



INVESTMENT COMMITTEE CALENDAR SHEET
Investment Committee Meeting of November 18, 2020

To: Members of the Retirement Board

Through: Jay Huish
Executive Director

From: William J. Coaker, CFA
Chief Investment Officer

Date: November 18, 2020

Agenda Item:

Science, Technology and Innovation – Guest Speakers

Background:

Continuing with our education in science, technology and innovation, SFERS is hosting three of our existing managers for a discussion on their outlook on investment opportunities in science, technology and innovation. Our special guests for this Investment Committee meeting are:

- Mr. Cian Cotter, Managing Director at Insight Partners. Insight, founded in 1995, invests in growth-stage technology, software and internet businesses, including growth equity, capital for M&A, take-privates, pre-IPO rounds, and recapitalizations.
- Mr. David Goel, Managing General Partner and Co-Founder of Matrix Capital Management. Matrix, founded in 1999, invests in leaders in innovation across multiple sectors, primarily in technology, software, cloud computing, media, communications, and the life sciences.
- Mr. Carl Gordon, Founding Partner and Head of Global Private Equity of OrbiMed Advisors. OrbiMed, founded in 2000, is a life sciences specialist. The firm invests globally and includes public and private equity as well as health care royalties. OrbiMed invests primarily in biotech, from public equity to early and late stage venture.

Recommendation: This is a discussion only item.

Attachments: Software Market Trends Update – Cian Cotter, Insight Partners
Matrix Capital Management Update – David Goel, Matrix Capital Management
Global Healthcare – Carl Gordon, OrbiMed Advisors

Software Market Trends Update

San Francisco Employees' Retirement System
November 2020

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Data as of 6.30.2020 unless otherwise noted — Confidential and Proprietary

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Is the software market at its
peak?

There have long been questions about software valuations

Tech stock bubble warnings rise amid coronavirus rally

By Business Insider Staff Reporter
Printed Tue 11/26/20 at 11:02pm. Archived Tue 11/26 at 9:26pm

0.000	0.000	0.000							
0.425	0.430	0.430	32T	AMA GROUP	0.140	0.145	0.140		
1.092	0.094	0.000	0	AMACEUS	0.220	0.225	0.225		
1.039	0.040	0.040	9HT	AMAL HLD	6.360	6.380	0.000		
2.160	2.170	2.160	16T	AMBERTECH	0.210	0.230	0.000		
2.020	2.030	2.030	27T	AMBITON	0.180	0.205	0.000		
0.085	0.080	0.000	0	AMST CLP	70.85	88.45	0.000		

BARRON'S

MARKETS AFTER THE BELL

Tech Stocks Surged and Pumped Some Air Back Into the 'Software Bubble'

By Alexandra Scaggs July 27, 2020 6:19 pm ET



After an unusual streak of underperformance, the [Nasdaq Composite](#) kicked off the week with a rally. [Wall Street](#) is back in a bubble.

Will Tech Unicorns Finally Shed Their Sparkle in 2020? What Experts Think

By Capria Balog - 01/06/20 10:17am

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SP500 ▼ 2.13%
50.81 2,347.29

