** Sophisticated approaches in mass spectrometry, immunoassays and validation via antibodies have been established over the last two decades to drive insights from proteins. Though these techniques have not yielded anything closer to a full human proteome, they still have advanced the world of proteomics significantly.

1) **Mass Spectrometry (LC-MS):** Early growth in mass spec-based proteomics approaches started in the late 1990s and early 2000s with the introduction of LTQ ion trap from Thermo Fisher and existing innovative Q-TOF instruments from other mass spec companies. Techniques that digested the proteins to peptides and yielded mass spectra that helped identify proteins came to be known as **Peptide Mapping**. Early experiments on these instruments yielded a few hundred proteins in leading labs but meaningful growth in proteomics came with the introduction of high-resolution instruments such as Thermo's Orbitrap with accuracy in assignment of proteins and overall depth of the proteome. BRKR is now building on that momentum with its timsTOF mass spec platform.

2) **Immunoassays/ antibodies and related approaches:** Growth in immunoassays came shortly after LC-MS with improvements to antibody production and specificity, particularly with the introduction of monoclonal antibodies. Immunoassays have strong adoption in clinical and low-plex uses, where their speed and simplicity make them ideal when only a few proteins need detection. The most popular immunoassay type is ELISA, which uses bound antibodies and fluorescence to detect analytes.



## Companies Serving the Proteomics Approaches (Legacy and Emerging)

### Current Proteomics approaches involve multiple modalities and techniques:

1. **Mass Spec (LC-MS):** Liquid Chromatography with Mass Spec is the most well-established proteomics technique, where the market adoption has been primarily driven by TMO's Orbitrap and now BRKR's timsTOF (since its launch in 2017). We currently estimate the mass spec research market size at \$4.5B of which proteomics is likely 15% to 20%.



2. **High-Plex Proteomics:** Emerging high growth proteomics technique using affinity reagents to detect proteins on a large scale.



3. **Immunoassays and antibodies:** An antibody-based protein detection technique often used for research and clinical applications.



4. **Spatial Biology:** A gene expression (RNA) and proteomics technique that provides information on specific regions or slices or tissue / cell samples in florescent images.



5. **Flow Cytometry:** A proteomics technique for staining and identifying proteins on the surface of cells.



6. **Emerging Technologies:** A number of differentiated approaches are emerging in the market.



## Current Proteomics Methods

|                                   | Mass Spec (LC-MS) | Immuno-assays | High Plex   | Spatial Biology | Flow Cytometry |
|-----------------------------------|-------------------|---------------|-------------|-----------------|----------------|
| # of Proteins                     | 1K - 3K           | 1-50          | 3K-7K       | 1-100           | 1-50           |
| Accessibility                     | Low               | High          | High        | Medium          | Medium         |
| Reproducibility                   | Medium            | High          | High        | Medium-high     | Medium-High    |
| Instrument Cost (Capital Expense) | High              | Low           | Low         | Medium          | Medium         |
| Required Expertise                | High              | Low           | Low-Medium  | Medium          | Medium         |
| Turn-around Time                  | Days - Weeks      | Few hours     | 24 – 48 Hrs | 4 Hrs           | 1-2 Hrs        |

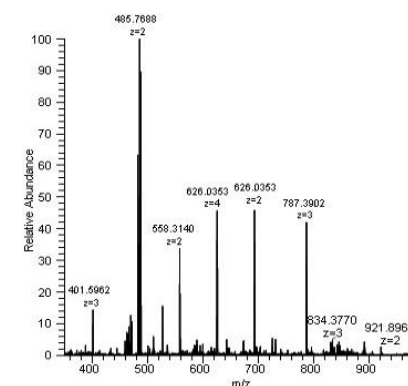
- **Current proteomics methods employ multiple techniques** that have been refined over the past few decades. **Mass Spec:** Though mass spectrometry has yielded a large number of publications, the technique requires generally expensive capital equipment with a critical number of instruments (mass spec core lab), extensive expertise in mass spec and liquid chromatography, making it harder for such a technology to be democratized widely. The data analysis is also complicated vs other approaches (that also have limitations) and the projects could take weeks to months to yield meaningful results. Still, mass spec is still the best when it comes to deeper analysis on select targets and for studying PTMs.
- **Immunoassays:** Though immunoassays have been around for a long time, their main limitation is limited multiplexing capabilities, and the performance is largely dependent on the antibodies.
- **High-plex proteomics:** The emergence of high-plex proteomics companies, including both Olink and Somalogic, promises to address one of the limitations of immunoassays with regards to multiplexing as both OLK and SLGC can deliver 3k and 7k proteins in an experiment. But still these techniques are heavily dependent on quality antibodies still with most of them being still polyclonal.

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# Mass Spectrometry

## Mass Spectrometry: The Current “Industry Standard” in Proteomics

- Mass spectrometry (LC-MS) is widely regarded as an analytical tool for measuring, detecting, and characterizing molecules including proteins both simple and complex mixtures.
  - The instrument measures the mass to charge ( $m/z$ ) ratio of ions to determine the molecular weight and composition of molecules in addition to quantifying the molecules – features that are extremely valuable to biopharma customers.
  - Mass spec is routinely used in biopharma to confirm or identify small molecules, assess drugs metabolism. Beyond that, the technology is used in environmental applications and food analysis. The technology in conjunction with liquid chromatography is utilized in multiple end-markets but the proteomics application has seen strong growth since late 1990's/early 2000's.
- Mass spec-based proteomics is regarded as the “gold standard” for protein and peptide analysis (single protein to few thousands) given the platform's sensitivity, mass range and performance that has steadily improved over the last two decades.
- Main vendors for LC-MS are Thermo Fisher, Agilent, Waters, Danaher (DHR), Bruker (BRKR), Perkin Elmer (PKI) and Shimadzu. Systems typically are priced anywhere **from \$350k - \$1M** and require significant operator expertise.
- TMO's Orbitrap (shown to the right) launched in 2005 has been the leading platform for many years in proteomics due to its unmatched resolution and analytical power but the addition of BRKR timsTOF has created competition for Orbitrap, with **BRKR timsTOF taking share** in this high-resolution proteins analysis segment.
- However, LC-MS is not without its drawbacks** that have limited the adoption in the market for these instruments: (1) cost of the instrument, (2) complexity – that drives labs to become specialized mass spec labs only, (3) very low throughput as the samples are run in a serial fashion unlike a sequencer where samples can be multiplexed, and (4) extensive sample prep to produce a clean sample and complex data on the back end that needs to be analyzed using multiple software tools.





# Key Mass Spec Proteomics Techniques

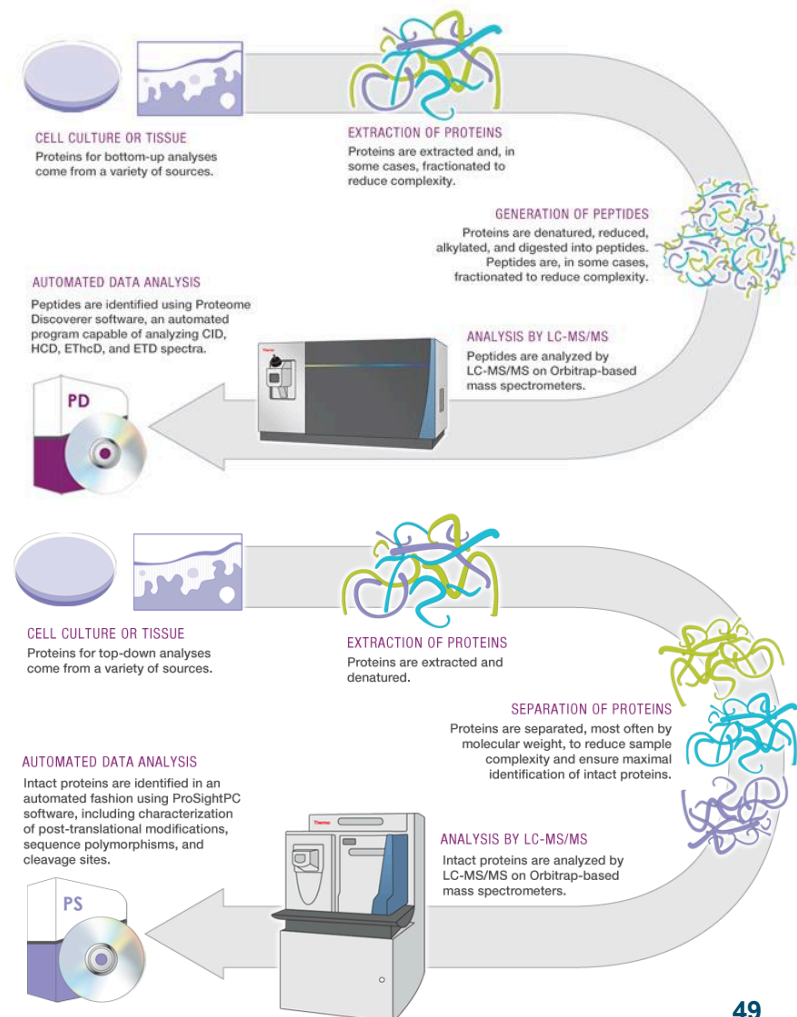
- **Peptide mapping and intact protein or subunit analysis** are key proteomics techniques that are widely adopted by both biopharma labs and academics to identify the amino acid sequence of a protein mixture, an intact protein or a protein therapeutic with its modifications. These techniques have become a standard and have found their way into the critical quality attributes (CQA) required for the validation and verification of monoclonal antibodies and complex therapeutics. We see increasing use of mass spec in biotherapeutics as protein and proteomics CQA's get incorporated into the routine bioanalytical analysis for biologics drugs.

## Peptide mapping (Bottom-up proteomics)

- Protein samples are digested into smaller peptide fragments, often using enzymes like trypsin to cut at consistent sites in the protein;
- The peptide fragments are separated by various attributes like size, charge or affinity through liquid chromatography and introduced to the mass spec where the sequence is identified through analysis of the resulting spectra.

## Intact protein analysis (Top-down proteomics)

- Intact Protein Analysis is also known as the “top-down” approach to protein analysis, in contrast to peptide mapping, which is “bottom-up”.
- Obtains similar information as peptide mapping, but tends to better preserve PTMs and identify distinct proteoforms in a sample.
- Relative to peptide mapping, the separation step can be more difficult, and the technique is not as automated as peptide mapping given the complexity of full intact proteins.