DOWJONES

DJI ▼ 2.37%

Markets

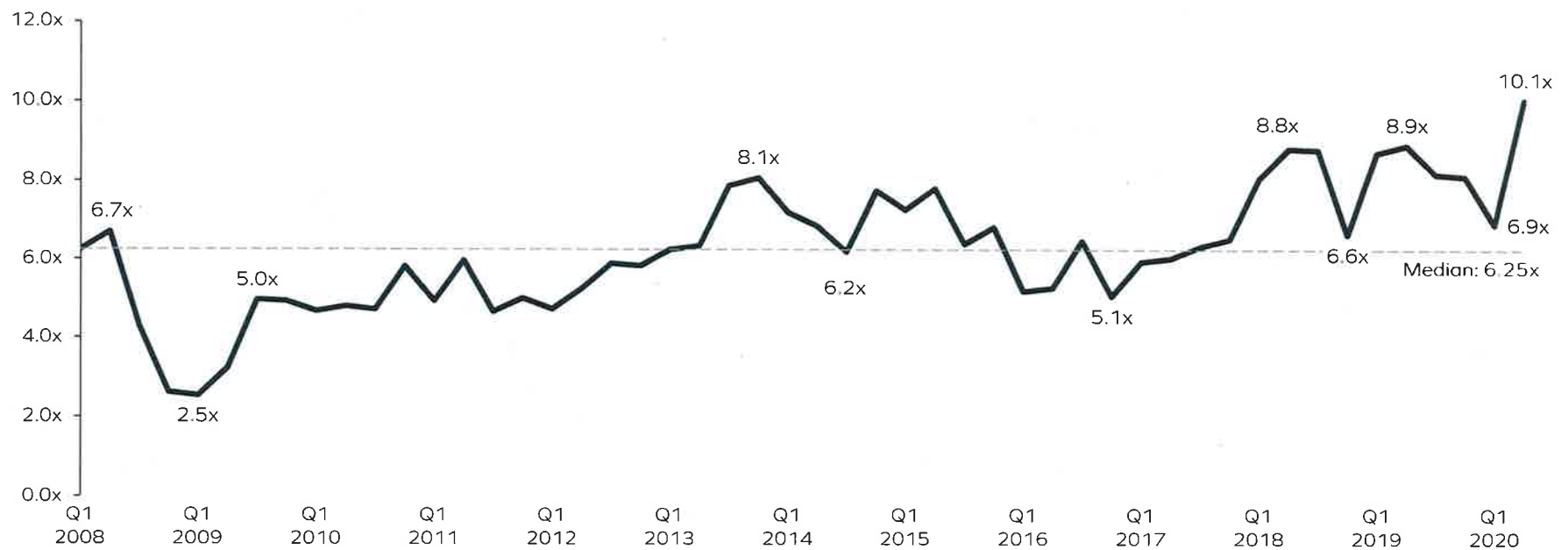
Bubble Warnings Get Louder With Nasdaq Erasing Huge Monday Rally

Photo: James - Michael - Taylor - Getty Images

SOURCE: Bloomberg "Bubble Warnings Get Louder with Nasdaq Erasing Huge Monday Rally", July 23, 2020 (<https://www.bloomberg.com/news/articles/2020-07-23/bubble-warnings-get-louder-with-nasdaq-erasing-huge-monday-rally>); Barron's "Tech Stocks Surged and Pumped Some Air Back Into the 'Software Bubble'", July 27, 2020 (<https://www.barrons.com/articles/tech-stocks-surged-and-pumped-some-air-back-into-the-software-bubble-1593311100>); Observer "Will Tech Unicorns Finally Shed Their Sparkle in 2020? What Experts Think", January 6, 2020 (<https://observer.com/2020/01/will-tech-unicorns-finally-shed-their-sparkle-in-2020-what-experts-think/>); ABC net "Tech stock bubble warnings rise amid coronavirus rally", July 14, 2020 (<https://www.abc.com/2020/07/14/tech-stock-bubble-warnings-rise-amid-coronavirus-rally/>).

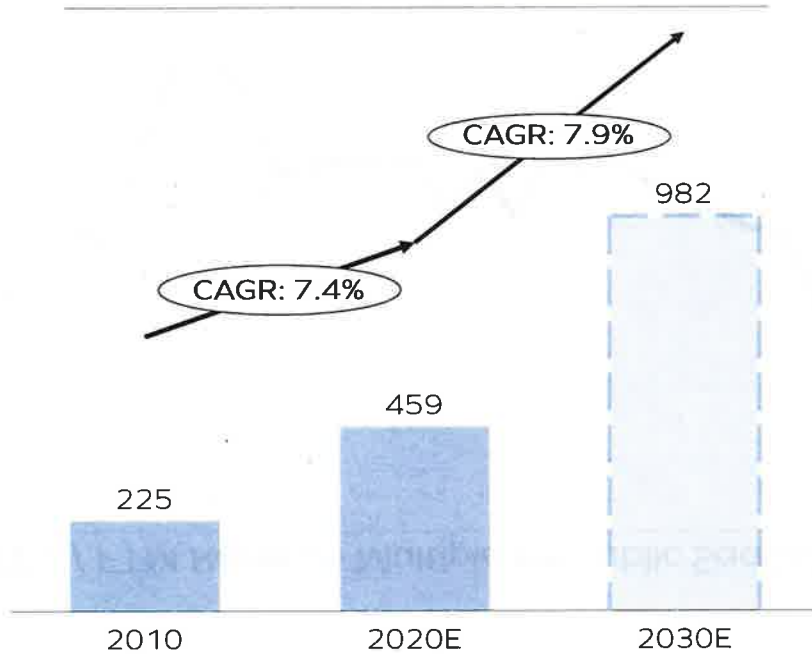
Multiples on public SaaS companies are at peak levels