## Thermo Fisher (TMO)

### TMO (OP; PT \$675)

- **A broad and diversified exposure to proteomics:** TMO is a large and diversified enterprise in life science tools that has wide exposure to proteomics in our view. Thermo owns the leading mass spec platform for proteomics with its Orbitrap franchise (launched in 2005) aided by its UPLC platform (Dionex). Adding to that is its legacy position in antibodies and reagents with the portfolio from the acquisition of LIFE technologies and Cryo EM offerings that provide insights into protein structure. Beyond that a number of TMO's product touch the proteomics ecosystem in a way that is hard to quantify.
- **TMO provides the broadest set of reagents** and tools serving the sample prep needs of proteomics application from sample to result. Thermo maintains an extensive catalog of primary and secondary antibodies, those used in ELISA kits and flow cytometry applications. Despite what appears to be a broad exposure, proteomics in its current state might still represent less than 10% of its \$36B 2021 revenue.
- **Mass Spec & Chromatography (LC-MS)**
  - **Instrumentation:** Wide range of mass spec and chromatography systems including Triple Quad MS, single quads, UHPLCs, GCs and sample prep solutions
  - **Market Leader:** The Orbitrap suite of instruments is regarded as the market leader in mass spec due to unmatched performance characteristics. But it is also important to keep in mind that not all Orbitraps are used in proteomics. Orbitraps are utilized where higher resolution data is needed – especially in biopharma and bioanalytical settings.
- **Immunoassays**
  - TMO has a comprehensive offering of antibody-based immunoassays including coated and uncoated ELISA kits, multiplex assays from Luminex and custom immunoassays.
- **Cryo-EM: Structural Biology**
  - Analyzes 3D structure of proteins with resolution to atomic level
  - Alternative to X-RAY crystallography and NMR for imaging the proteins



| TMO Key Metrics      |           |
|----------------------|-----------|
| Market Cap           | \$239,899 |
| 2022 Revenue         | \$38,110  |
| 2025 Revs (LT guide) | \$44,342  |
| Operating Margin     | 30%       |
| 2022 EPS             | \$22.17   |
| EPS Growth           | 13%       |

(\$M) except EPS

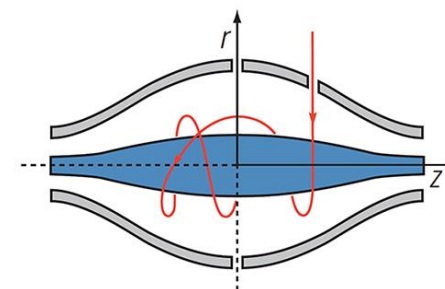
# Significance of the Orbitrap Platform in Proteomics

## TMO (OP)

- **Orbitrap gained large market share in proteomics and protein analysis, thanks to its superior resolution**, accuracy and sensitivity. After its launch in 2005, the instrument took steady share from Q-TOF (Quadrupole Time of Flight) instruments given its superior resolution. The resolution was necessary in obtaining the accuracy of the peptide fragments that were generated in proteomics experiments.

## History

- Launched in 2005, the first orbitrap mass spec was the first fundamentally differentiated MS to launch in two decades. TMO acquired the technology from HD Technologies (Manchester, UK) with its chief scientist Alexandar Makarov driving the innovation in the early stages. The instrument was priced at \$500k-\$900k depending on different features, including high-energy collision dissociation (HCD), electron-transfer dissociation (ETD) and matrix-assisted laser desorption/ ionization (MALDI) capabilities.
- The Orbitrap technology works by detecting ions oscillating around a central orbital-shaped electrode, separating the sample via the differences in frequency between different ions. These ions create an oscillation on an outer electrode, which enables the mass spectra to get acquired in a smaller instrument size. We believe the Orbitrap franchise grew to deliver 500-600 instruments (at \$600k each) combined with TMO's leading Dionex UPLCs at the peak of the market (2009 – 2015), though the growth run rate has now stabilized 16 years after the launch of the instrument.
- The platform continued to evolve with Exactive as a single-stage MS Orbitrap instrument launched in 2008. A number of iterations of the technology including Q Exactive - a tandem MS that scaled Orbitrap down to benchtop level and Orbitrap Elite followed by its high-end instrument Lumos, which increased the speed, resolution, and analysis quality of Orbitrap after its launch in 2011.



# Bruker Corp. (BRKR) Positions for Growth in Proteomics

BRKR (OP; PT \$100)

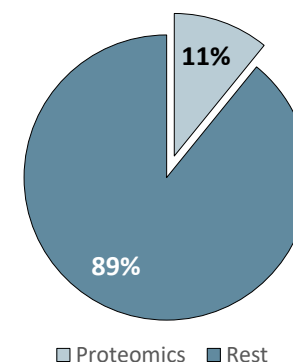
- We believe BRKR is positioned to benefit from the wave of innovation in proteomics, and we see higher revenue growth potential from the ongoing portfolio shift as part of Project Accelerate 2.0 and new products that are set to drive the growth ahead.

## Proteomics Offerings

- Proteomics and Spatial Biology are two “break out” markets, with BRKR estimating they can service \$2B in proteomics and \$1B in spatial today.
- Today, **\$200-250M of BRKR revenue is levered to proteomics market with the potential for proteomics contributing 30-40% of revenue by 2030**, according to the management.
- BRKR’s proteomic exposure includes the timsTOF platform, UHF NMR, X-Ray Crystallography, SPR Protein Interactions, and Spatial Proteomics. The timsTOF platform, followed by its spatial offerings, are expected to be the fastest growing products within the proteomics segment for BRKR.

|                             | Estimated 2021 Revenue Contribution | Growth Prospect |
|-----------------------------|-------------------------------------|-----------------|
| UHF NMR (Protein structure) | ~\$135M                             | Medium          |
| timsTOF                     | ~\$80M                              | High            |
| X-Ray Crystallography       | ~\$10M                              | Low             |
| SPR Protein Interaction     | ~\$10M                              | Low             |
| Spatial Proteomics          | ~\$8M                               | High            |
| <b>Proteomics Total</b>     | <b>~\$228M</b>                      |                 |

Total Revenue: \$2.3B (2021E)



Proteomics Rest



| BRKR Key Metrics     |          |
|----------------------|----------|
| Market Cap           | \$12,773 |
| 2022 Revenue         | \$2,514  |
| 2025 Revs (LT guide) | \$2,961  |
| Operating Margin     | 16%      |
| 2022 EPS             | \$1.94   |
| EPS Growth           | 13%      |

(\$M) except EPS

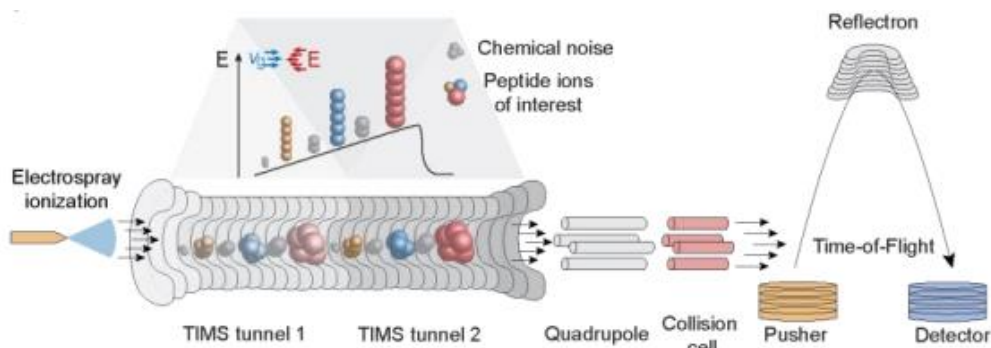
Source: BRKR, Company filings, SVB Leerink Research

# Bruker Corp. (BRKR) Disrupts the Proteomics LC-MS Market with timsTOF

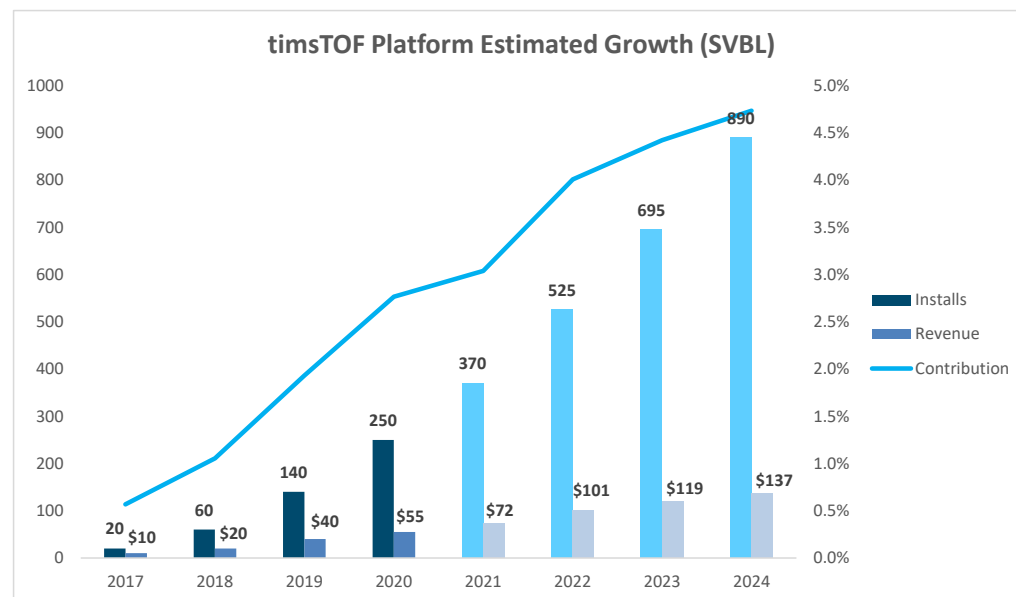
BRKR (OP; PT \$100)

## ▪ timsTOF Mass Spectrometry

- timsTOF is an innovative mass spec launched in 2017 and upgraded in 2021 that offers differentiated speed of analysis (50-200 samples per day and > 100 Hz speed) and is the first MS system to meaningfully challenge TMO's Orbitrap's position in proteomics applications.
- In June 2021, BRKR launched the highly sensitive **timsTOF trueSCP**, which enables unbiased and deep single cell proteomics (SCP) with quantitation of ~1.5k proteins per cell (a collaboration with Matthias Mann lab). We believe that timsTOF trueSCP holds potential to drive growth as more proteomics researchers explore single cell analysis capabilities of the instrument (high sensitivity).
- **Acquisition speed** is key: timsTOF uses trapped ion mobility spectrometry (tims) to separate ion samples and control ion flow before sending them through a Q-TOF system for further analysis. The separation occurs via gas flow counteracted by an adjustable electrical field that controls ion flow. This enables high speed and high sensitivity with less sample.
- Currently timsTOF has 300+ installs in the field and \$75M+ annual run rate in revenue. About half of timsTOFs use the BRKR LC.



Schematic of the timsTOF platform



Source: Company filings, SVB Leerink Research, "Ultra-high sensitivity mass spectrometry quantifies single cell proteome changes upon perturbation" *Mann et al*

# Bruker Corp. (BRKR) Poised to Maintain Its Leadership in NMRs

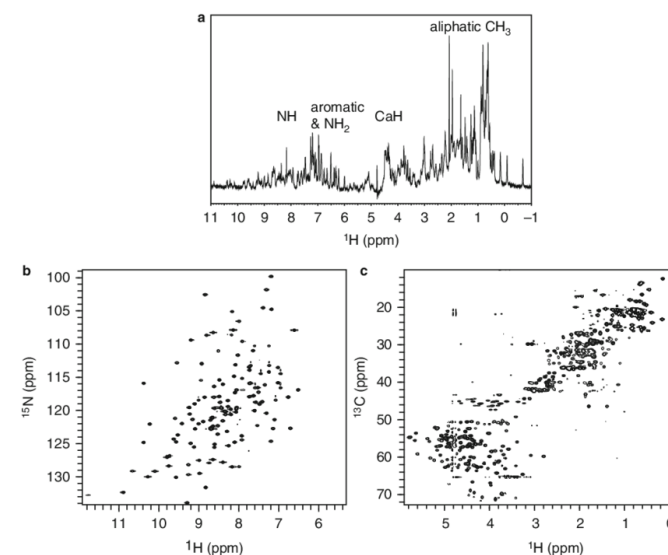
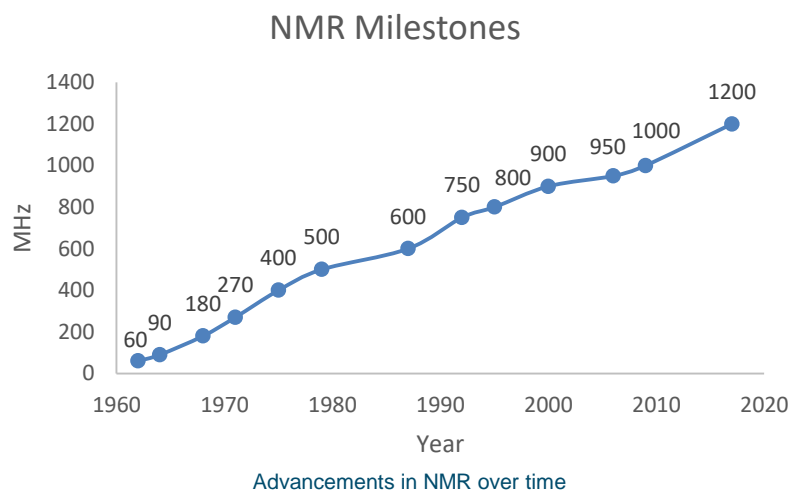
BRKR (OP; PT \$100)

## UHF NMR helps drive advances in understanding of proteins and protein complexes

- Ultra High Field Nuclear Magnetic Resonance (UHF NMR) system can structurally resolve complex protein structures and protein-protein interactions. UHF NMRs are used to study protein dynamics and interactions.
- BRKR is unique in its ability to achieve >1 GHz NMR thanks to its breakthrough novel hybrid technology with advanced high and low-temperature superconductors (HTS, LTS) that can sustain stable magnetic field strength.
- Proteins consist of atoms that have their own magnetic spin. NMR measures the shift in spin when acted on by the instruments' electric field. The atom's location in 3D space relative to others affects the shift, enabling researchers to resolve the structure of a protein or other protein dynamics.
- UHF NMR with GHz class magnets run \$10M+ per system each and BRKR has managed to keep a steady stream of installations over the last 2 years. UHF NMR is currently a ~\$125M+ growing business.