TEV / FTM Revenue Multiple for Public SaaS Companies

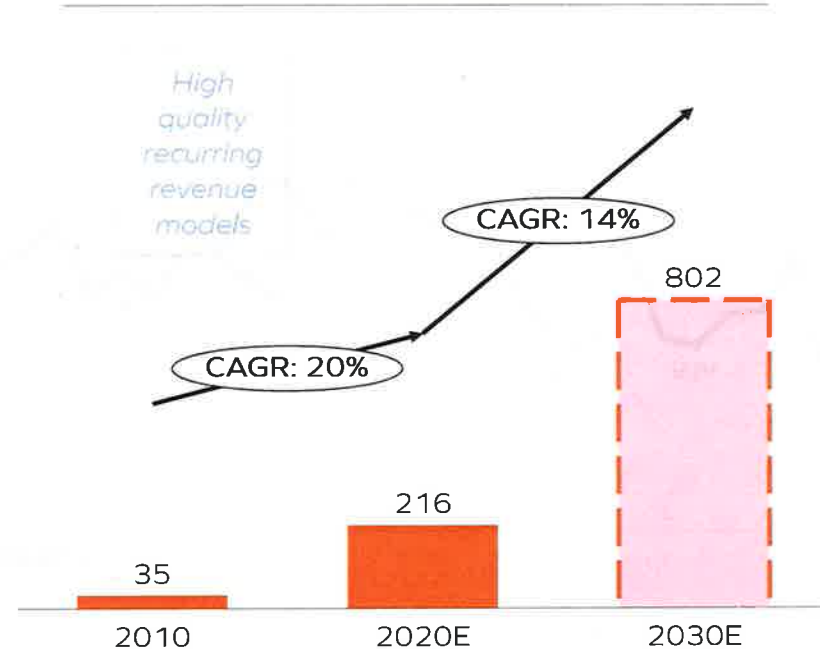


Software markets – in particular SaaS – are growing fast

Global Software Spend, *USD billions*¹



Global SaaS Spend, *USD billions*²



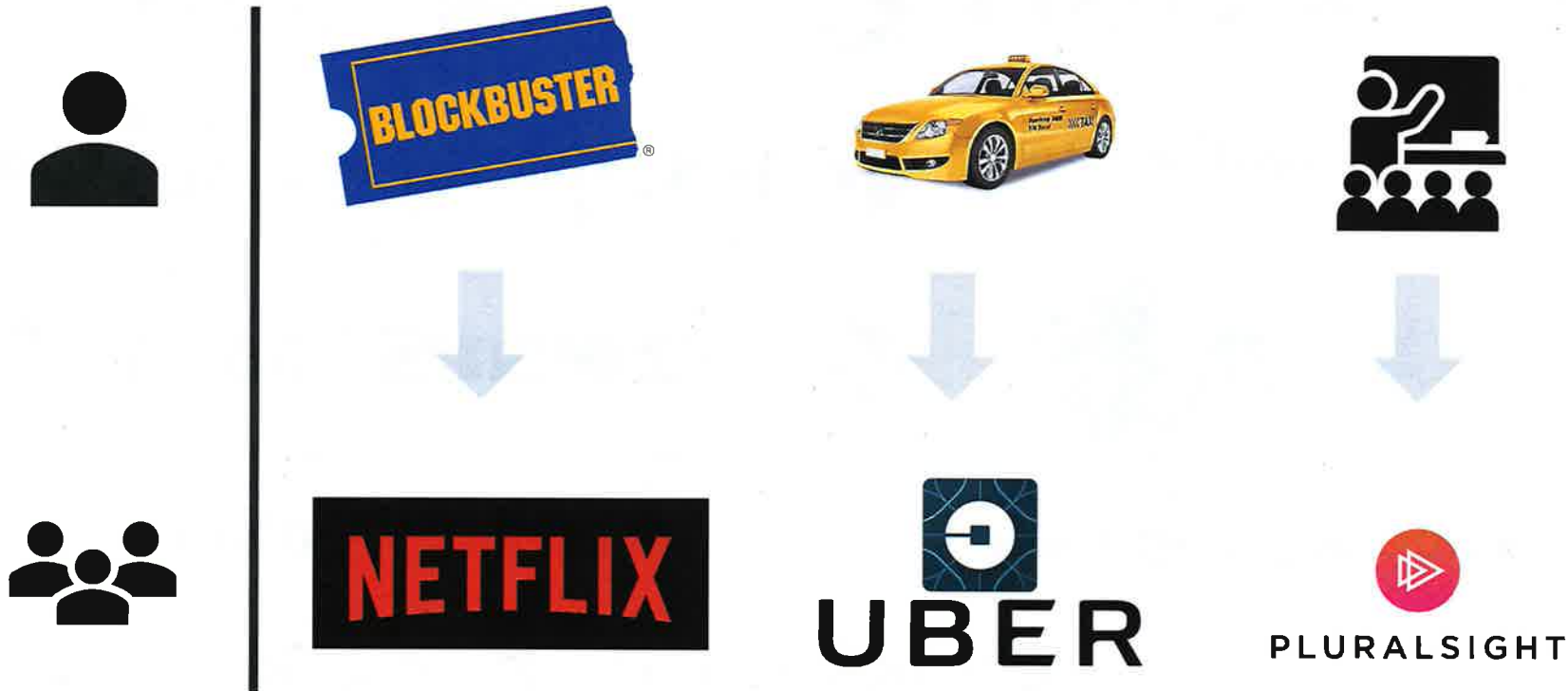
SOURCE: Gartner Market Databook, 3Q2020 and June 2009; Gartner Public Cloud forecasts in 2019 and 2011.