1.2 GHz system offered by BRKR



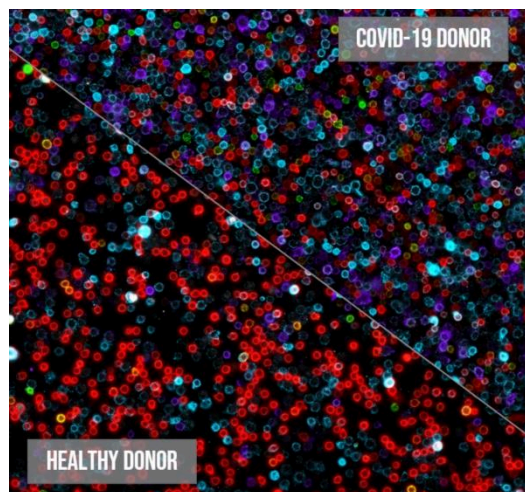
Example NMR measurements

# Bruker Corp. (BRKR) to Participate in the Spatial Market

BRKR (OP; PT \$100)

## ▪ Spatial Proteomics

- In 2020, BRKR acquired Canopy Bioscience and its ChipCytometry platform that can analyze up to 10K cells in suspension or tissue.
- BRKR has 250+ validated biomarkers for the platform, offering panels with applications in immunology, immunoncology and neuroscience that can interrogate up to 20 proteins in a single experiment.
- ChipCytometry can automatically quantify cell types and targeted protein expression across 8 logs of dynamic range, enabling visualization of high and low count cells.
- BRKR estimates spatial biology as a \$3-5B TAM, of which they can service ~\$1B with Canopy and other non-proteomic spatial offerings.
- BRKR sells a manual and automated version of the system for \$290K and \$380K, respectively, and sees potential for 50K-75K pull through long term as adoption broadens.
- Canopy Bioscience is also a CRO service largely serving pharma currently.



## Waters Corp. (WAT) Has a Small but Growing Footprint in Proteomics

WAT (MP; PT \$385)

- Though we rate WAT as Market Perform given earlier sales force realignment challenges and its limited exposure to emerging standards including MAM (Multi-Attribute Monitoring) vs the competitors, we do see strong uptake of instruments in the last 3 quarters reflective of improving sales effectiveness and its replacement cycles. WAT has a strong suite of Q-TOF instruments, some of which including its Xevo and Synapt (ion mobility) line are traditionally used for Proteomics applications. Mostly recently its launch of the Multi Reflecting TOF or MRT instrument positions WAT for high resolution tissue imaging applications in proteomics.
- **Liquid Chromatography (LC)**
  - The company is the **market leader in LCs and columns** where WAT has been “spec’d” into several Biopharma manufacturing processes – leading to its strong position in QA/QC.
  - Offers best-in-class UPLC and HPLCs. Although there have been many fast followers in this area that have eroded their leadership.
  - Still, a majority of WAT sales are from LC instruments, service, and columns.
- **Mass Spec Systems**
  - **Instrumentation:** Waters has a wide array of mass spec offerings including Single Quads, Q-TOFs, Triple Quads, and Ion Mobility. Its BioAccord instruments is designed to bring mass spec to biomolecular QA/QC in the longer-run. BioAccord can perform a number of intact and subunit analysis to help characterize the protein biomolecules and the PTMs.
  - **WAT’s MRT holds promise:** Their newest instrument, the Multi Reflecting TOF (MRT) platform, combines with DESI and MALDI imaging sources to offer high resolution (200K FWHM) imaging of peptides in a sample. MRT uses a multi-reflecting 50m ion path to give finer resolution with a manageable footprint and is capable of visualizing tissue sections at < 10 microns, enabling single cell resolution.
- **Empower:** The Empower CDS is WAT’s flagship chromatography data system used widely in QA/QC markets, though has limited to no impact on the proteomics applications.



| WAT Key Metrics      |          |
|----------------------|----------|
| Market Cap           | \$24,151 |
| 2022 Revenue         | \$2,900  |
| 2025 Revs (LT guide) | \$3,264  |
| Operating Margin     | 30%      |
| 2022 EPS             | \$10.68  |
| EPS Growth           | 10%      |

(\$M) except EPS



## Agilent (A) Provides Select Touchpoints in Proteomics

A (OP; PT \$170)

- Agilent is a diversified enterprise across both healthcare and chemical and energy markets. Though Agilent holds a leading position in LC-MS for environmental applications, the company has gained steady position in biopharma and within CROs and CDMOs. Many of the applications that are routine on Agilent Q-TOF instruments - such as peptide mapping and MAM for biologics used to be mainstays of proteomics but are now routinely used to characterize biomolecules in developmental stages of a biological mAb or similar drug.
- Chromatography**
  - LC:** Market leading front-end LC workflows through InfinityLab Series including HPLC systems, columns, components, accessories
  - GC:** Leading market share in Gas Chromatography (GC) market with estimated 65%+ share across key applications including Energy, and Industrial. Though that has no exposure to proteomics
- Mass spec & LC-MS:**
  - Instrumentation:** Agilent has a wide range of mass spec options including Triple Quads, Q-TOFs, Single Quads with integrated sample prep, LC, and software workflows. But again, most common proteomics instruments are still the 6500 Q-TOF line up. These Q-TOF instruments range from \$350k - \$700k and offer some competition to the competitors Q-TOF offerings in the market but are still not as competitive to TMO's Orbitrap or BRKR's timsTOF when it comes to proteomics applications.
- Dako: Leading IHC-Based Pathology Franchise**
  - Large antibody-based menu for wide variety of targets and applications
  - Automated staining and diagnostic platform for H&E, IHC, ISH, and CDx applications
  - 1k+ of installed base in 80+ countries



| A Key Metrics        |          |
|----------------------|----------|
| Market Cap           | \$52,189 |
| 2022 Revenue         | \$6,750  |
| 2025 Revs (LT guide) | \$8,106  |
| Operating Margin     | 19%      |
| 2022 EPS             | \$4.31   |
| EPS Growth           | 11%      |

(\$M) except EPS

# 908 Devices (MASS) Building Its Position in Proteomics with ZipChip Platform

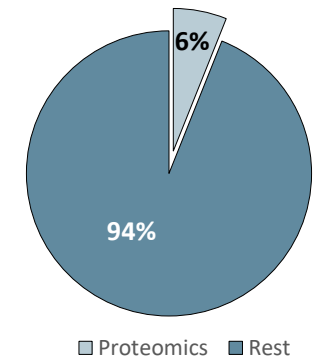
## MASS (OP; PT \$65)

- We remain OP on 908 Devices and see it as a high-growth LST company that has fundamentally reengineered mass spec to deliver significant ease of use, small form factor and fast turnaround with accurate results - leading to expansion of its applications into new markets in a way not seen before. Though MASS is known for its handheld forensic device Mx908 and its bioprocessing analytical instrument REBEL, the ZipChip technology has seen growth in biopharma accounts with peptide and protein applications.

### ZipChip

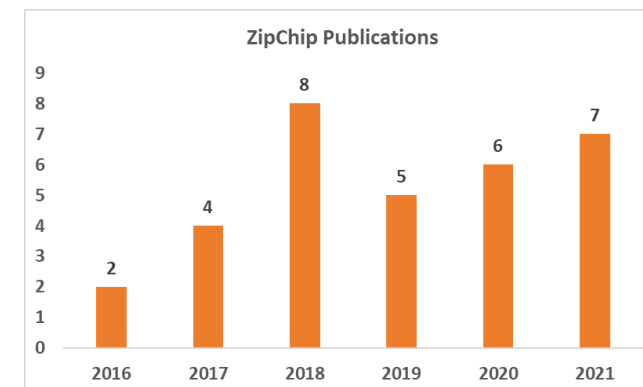
- A sample prep and automation device that leverages core capillary electrophoresis (CE) technology to expedite and simplify pre-analytical steps and is mounted onto a third-party mass spec. Compatible MS systems include popular systems like TMO's Q-Exactive, Orbitrap Fusion, and SCIEX's Qtrap.
- **Significant time savings:** Runs about 5 minutes vs. traditional 30 – 60 minutes of traditional LC method.
- Publications from Amgen [MP] and GSK [MP] highlight the platform's use in measuring critical quality attributes (CQAs) of protein products at a faster speed and with comparable quality relative to traditional LC-MS.
- As of 2Q21, MASS has placed 168 ZipChip interfaces.
- MASS recently hired Dr. Will Thomas from the Duke Proteomics Core Facility as Principal Scientist to adapt ZipChip to proteomic applications.

Total Revenue: \$41M (FY21E)



| MASS Key Metrics |         |
|------------------|---------|
| Market Cap       | \$1,006 |
| 2022 Revenue     | \$52    |
| 2022-2025 CAGR   | 17%     |
| Operating Margin | N/A     |
| 2022 EPS         | N/A     |
| EPS Growth       | N/A     |

(\$M) except EPS



Source: Company filings, SVB Leerink Research

## Other Mass Spec Offerings Levered to Proteomics

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DHR, 7701-JP (Not Rated)

- **SCIEX (DHR)**

- **MS Instrumentation**

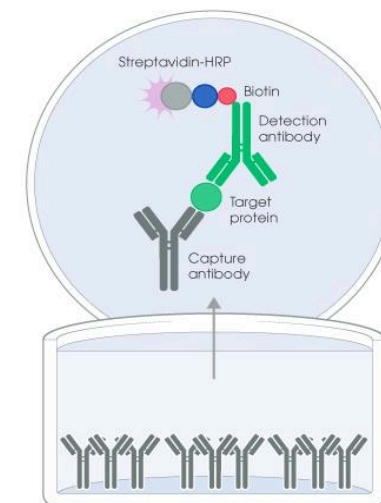
- Wide range of mass spec options including Triple Quads, Q-TOFs, MALDI-TOF, Single Quads, Ion Trap with integrated LC and software workflows
    - Market leading position in Triple Quads, which serves key end markets like biopharma, diagnostics, and academic labs
    - The new ZenoTOF 7600 system features a Zeno trap for 5-20x greater sensitivity and electron-activated dissociation fragmentation to tune experiments for intact and PTM protein analysis
    - The Triple Quad 7500 system has a 4x improvement in quantification sensitivity relative to the previous generation instrument and covers a dynamic range of 6 logs
    - DHR management expects SciEx to grow revenue MSD+, with 40% of growth coming from new product lines

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# Antibodies and Immunoassays

## Existing Methods: Immunoassays

- **Immunoassays** is a category of bioanalytical method that depends on interaction between an antigen and antibody. The test is designed to detect a specific protein target or antigen. The technique has been around for decades and is widely used in both research and diagnostics today.
  - The most common method is **ELISA**, which typically uses a capture antibody and reporter enzyme to detect the target protein.
- The main vendors for research use only (RUO) ELISA assays or instruments are Biotechne, AbCam, Luminex (now Diasorin), Quanterix, MSD [Not Rated], Gyros (Mesa Labs) and Millipore Sigma among a few others. Among diagnostics, companies with immunoassays mostly for commercial diagnostics, the line-up includes Abbott [MP, Antalfy], Roche [Not Rated], Diasorin [Not Rated] and Siemens [Not Rated].
- Due to the **repeatability and consistency of immunoassays**, there are widespread healthcare applications including Dx, biopharma studies, PK studies, therapeutic development, biological research experiments, and food safety.
- **Ease of use, cost per sample, and system cost** are key and much more favorable compared to mass spec leading to more adoption in “routine” applications.
  - Immunoassays are mostly used in targeted applications and less frequently in exploratory mode. Immunoassays do not have the depth or flexibility in analytical power compared to a mass spec and can only multiplex up to 50 targets at time (most are under 10 targets).
  - A major drawback to immunoassays is **off-target effects** or non-specific binding experienced with some assays and particularly when the assay is multiplexed.
- **Antibodies form the Achilles heel of immunoassays** and are the core component to the success of these assays benefitting supplier such as Biotechne and Abcam.



## RUO Antibodies and Reagents: The Picks and Shovels of Proteomics

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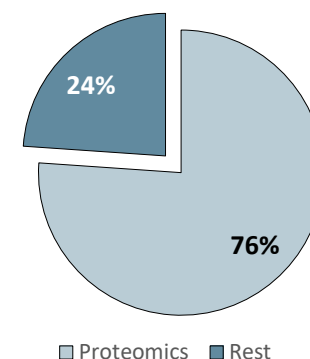
- **Antibodies** are highly specific proteins created by the immune system that only bind to one or a few select areas on a protein (known as the epitope). This specificity makes antibodies ideal for targeted proteomics applications (i.e., ELISA, western blot, spatial biology and flow cytometry), where the presence of specific proteins is being analyzed.
- **We expect leading RUO antibodies catalogs to grow high-single digits with prior estimates of the market growing at mid-single digits.** We expect to see market leaders seeing even higher growth as contribution from proteomics applications brings more business to antibodies suppliers. TECH is expecting a conservative 9% – 11% growth in its RUO antibodies business. Also, it is important to note that RUO antibodies is a 70% gross margin business – something we believe the leading RUO antibodies companies will only enhance.
- **Antibodies are valued for their high specificity** and ability to “pull down” a select target protein or molecule of interest – a feature that is impossible to match with any other technologies in life science tools. Given the sheer number of targets or antigens, the number of antibodies has soared across the industry with nearly 1M antibodies being used today. But these antibodies range from fewer high quality to a large number of low-quality ones in the market.
- Though the **RUO antibodies market is highly fragmented**, large vendors including Abcam, Biotechne, Thermo Fisher, Cell Signaling [Not Rated] and Biolegend form the largest chunk of the market (nearly 75%) with the rest of the market being significantly fragmented and lower scale. Also, there is an increasing but slow shift from polyclonal antibodies to monoclonal among the suppliers.
- **Breadth and quality of the antibody catalog provides a strong competitive moat for suppliers.** With thousands of products available, many antibody suppliers act as one stop shops. Validating antibodies and ensuring that they only bind to the target protein takes investment and time, making trusted suppliers and their products attractive. Once an antibody is launched on the market and is recognized as a quality antibody clone that is used in a number of protocols and papers, it tends to provide an annuity like steady revenue stream.
- **Royalty stream adds to the existing competitive moats** - Antibodies catalog companies also have OEM supply agreements or receive royalties for these antibodies used in the customer test kit.
- **Proteomics experiments need validation** - be it mass spec or high plex proteomics requires validation via antibodies after the initial discovery phase – thus driving meaningful revenue for RUO antibodies suppliers.

## Biotechne (TECH): Most Well Positioned to Benefit from Proteomics

### TECH (OP; PT \$575)

- Biotechne is most levered to proteomics, in our view, with proteins being core to the company (75% of the business) and a catalog of >425k antibodies. Proteins and Proteomics is central to TECH, and the company is well recognized for its leading position in all things proteins when it comes to early-stage discovery and pre-clinical research. These products include its RUO antibodies, cytokines and high-value reagents that garner 70%+ gross margins and are recurring. We view TECH as a high-growth research tools engine consisting of 80%+ consumables business that is positioned to drive growth in key end-markets of preclinical discovery, Proteomics, cell and gene therapy, and liquid biopsy markets longer term.
- RUO Antibodies and Proteins**
  - Bio-Techne is one of leading providers of research use only (RUO) antibodies for researchers through R&D systems and Novus Biologicals. The catalog consists of >425k antibodies (both poly and monoclonal) under these brands.
  - TECH's antibodies are used for standalone experiments but also the content inside automated platforms including Luminex, TECH's Ella, Nanostring, spatial and other emerging high-plex systems such as OLK.
  - We expect TECH to benefit as "Intel [Not Rated] Inside" for emerging high plex platforms such as OLK where its already supplying nearly half of the antibodies on that platform.
  - With the expanding biopharma, academic and the emerging next-gen proteomics markets TECH is expected to yield mid- to high-single-digit growth in its core proteins (Abs, cytokines, consumables) and sustained mid- to high teens growth in its unique Simple Plex and Protein Simple platform.
  - TECH recently reported that **90% of the Simple Western boxes were sold without a demo**, signifying the broad awareness of the product in the labs and among researchers. Recall that protein western is a labor-intensive application that was automated by the Simple Western platform.
  - GMP Proteins for Cell & Gene Therapy** - Most important and a high growth area is GMP Proteins – a business which is only \$10-20M today but holds potential to be \$200M-300M in the next 5 years.

Total Revenue: \$916M (FY21E)



| TECH Key Metrics     |          |
|----------------------|----------|
| Market Cap           | \$21,145 |
| 2022 Revenue         | \$1,080  |
| 2025 Revs (LT guide) | \$1,709  |
| Operating Margin     | 39%      |
| 2022 EPS             | \$7.72   |
| EPS Growth           | 21%      |

(\$M) except EPS

# Biotechne (TECH): Most Well Positioned to Benefit from Proteomics

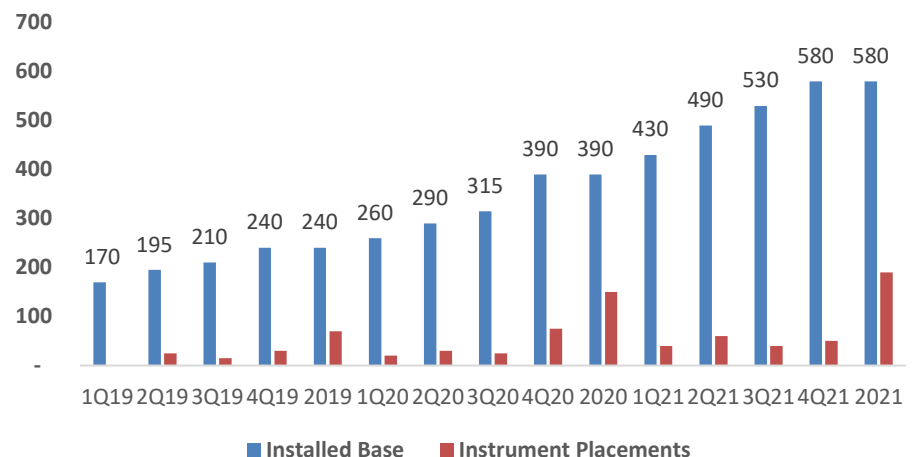
TECH (OP; PT \$575)

## Analytic Instruments

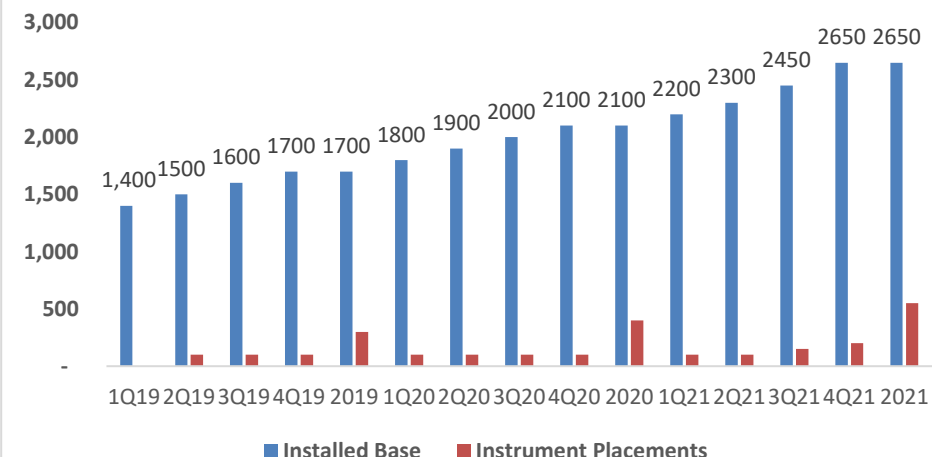
- Although only 10% of sales come from instruments, TECH's instrument portfolio automates major proteomic techniques and is projected to have a 17% CAGR FY21-26.
  - Simple Plex (Ella):** Automated ELISA instrument that can multiplex up to 8 targets and is very cost effective.
    - As of FY21, pull-through is ~\$25K, about 50% of instrument price (~\$50k).
    - TECH is making efforts to expand Ella into diagnostics and cell and gene therapy applications.
  - Simple Western:** The systems automates the traditionally laborious Western Blot experiment.
    - In FY4Q21, 90% of Simple Western sales didn't require a demonstration.
    - Provides two offerings: lower-cost Abby for academic customers and premium Jess for pharma customers.