¹ 2030E projection based on 7.9% CAGR in Gartner projection for 2019-2024.

² 2010 estimate of \$35B from Gartner excludes Cloud Advertising; IaaS category excluded across all years; 2030E projection based on 14% CAGR in Gartner projection for 2018-2022.

Note: Certain statements presented above that are not historical facts may contain forward-looking statements regarding the intentions, expectations, objectives and targets of the relevant Insight funds. Any such forward-looking statements are based on assumptions Insight believes to be reasonable, but are subject to a wide range of risks and uncertainties and, therefore, there can be no assurance that actual results may not differ materially from those expressed or implied by such forward-looking statements.

Internet and mobile adoption driving network effects that can make markets bigger, faster



These trends are changing the growth and valuation trajectory of next gen software

Legacy Companies

(Valuation at acquisition, USD billions)

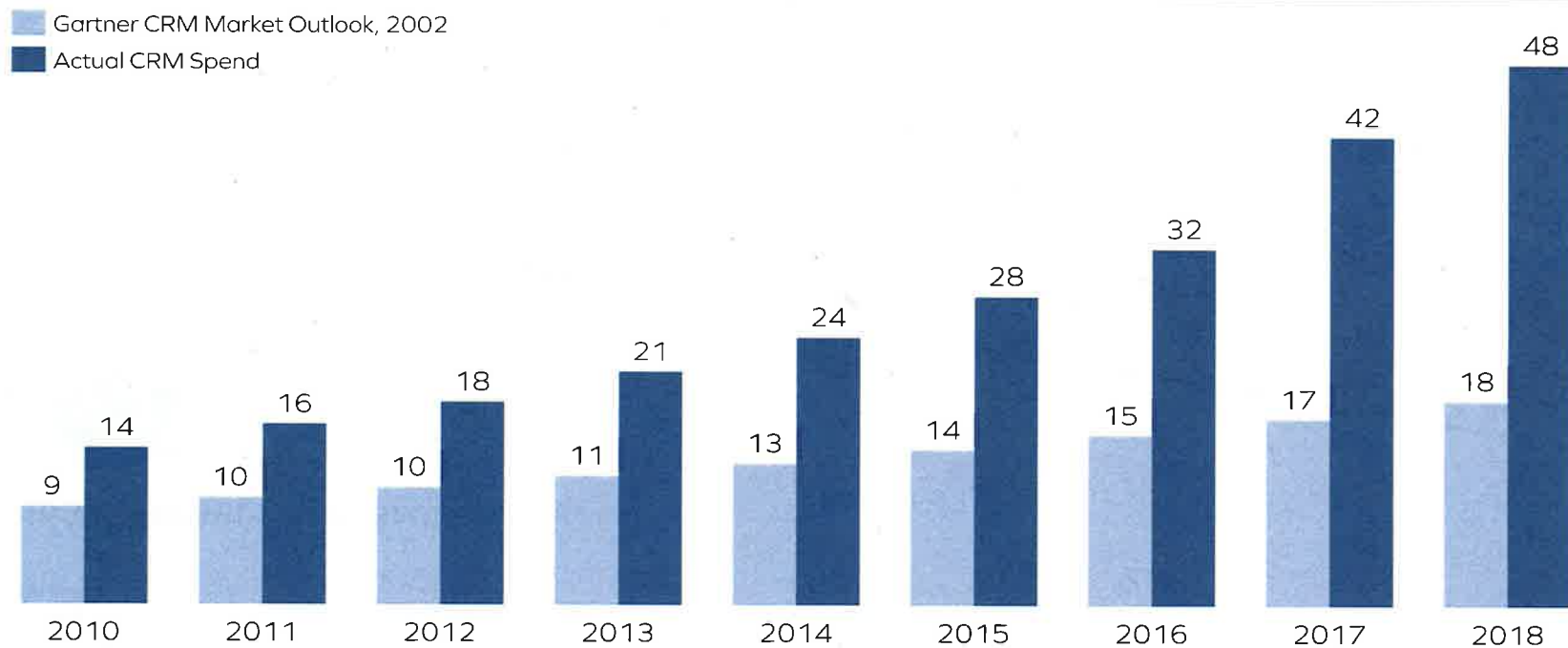
Next Gen Companies

(Market cap¹, USD billions)

CRM	\$5.9B 2005	SIEBEL	➤➤		\$180B
ERP	\$10.3B 2004	PeopleSoft	➤➤		\$47B
Infra	\$1.6B* 2018	 bmc REMEDY	➤➤	servicenow	\$81B

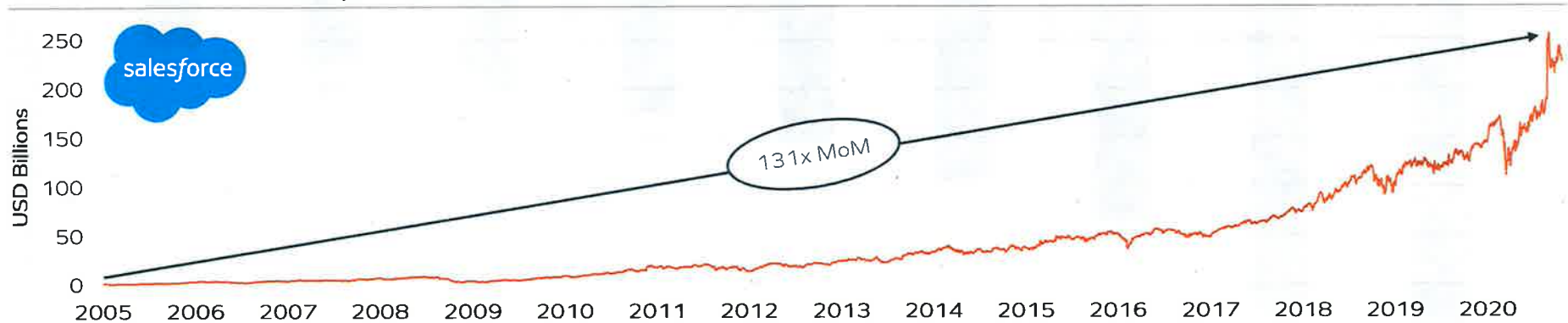
Even experts have a hard time projecting the growth of end markets for software products

CRM Market Spend, *USD billions*



Markets consistently undervalue compounded growth

Salesforce Market Capitalization, *USD billions*



Sample headlines

2007

Salesforce is on Fire:
So Why Am I Short
Its Stock?

"I am of the firm belief that a speculative bubble has been built around this stock."

2008

Salesforce.com
Worth Half Its
Current Price

2010

Salesforce: A good
short at its current
valuation

"People have been saying CRM is too highly valued for some time now."

2012

Salesforce.com is an
irrational investment

"The most shocking aspect of CRM's valuation is how rationally irrational it is."