Simple Plex Instrument Install Base



Simple Western Instrument Install Base



Source: Company filings, SVB Leerink Research



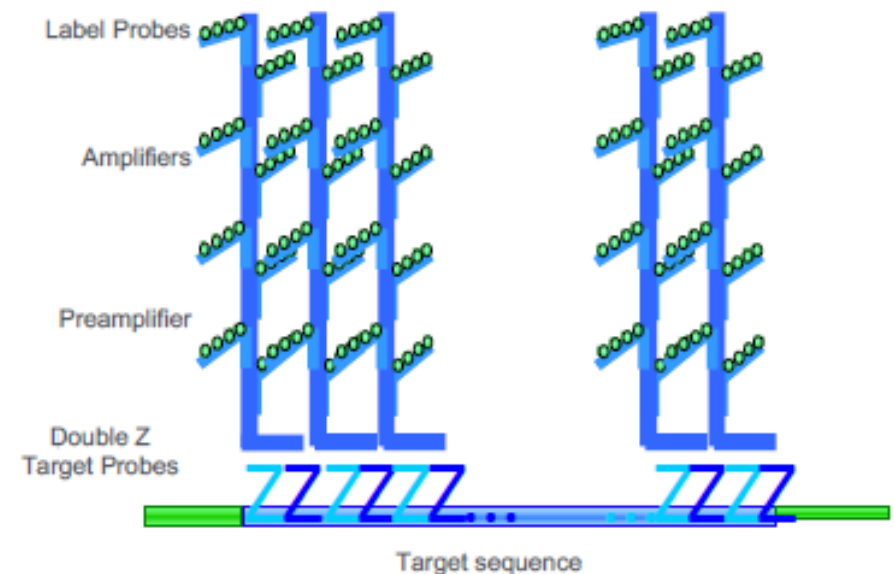
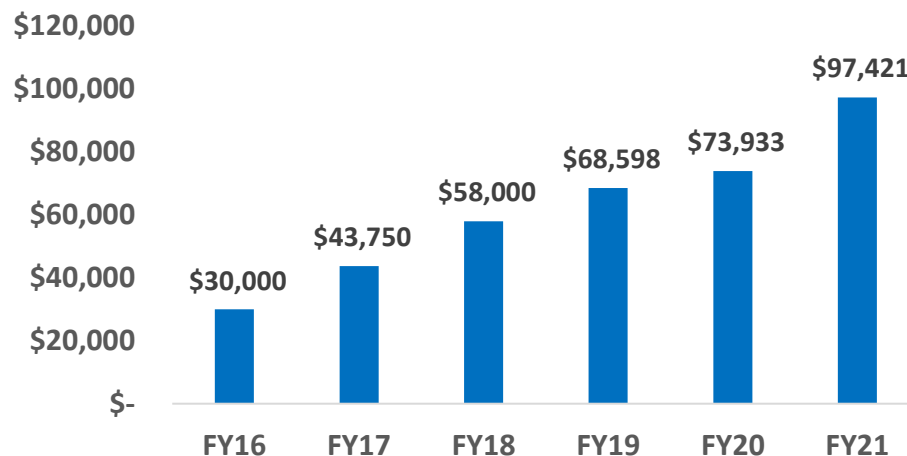
## Biotechne (TECH): Most Well Positioned to Benefit from Proteomics

TECH (OP; PT \$575)

### ▪ Spatial Biology

- TECH entered the spatial biology market with the 2016 acquisition of ACD for \$250M.
- The spatial biology business is ~5% penetrated in a \$1-2B market (company estimate) and TECH expects company revenue to grow 20-30% as the overall market expands to \$4-5B.
- ACD can analyze up to 48 analytes with single cell resolution in any tissue sample type.
- TECH currently operates in the translational research space, where the aim is to validate known targets at mid-plex. The company is looking to expand to the clinical Dx space in the next five years.
- ACD technology uses pairs of Z-shaped probes that bind to the target. Then L-shaped scaffolds bind onto the probes, but only if there is a pair on the Z-shaped probe. This scaffolds supports fluorescent tags that spatially map the targets.

### Estimated ACD Revenue

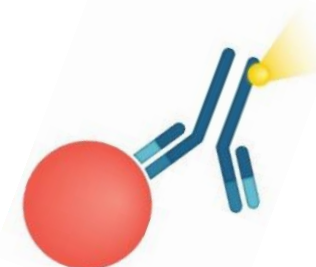
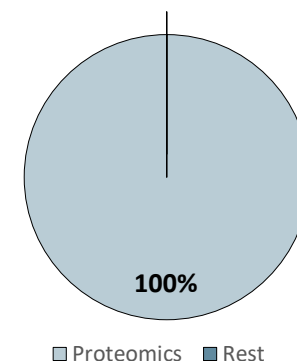


# Abcam (ABCM) – Proteomics at Its Core with Leading Position in RUO Antibodies

ABCM (OP; PT \$25)

- Abcam is a leading provider of research use (RUO) antibodies that is expanding into near-adjacencies of proteomics and high value life-science reagents to deliver targeted £450-500M in revs by FY2024E from just £323M today. **See our ABCM Initiation here (LINK).**
- RUO Antibodies – High Quality Monoclonals**
  - ABCM is a market leader in RUO antibodies with widest product catalog in the industry composed of 100k products and over 300k SKUs. The company has more higher quality monoclonal antibodies and the mix of monoclonals to polyclonal is slowly shifting towards monoclonals as they deliver higher quality and specificity.
  - We estimate ABCM has leading share at ~20% of total market and is more skewed to the academic labs. Recall, top 5 players in RUO antibodies have 75% of market. RUO antibodies are high margin products (~70% GM) with an opportunity to elevate that to 80% for in-house products – with ABCM working to reach that gross margin longer term.
- Antibody Labelling and Conjugation – Further Expansion into Proteomics**
  - Lightning-Link® from Expedeon (a proteomics company) allows customers to easily add > 45 labels to antibodies. These labels include dyes, oligos, and fluorescent proteins. ABCM acquired Expedeon for 120M Euros in 2020. Up to 80% of ABCM customers label their antibodies, and the company plans to extend the technology into metal and oligo labelling.
  - ABCM also announced exclusive rights for BrickBio's [Not Rated] recombinant technology in research and diagnostics provides an internal solution for conjugating a second molecule to an antibody.
- Dx & Drug Development**
  - The company is also pursuing the clinical market by leveraging antibody expertise to help develop Dx and therapeutic products with commercial partners in both areas. As we highlighted earlier, the potential for proteomics Dx remains underappreciated today but is likely to be a major theme in the longer run with antibodies being plugged into the assays – driving the scale needed in the longer run.

Total Revenue: £300M (FY21E)



| ABCM Key Metrics     |         |
|----------------------|---------|
| Market Cap           | \$4,699 |
| 2022 Revenue         | \$521   |
| 2025 Revs (LT guide) | \$670   |
| Operating Margin     | 15%     |
| 2022 EPS             | \$0.37  |
| EPS Growth           | 21%     |

(\$M) except EPS

# Abcam (ABCM) – Proteomics at Its Core with Leading Position in RUO Antibodies

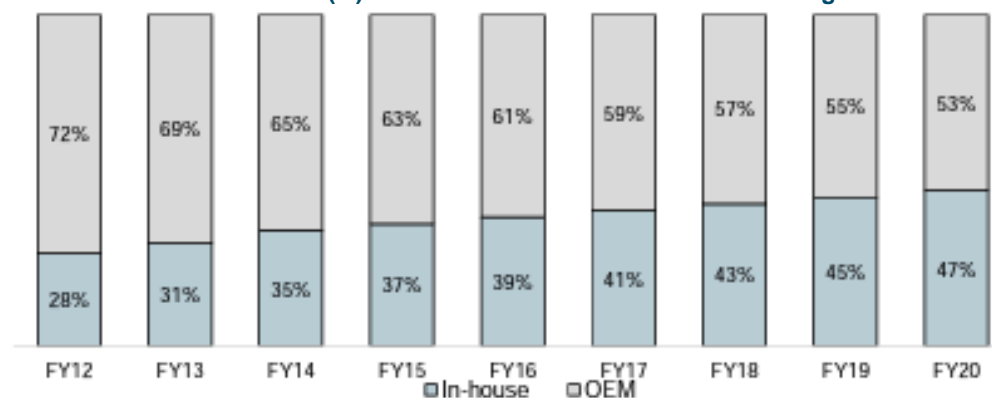
ABCM (OP; PT \$25)

- Abcam is differentiated in four key areas, in our view, driving share gain and revenue growth with researchers and labs: 1) Product breadth and quality, 2) Data Analytics, 3) Brand Leadership, and 4) Robust Validation

## Product Breadth and Quality

- Abcam has extensive product quality assurance programs ongoing, has altered manufacturing processes to become more reliable and consistent, and has ongoing quality management of OEM products offered in their product menu. Abcam also has industry-leading data with the most antibody knock-out validations on the market at over 3k. Abcam continues to shift from 3rd party providers to in-house products driving margin expansion with additional upside acting as a long-term tailwind.

Revenue Contribution (%) of In-House vs. OEM Revenue to Catalogue Revenue



## Data Analytics

Source: Abcam

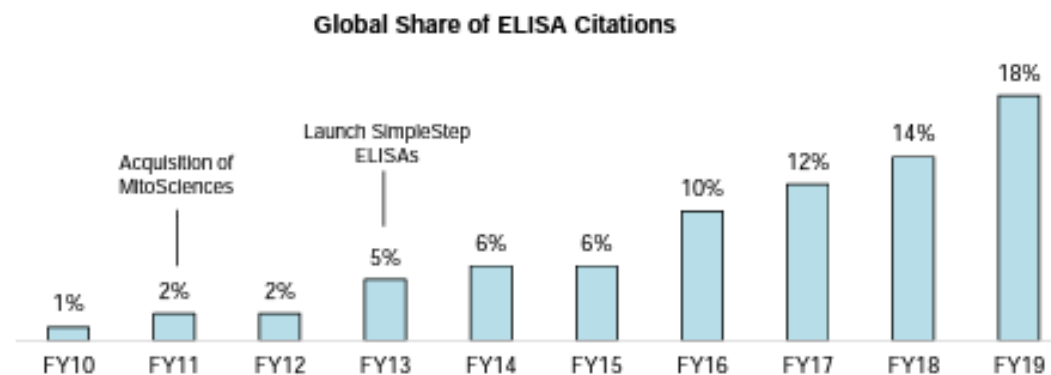
- Abcam was one of the first antibody providers to have a strong online presence beginning in 1998. Their e-commerce solution allowed customers to easily browse through products, view validation data, and purchase their orders online. Abcam's search engine optimization (SEO) efforts have led to increased traffic to the site over the years. Abcam holds the top web search position for approximately 10k of the leading primary antibody search terms and appears on the first page in approximately 1/3 of searches as compared to 20% for the next closest competitor. Abcam has accumulated over 20 years of digital data from over 20 external and internal data sources including 448k product updates from customers and systematic analysis of clinical trial data. Abcam's predictive analytics software can leverage these data to generate insights into product development.

# Abcam (ABCM) – Proteomics at Its Core with Leading Position in RUO Antibodies

ABCM (OP; PT \$25)

## ▪ Brand Leadership

- Brand recognition is important for not only acquiring new customers but driving repeat ordering within the existing customer base. The most effective marketing in the antibody industry is research citations. Researchers will go through previously published research where the authors cite the supplies, reagents, and instruments used. Abcam's share of the global antibody research citations has grown from the mid-teens in 2012 to almost 25% in 2019 while the share of citations from the aggregate next five competitors declined 15 points from roughly ~75% to ~60% today. In ELISA immunoassays, we've seen a similar increase from a lower base of ~1% in 2010 to ~18% in 2019 added by the launch of Abcam's SimpleStep ELISA product in 2013. Importantly, citations tend to be lagging indicators of market share gain as the research work is done 1-2 years before the final data are published.



Source: Abcam

Note: Exact percentages are approximated based on chart provided by Abcam

## ▪ Robust Validation

- Abcam spends considerable effort in high quality validation of its antibodies. Abcam's validation data are robust with knock-out validation and employ multiple methods of validating their products. Validation data and the lineage (how the antibody was made) are both crucial supporting elements to any RUO antibody product. Researchers want to know the antibody produces consistent and high-quality results – and is highly reproducible. Pricing pressure is not common in the industry as a researcher is not going to sacrifice quality (and time) to save a price on antibodies or reagents that might not be productive. The data integrity and time spent are more valuable to the customer. In our conversations with management and MEDACorp KOLs, we learned Abcam maintains premium price in the market given its brand reputation and breadth of supporting validation data.

## Other Antibodies, Reagent Companies

PKI (NC), Cell Signaling Technology (Private)

- **BioLegend (acquired by Perkin-Elmer, PKI)**

- Acquired for \$5.25B, ~14x 2022 forward 2022 \$380M sales, with a mid-teens revenue CAGR projected onward.
- Biolegend is recognized for its flow-cytometry antibodies. High margin, highly recurring revenue for research products.
- Combined with PKI's RUO portfolio, creates a ~700M (2022E) revenue business with low double-digit growth.
- >1K products introduced annually for applications spanning flow cytometry, immunoassays, and recombinant proteins.
- San Diego facility to become the PKI's Center of Excellence in research reagent development.

- **Cell Signaling Technology**

- According to CiteAb, Cell Signaling (CST) distributes 37 of the 100 top cited antibodies in 2020. Though that is not a complete reflection of its market share (as biopharma is not adequately represented), it does provide a view into the strong presence of CST's antibodies in the market.
- CST's Entire portfolio is designed and manufactured in-house, and the company offers a resource called PhosphoSitePlus that offers information and tools used for PTM analysis of proteins.

## Quanterix Corp. (QTRX)

### QTRX (OP; PT \$70)

- We remain OP on QTRX with a view that the company is delivering a conservative 30-40% revenue CAGR profile and deriving more than 50% of its revenues from biopharma customers that are willing to pay a premium for QTRX's improved sensitivity.
- **Simoa**
  - QTRX's Simoa technology delivers 100x-1,000x more sensitive protein and nucleic acid biomarker measurements vs traditional immunoassays.
  - Mostly used in Neurology clinical trials to detect lower abundance proteins in plasma.
  - Slightly over 50% of customers are CRO/Pharma and the rest are academic.
  - The company replaced a large fleet of its older HD1 instruments with updated HD-X, that is expected to drive more utilization among the install base.
  - Uniquely positioned to benefit from clinical trials ramp up for Alzheimer's Disease as biopharma companies look to use blood based non-invasive detection of AD in clinical trials.

### ▪ Clinical Development

- QTRX core revenue growth and long-term outlook depends on participating in the growing base of neurology clinical trials across Alzheimer's, Parkinson's, Multiple Sclerosis and other indications. We remain confident that Simoa's superior sensitivity should continue to gain and edge over the competitors in the clinical trials.

### ▪ Nf-L Antibody

- QTRX acquired an antibody supplier Uman Diagnostics, the leading developer of Nf-L antibody clone that is preferred in multiple experiments.
  - Nf-L is emerging as a key biomarker in Neuro diseases including Alzheimer's, MS, and Parkinson's disease.
- Several collaborations with leading Clinical Dx companies (Abbott, Siemens) brought their Simoa technology to clinical diagnostics for Neuro health.

Source: Company filings, SVB Leerink Research



| QTRX Key Metrics |         |
|------------------|---------|
| Market Cap       | \$1,935 |
| 2022 Revenue     | \$124   |
| 2022-2025 CAGR   | 26%     |
| Operating Margin | N/A     |
| 2022 EPS         | N/A     |
| EPS Growth       | N/A     |

(\$M) except EPS

## Other Immunoassay Instrument Providers

LMNX (Not Rated), MSD (Private, Not Rated), MLAB (Not Rated)

### ▪ Luminex (part of DiaSorin)

- Uses micrometer beads dyed with a mixture of two-three dyes to create a collection of color-coded beads that can each code for a single analyte in the sample.
- Microbeads are incubated with the sample and use sandwich ELISA to capture proteins. The beads are sent through a flow-system, where a laser excites the bead dye and a fluorescent tag on the captured sample to determine the presence and identity of a protein.
- The flow-based system allows results in as little as 20 min and microbeads can multiplex up to 100 proteins.

### ▪ Gyros Protein Technologies (part of Mesa Labs)

- CD immunoassay format uses centrifugal and capillary force to precisely control the sample flow, eliminating the need for incubation and shortening run time, making it possible to collect 112 data points per hour per CD.
- The nanoliter scale fluidic system on the CD reduces interference from other proteins in complex samples (i.e., blood), reducing the need for sample pre-treatment and extending the dynamic range to 6 logs.

### ▪ Meso Scale Discovery

- Uses electrochemiluminescent labels on detection antibodies to bind on proteins captured on a MULTI-ARRAY plate, which includes an array of capture antibodies for up to 10 analytes.
- A current is applied to excite the label and an image is captured and analyzed to quantify proteins.
- MSDs instruments can analyze 1 96 well plate in 1-2 min, enabling high throughput analysis of samples.

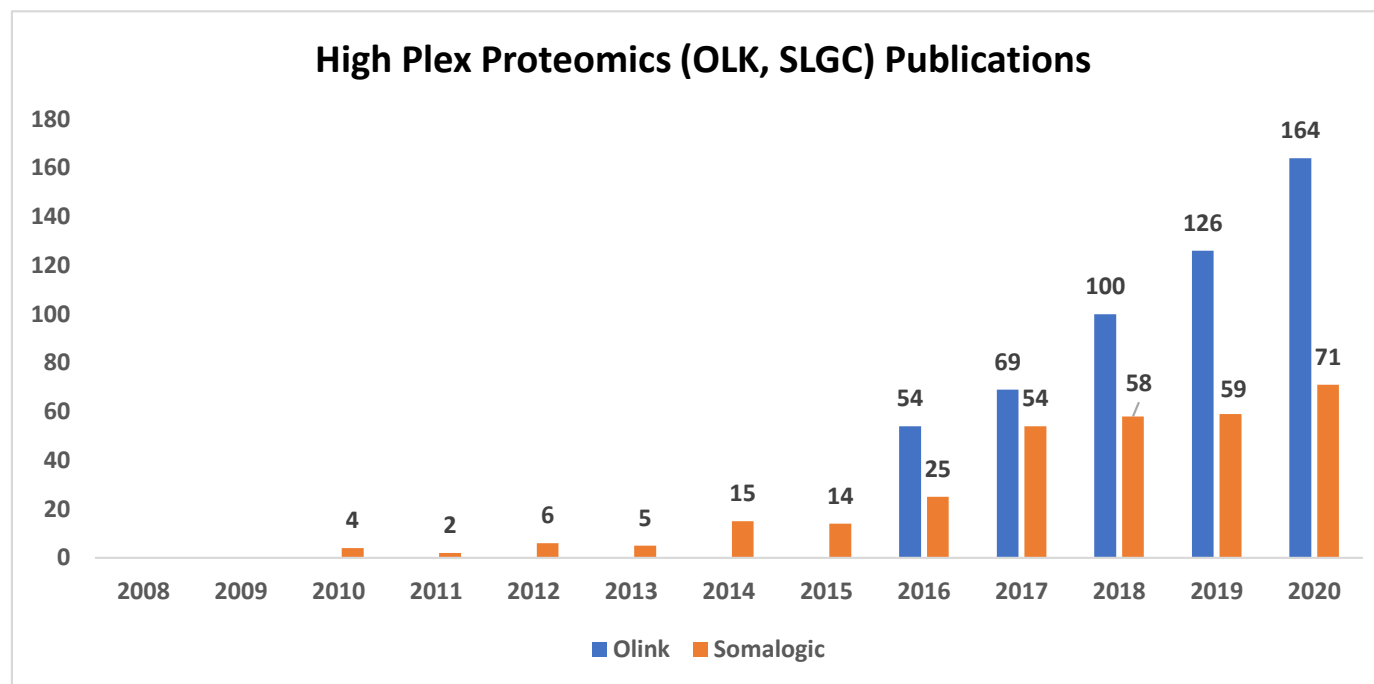
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# Emerging Method: High-Plex Proteomics



## New Kids on The Block: Driving High Growth with High-Plex Proteomics

- **High-Plex Proteomics** encompasses technologies that can accurately and reproducibly detect and measure 100s of proteins to several thousand in a single sample and a single experiment. In our view these technologies are the protein equivalent of the DNA microarrays. Recall that DNA microarrays provided insight into gene expression prior to the growth in NGS.
- Two emerging high growth technologies from Olink and Somalogic are serving this market. One can detect 20 – 3,000 proteins in the case of Olink and 7,000 in the case of Somalogic in 24 – 48 hours, which is already superior to what mass spec is delivering in terms of the list of proteins in a peptide mapping experiment.

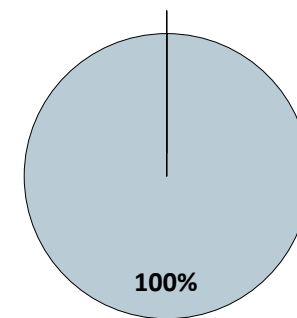


# Olink Proteomics (OLK): Applying Antibodies and NGS for a Higher Plex

OLK (OP; PT \$50)

- We remain OP, as we believe OLK is leading what we view as the next massive growth market in LST: Proteomics. Olink’s elegant and clever PEA technology delivers highly multiplexed protein panels that leverage genomics to solve Proteomics in ways not seen before. **See our OLK Initiation here [\(LINK\)](#)**

Total Revenue: \$93M (FY21E)



Proteomics Rest

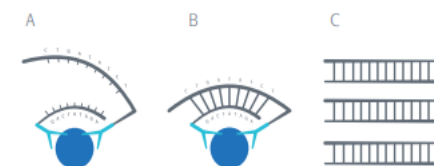
## Proteomics Exposure

### High-Plex Proteomics

- Olink is pioneering an entirely new area of Proteomics: high plex proteomics. With PEA technology, OLK can measure up to 3k proteins in a single run.
- With Explore product line, Olink plans to develop assays that can measure up to 10k proteins. Recall we estimate there are only 10k -12k proteins in human plasma proteome.

### PEA Technology is a Clever Way to Measure Proteins

- Proximity Extension Assay (PEA) uses a dual antibody approach and DNA hybridization event to generate a signal that is readout by PCR and NGS.
- Two antibody binding events instead of one increases specificity while Olink is also leveraging the signal amplifications of next-gen sequencing and PCR.



### Large Application Set

- High plex and high throughput. Proteomic can finally enable very large population style experiments such as the UK Biobank project where OLK plans to run 56k samples for the project.
- Biopharma Drug discovery and development: By covering more of the Proteome and lower abundant proteins, OLK’s tech opens up a new set of drug targets for Pharma.
- Dx Assay Development: We believe Olink’s technology will ultimately be used as a diagnostic test in clinical care – although these products require large datasets and validation before use.

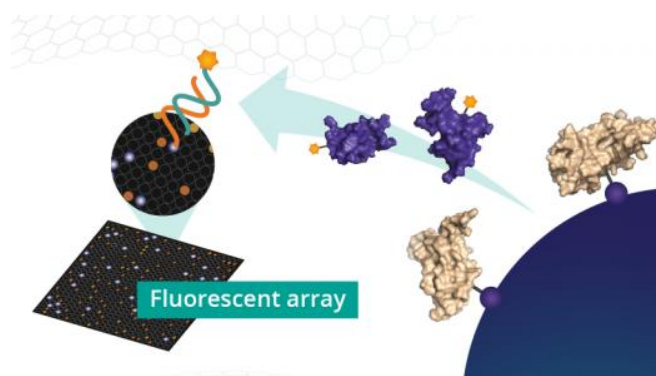
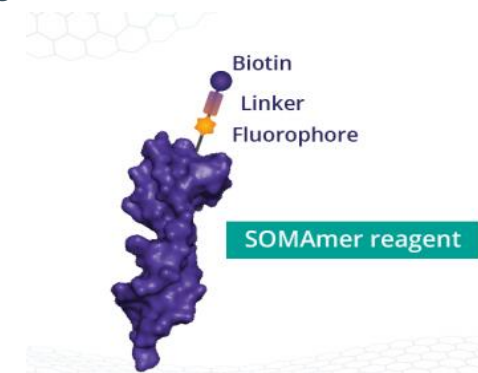
| OLK Key Metrics  |         |
|------------------|---------|
| Market Cap       | \$2,935 |
| 2022 Revenue     | \$146   |
| 2022-2025 CAGR   | 49%     |
| Operating Margin | N/A     |
| 2022 EPS         | N/A     |
| EPS Growth       | N/A     |