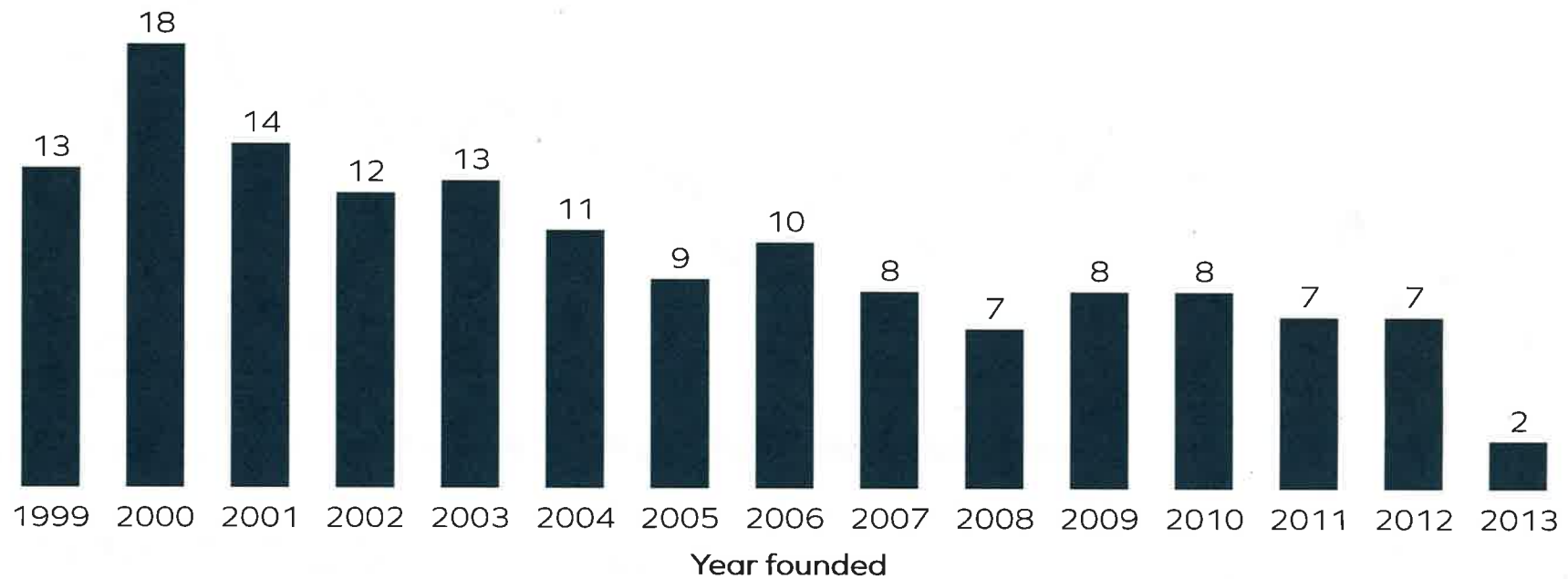
2014

Salesforce: As an
investment, a spent
force

"Salesforce.com common stock is highly overvalued."

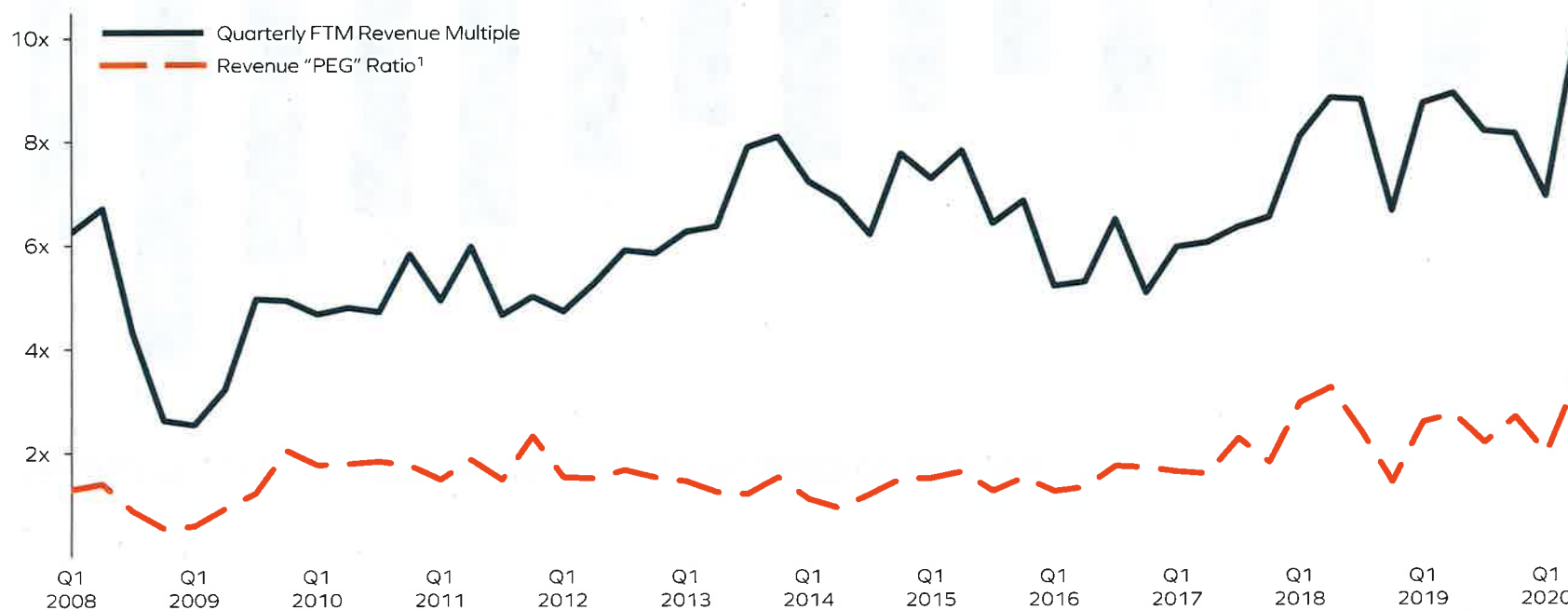
SaaS companies are getting bigger, faster

Median time to >\$100M revenue for public SaaS companies, *years*



Adjusted for higher growth, valuations on software companies remain consistent

TEV / Total Forward Revenue Multiple for Public SaaS Companies



SOURCE: Capital IQ as of August 5, 2020. Comp set includes: AVL, AYY, BL, BOX, CDAY, CRM, CRWD, CSOD, DDOG, DOCU, ENV, HUBS, INST, LOGM, MIME, NEWR, NOW, PD, PFPT, PS, SHOP, SMAR, SPSC, SVMK, TEAM, TWLO, TWOU, VEEV, WDAY, WORK, YEXT, ZEN, ZM, ZUO.

¹ Revenue "PEG" Ratio is defined as the FTM Revenue Multiple divided by the TTM growth rate (multiplied by 100).

How is **COVID-19** affecting
the current market
environment?

COVID-19 has accelerated digital transformation...

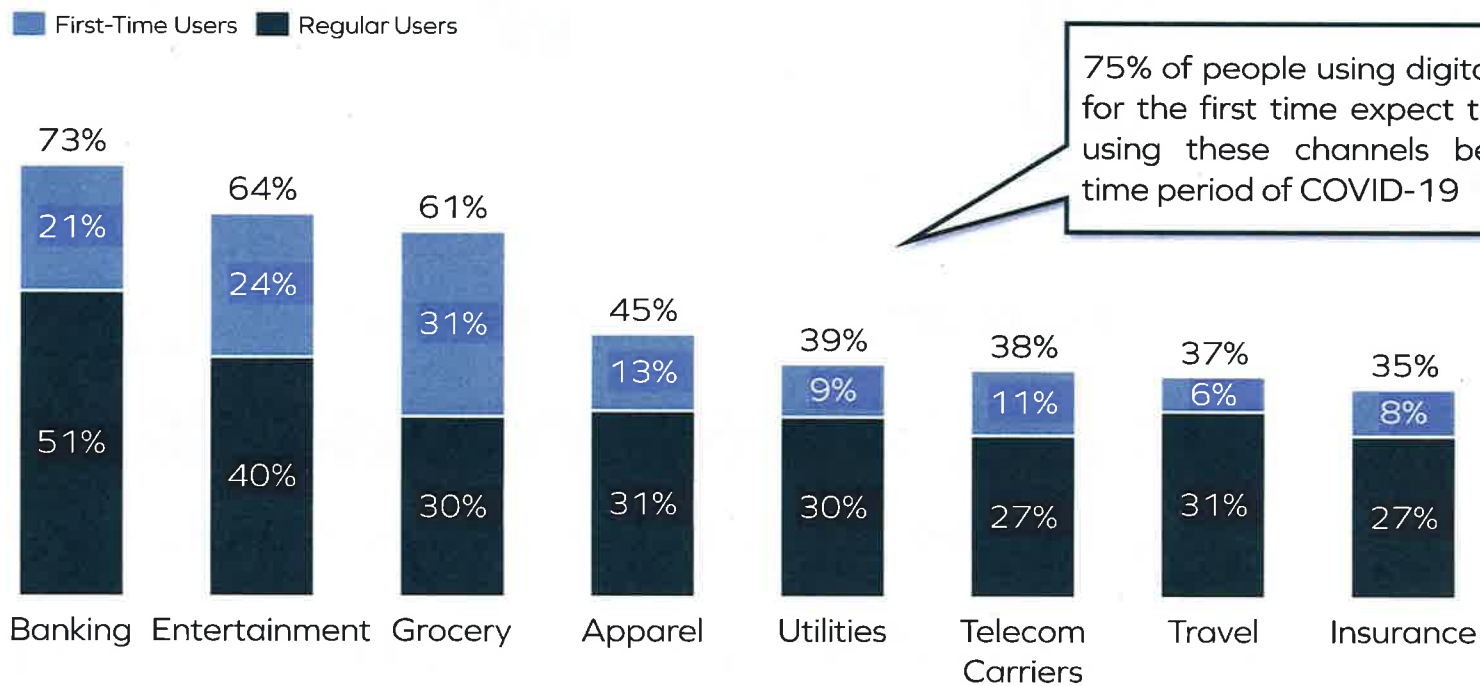
“ We’ve seen **two years’** worth of digital transformation in **two months**
– Satya Nadella, CEO, Microsoft