(\$M) except EPS

# Somalogic: Aptamer bringing higher level of “plexing”

Not Rated

- The company uses a proprietary **SOMAmer (aptamer)** reagent that bind to specific protein targets, and uses competition to prevent non-specific binding.
  - Somalogic uses an array format and fluorescent imaging to measure protein expression.
  - Aptamers are synthetic sequences of ssDNA with protein-like components for binding to proteins.
- Somalogic has built a library of over **7k aptamers** that can be used in a single assay.
  - The goal is to move to **10k proteins** and even higher over time.
  - Expanding into panel offerings that include **~900 biomarkers**, with the option to get access to the remainder of the data for the 7K biomarkers.
- Our MEDACorp KOLs indicated **adoption was muted in early years** due to Somalogic’s business model which demanded the researcher forfeit the intellectual property of the discovery conducted via proteomics.
  - The company have **pivoted** to a more open access model in recent times. Also focused on developing clinical assays.



| SLGC Key Metrics |         |
|------------------|---------|
| Market Cap       | \$2,313 |
| 2022 Revenue     | \$100   |
| 2022-2025 CAGR   | 40%     |
| Operating Margin | N/A     |
| 2022 EPS         | N/A     |
| EPS Growth       | N/A     |

(\$M) except EPS

## High Plex Proteomic Comparison

# High-Plex Proteomics

|                      | Olink                                     | SOMAscan                            |
|----------------------|---|-------------------------------------|
| # of Analytes        | 48 / 96 / 3,072                           | 7,000                               |
| Cost per Sample      | \$100 (Target) - \$500 (Explore)          | \$500 - \$700                       |
| Product Segmentation | 3 Offerings (Custom, Mid Plex, High Plex) | 1 Offering (Data subsets available) |
| Turn-around Time     | 24 Hrs – 36 Hrs (kits)                    | 48 hrs (service)                    |
| Accessibility        | High (kits, service)                      | Medium (service)                    |
| Specificity          | High                                      | High                                |
| Limit of Detection   | 4 pg/mL (100 fg/ml – 0.13 mg/ml)          | 5.3 pg/mL                           |
| Variance             | 10%                                       | 5%                                  |
| Dynamic Range        | 10 logs                                   | 10 logs                             |

## ILMN's Role in High-Plex Proteomics

- **Proteomics is a new application leveraging ILMN's SBS technology to read out sample results.**
  - Antibodies tagged with oligonucleotides play an integral role in high plex proteomics, where a specific sequence identifies a specific protein.
- **Advantages of DNA Sequencing**
  - DNA sequences can be easily amplified (something not possible with PCR) with relatively high fidelity, enabling analysis of low concentration samples and a highly parallelized process.
  - Leverages a large, pre-existing install base (~17,000 ILMN instrument installs).
  - Reduces complexity of the data from a base 20 (one for each amino acid) to base 4 (one for each nucleic acid).
- **ILMN could see upside in the longer-term from Proteomics**
  - We see ILMN benefiting from the growth in proteomics as technologies that translate protein information into DNA proliferate in the longer-term. Currently, Olink utilizes ILMN sequencers for reading its Explore kits on the back-end and we believe Somalogic could also explore using NGS as the read-out.



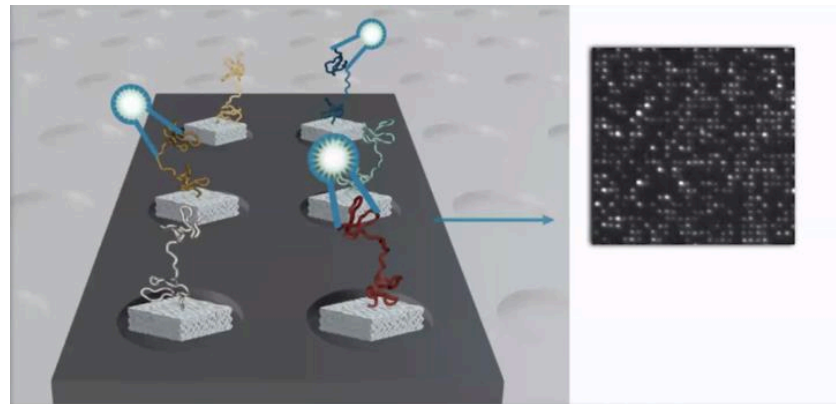
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# Emerging Technologies

# Nautilus: Single Molecule Hyperdense Array Enabling a Deeper Interrogation of Proteome

Not Rated

- Nautilus is an early-stage Proteomics company developing a **hyper dense, miniaturized protein microarray** that leverages robust data science and computational software to measure the proteome.
  - The instrument would be revolutionary and create a category of its own - **not leveraging existing methods of mass spec or NGS**. Early indications point to **\$1M ASP** and the company is expected to release data from its ongoing collaboration with Genentech [Not Rated].
  - **Most “out of the box” approach:** Nautilus approach is the most differentiated and unique among the new entrants in the proteomics market. The KOL feedback suggests NAUT to be the most out of the box approach in their view ([LINK](#) to Proteomics Series).



- The array has **10 billion landing pads** per chip, enabling single molecule resolution.
- Nautilus reagents and tagging agents are designed in-house, but company plans to encourage open-source format where researchers can leverage off-the-shelf antibodies to go after new targets.
- With each cycle that is run, the resolution of the instrument improves. The system currently under development could cover 95%+ of proteome in early experiments, vs mass spec, which only detects 8% of proteins from blood and 20-30% of proteins from tissue sample.

Source: Nautilus, Company Filings, SVB Leerink Research

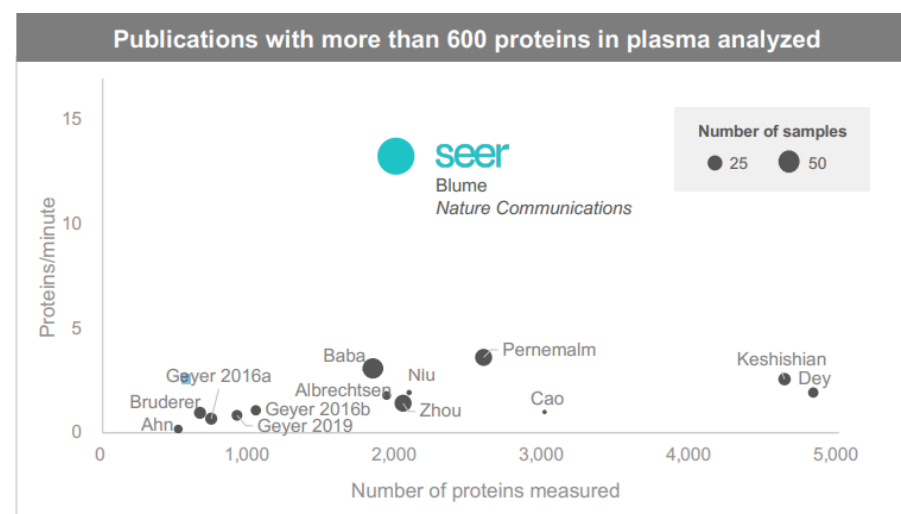
## Seer: Innovative nanoparticle technology to improve LC-MS sample prep and throughput

Not Rated

- Seer has engineered **proprietary nanoparticles** designed to seek out specific proteins for detection.
- The product suite consists of: **consumables** (nanoparticles, reagent mix), an **instrument** (for automation) and **software** for data analysis.
  - Importantly, the core “read-out” technology remains mass spectrometry vs. other modalities who are creating an entirely new read-out platform or leveraging NGS.



- Seer currently has a library of **275+ unique NPs** with a growing pipeline of particles in development.
- Leveraging mass spec workflow, Seer enables up to **48 samples to be processed in a 24-hour period**.
  - Claim to reach 2k proteins over longer experiment times. (Figure to the right)





## Quantum Si: Semi-Conductor Sequencing

Not Rated

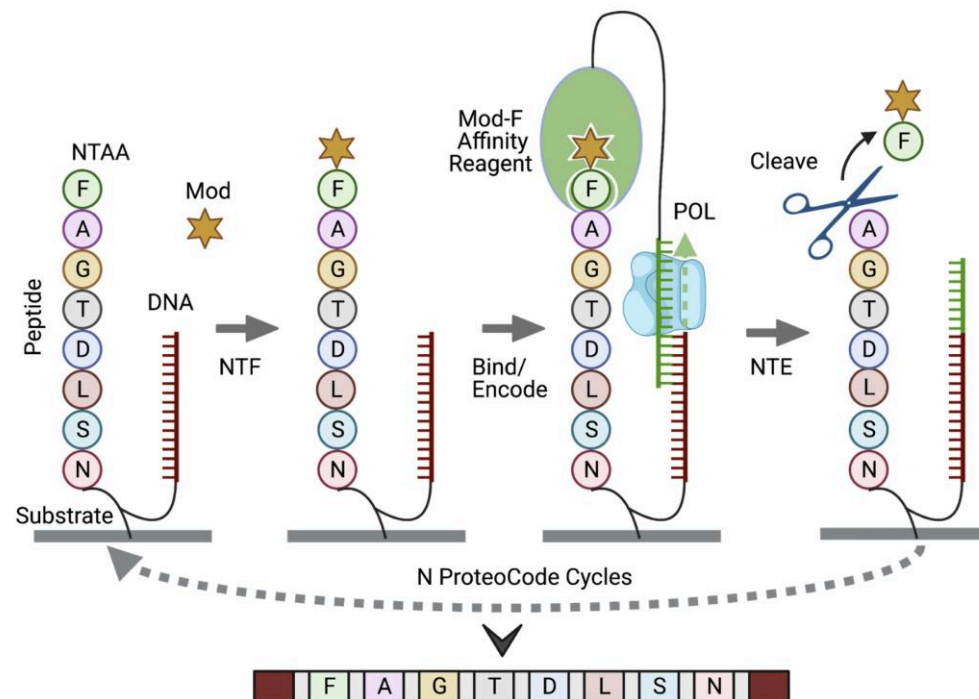
- Quantum Si leverages semiconductor-based technology to power a massive-parallel single photon counting device but we have not seen any publicly available data from the instrument. Data will be key to gaining comfort with the potential adoption in the market.
- The chip allows the user to “read” the amino acid sequence and post-translation modifications on a single molecule basis using fluorescence intensity and duration and kinetic information of the amino acid and detector protein.
- The company has developed a custom sample prep platform, benchtop instrument (the analyzer) and software offering for labs.
- The company remains in the initial stages of commercialization providing Early Access to a select few labs to build presence in the market. Quantum Si has goals of reaching over 5k instruments and close to \$200M in revenue by 2025. The company has over 550 issued or pending patents on their semiconductor technology.



# Encodia: Translating Proteins to DNA to Deliver on Protein Sequencing

Market Cap: Private; Not Rated

- Encodia is developing a **single molecule protein** sequencing technology, which determines the sequence of amino acids in a peptide.
- ProteoCode**
  - A reverse-translation technology that sequentially maps an amino acid to a DNA tag, which gets sequenced on an NGS instrument.

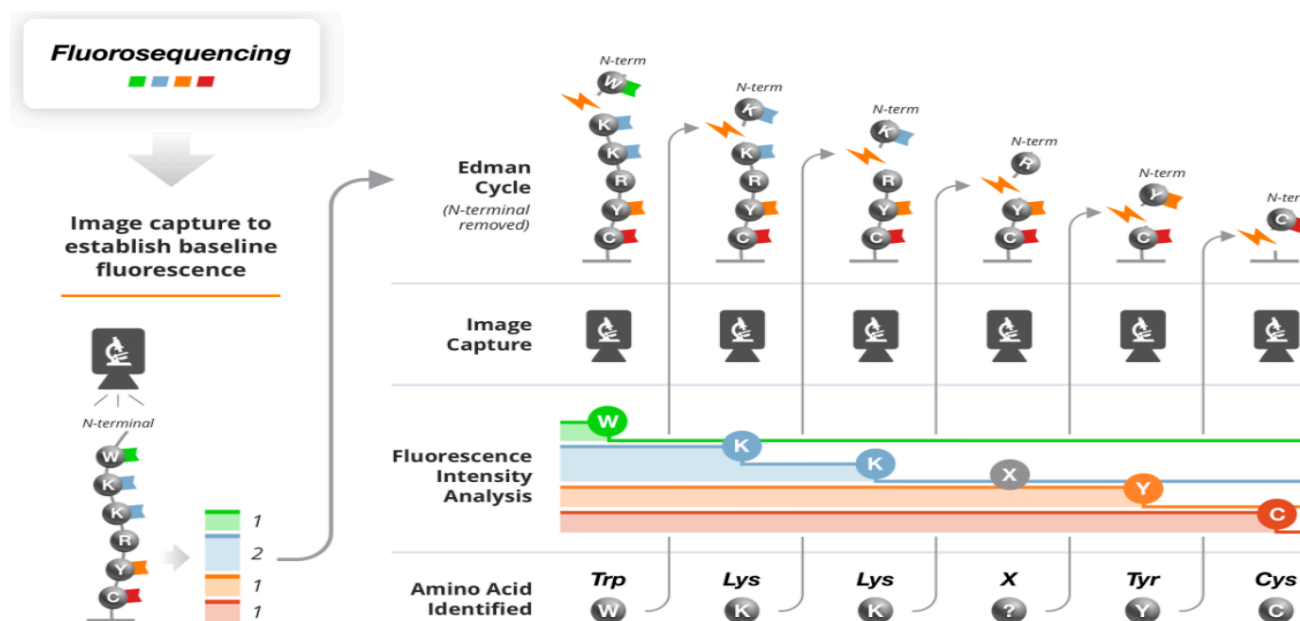


Each DNA molecule contains  $n$  barcodes, wherein each barcode identifies an amino acid.

## Erisyon: Using Fluorescence to Sequence Proteins

Market Cap: Private; Not Rated

- Erisyon is also developing a **single molecule protein** sequencing technology. Unlike Encodia, their technology is separate from the NGS workflow.
- **Fluorosequencing**
  - The amino acid sequence is determined by the **fluorescent signal of tagged amino acids**. Only four acids are tagged, since up to 95% of proteins can be identified this way when referencing a database.
  - Can absolutely quantify peptide concentration without the need of external calibrant.
  - While unable to perform “de novo” protein analysis, we see most proteomics applications looking for previously known proteins as opposed to discovering entirely novel ones.

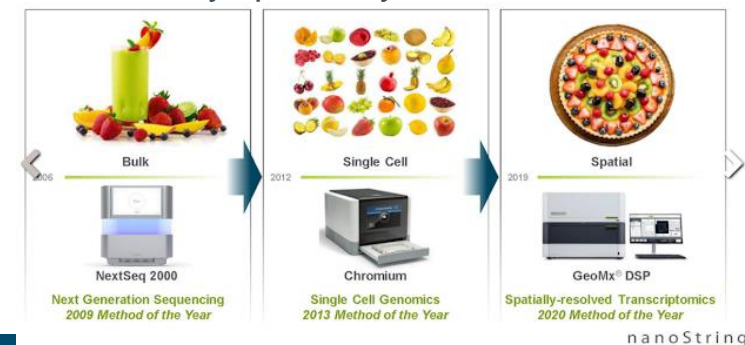
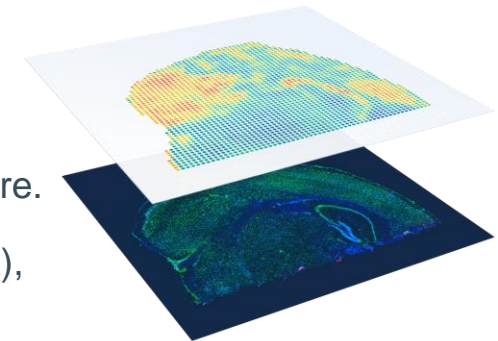


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# Spatial Biology

## Emerging Methods: Spatial Biology

- Spatial Biology is an emerging technology that interrogates not only the presence of analytes, but also its position in the tissue or the microenvironment.
  - Often targets RNA transcripts or proteins in fresh frozen or FFPE tissue
  - Resolution can range from multicellular to intracellular
- To visualize the analytes on a tissue sample, most spatial biology workflows use complementary DNA strands for transcripts or antibodies labeled with DNA or fluorophore.
- Key vendors are NanoString (NSTG), 10x Genomics (TXG), Akoya Biosciences (AKYA), Bruker (BRKR) and Fluidigm (FLDM).
- Spatial Biology is of particular interest in oncology, neurology and other research areas where spatial context of tissue heterogeneity plays an important role.
- **Antibodies** are a core part of sample prep for certain spatial biology platforms, especially in spatial proteomics.
- **Ease of use, cost per sample, and system cost** are favorable compared to mass spec, though higher than for immunoassays.
  - Limits to multiplexing are similar to immunohistochemistry, where antibody specificity and crowded signals can limit number of analytes.
  - Most spatial biology instruments require an NGS instrument which can increase upfront cost.



## NanoString Technologies (NSTG)

Not Rated

- NanoString is a mid-cap company serving the spatial markets using its transcriptome technology (GeoMx) and is poised to maintain a strong presence in spatial biology market with its transcriptomics solution that also enables spatial protein detection. Currently only 15% of NSTG is levered to proteomics and antibody-based detection.

### GeoMx Digital Spatial Profiler (DSP)

- NSTG's flexible spatial biology offering is capable of analyzing the whole transcriptome and profiling data for 100s of validated Protein analytes from up to 12 tissue slides per day in fresh frozen or FFPE tissue samples.
- Antibodies tagged with photocleaving oligonucleotide barcodes are added to stained tissue samples. Through a live view of the tissue, researchers can select a region of interest and expose the area to UV light, thus removing the barcode.
- Oligonucleotides can be analyzed on NSTG's nCounter platform or an ILMN NGS platform. Note: VCYT acquired global rights to manufacture and sell the nCounter platform.
- As of 2Q21, NSTG has installed approximately 190 GeoMx DSPs with an avg pull through of \$82K, and customers have published approximately 60 peer-reviewed scientific papers using GeoMx.



### Spatial Molecular Imager (SMI)

- NSTG's next spatial biology offering, expected to launch in 2H22.
- While GeoMx images regions containing many cells, SMI is intended to analyze up to 1K analytes from a single cell within intact tissue samples.
- SMI uses in situ hybridization (ISH) to detect and visualize biomarkers inside of the cell.

| NSTG Key Metrics |         |
|------------------|---------|
| Market Cap       | \$2,264 |
| 2022 Revenue     | \$185   |
| 2022-2025 CAGR   | 13%     |
| Operating Margin | N/A     |
| 2022 EPS         | N/A     |
| EPS Growth       | N/A     |

(\$M) except EPS

## 10x Genomics (TXG)

Not Rated

- 10x Genomics is a mid-cap company that started single cell genomics space and is moving into the spatial biology market with their Visium platform.
- Visium**
  - A sample prep solution that can detect up to the whole transcriptome and 2-3 proteins.
  - Fresh frozen or FFPE samples are loaded onto the Visium slide, which is divided into 5K barcoded regions that each contain capture probes. Cells are permeabilized to release RNA and target proteins are fluorescently stained.
  - The cell samples are then imaged, and a cDNA library is created from the probe –RNA transcript hybridization before it is sequenced on an NGS instrument.
  - TXG algorithms process the sequencing data to resolve where the transcript was captured based on a spatial barcode and unique molecular identifier (UMI).
  - High resolution platform averaging 1-10 cell resolution depending on tissue type.
  - The workflow solution was launched in 2019, with FFPE sample capabilities added in 2Q21.
  - Currently has 120 papers and preprints using the workflow.
  - Applications: 1) Gain a complete view of disease complexity, 2) Biomarker discovery, 3) Map the spatial organization of cell atlases, 4) Identification of spatiotemporal patterns.



| TXG Key Metrics  |          |
|------------------|----------|
| Market Cap       | \$17,094 |
| 2022 Revenue     | \$681    |
| 2022-2025 CAGR   | 25%      |
| Operating Margin | N/A      |
| 2022 EPS         | N/A      |
| EPS Growth       | N/A      |

(\$M) except EPS

## Akoya Biosciences (AKYA)

Not Rated

- Akoya Biosciences is a small cap company focused on spatial biology instruments in the discovery, translational and clinical research markets.
- **CODEX**
  - AKYA's discovery research platform that enables identification of >40 biomarkers in tissue.
  - Uses antibodies conjugated with a library of oligonucleotides to detect the presence and location of the desired biomarkers in a fresh frozen or FFPE tissue sample.
  - Provides single-cell resolution down to 600 nm or 250 nm depending on microscope objective used (20X and 40X respectively).
  - As of 2Q21, AKYA has placed 145 CODEX instruments.
- **Phenoptics**
  - A high throughput platform targeted for the translation and clinical research market.
  - Capable of analyzing cells in situ, fresh frozen, or FFPE and measures fluorescence markers with subcellular resolution.
  - Integrates multiplexed immunohistochemistry, imaging, and analysis to quantitatively capture systems biology data with cellular detail while retaining spatial context.
  - As of 2Q21, AKYA has placed 473 Phenoptics instruments.
- AKYA has been mentioned in >135 publications in 1H21, compared to 109 in all of 2020.



| AKYA Key Metrics |       |
|------------------|-------|
| Market Cap       | \$584 |
| 2022 Revenue     | \$69  |
| 2022-2025 CAGR   | 24%   |
| Operating Margin | N/A   |
| 2022 EPS         | N/A   |
| EPS Growth       | N/A   |

(\$M) except EPS



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# Appendix

## Glossary of Terms

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- **m/z ratio:** the mass-to-charge ratio. The measurement obtained from an MS instrument that helps identify the analyte.
- **Time of Flight (TOF):** a type of mass spec that determines the m/z ratio of ionic analytes based on differences in the time it takes for a molecule to be detected after sent through an electric field. Larger ions will take longer because their velocity is lower relative to a smaller ion for the same amount of kinetic speed.
- **Desorption Electrospray Ionization (DESI):** an imaging mass spec technique that uses microdroplets from an electrospray source that dissolved protein on a tissue sample and releases (desorbs) them into a mass spec. This allows analysis of a sample in its natural state.
- **Matrix Assisted Laser Desorption/ Ionization (MALDI):** a mass spec ion source that embeds sample analyte in a crystallized matrix, which ionizes along with the analyte when targeted by a laser beam.
- **Quadrupole-TOF (QTOF):** a type of mass spec that uses four parallel electrode rods (the quadrupole) which filter for ions with a specific m/z ratio by creating an oscillating electric field, causing all other ions to collide with the rods.

## Disclosures Appendix

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I, Puneet Souda, certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

| Rating    | Count | Percent | IB Serv./Past 12 Mos. |         |
|-----------|-------|---------|-----------------------|---------|
|           |       |         | Count                 | Percent |
| BUY [OP]  | 196   | 76.3    | 101                   | 51.5    |
| HOLD [MP] | 57    | 22.2    | 9                     | 15.8    |
| SELL [UP] | 4     | 1.6     | 0                     | 0.00    |

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**Outperform (Buy):** We expect this stock to outperform its benchmark over the next 12 months.

**Market Perform (Hold/Neutral):** We expect this stock to perform in line with its benchmark over the next 12 months.

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The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

For the purposes of these definitions the relevant benchmark will be the S&P 600® Health Care Index for issuers with a market capitalization of less than \$2 billion and the S&P 500® Health Care Index for issuers with a market capitalization over \$2 billion.

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