“ I used to say that with modern digital sales capabilities, sales changed more in the past **five years** than in the past **50 years**. I should say now that sales changed more in the past **five months** than in the past **five years**
– Joël Le Bon, Associate Professor, The Johns Hopkins Carey Business School

“ Today, we are witnessing what will surely be remembered as a **historic deployment of remote work and digital access** to services **across every domain**, including medicine, education, government, entertainment and more
– Bob Swan, CEO, Intel

...across all industries

Digital adoption by industry resulting from COVID-19, % of digital access

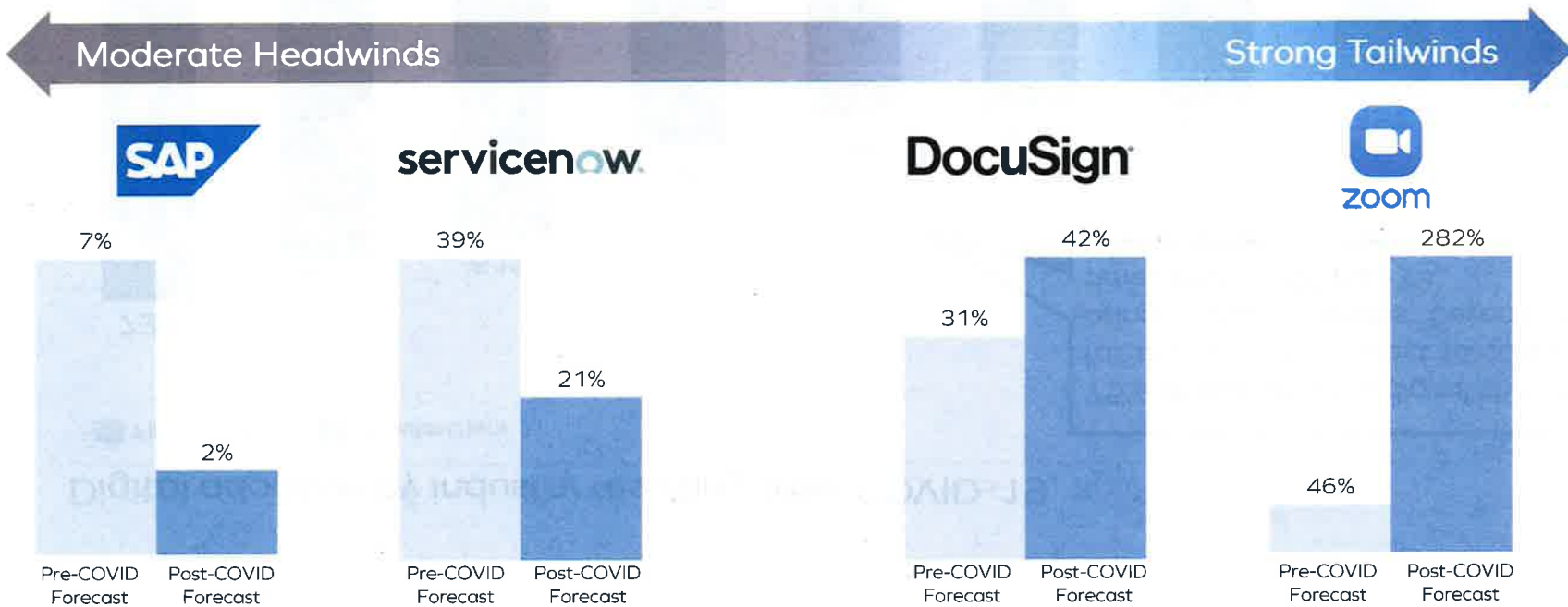


75% of people using digital channels for the first time expect to continue using these channels beyond the time period of COVID-19

Note: Figures may not sum to listed totals because of rounding.

Companies benefitting in this environment are outperforming, and others still anticipate growth

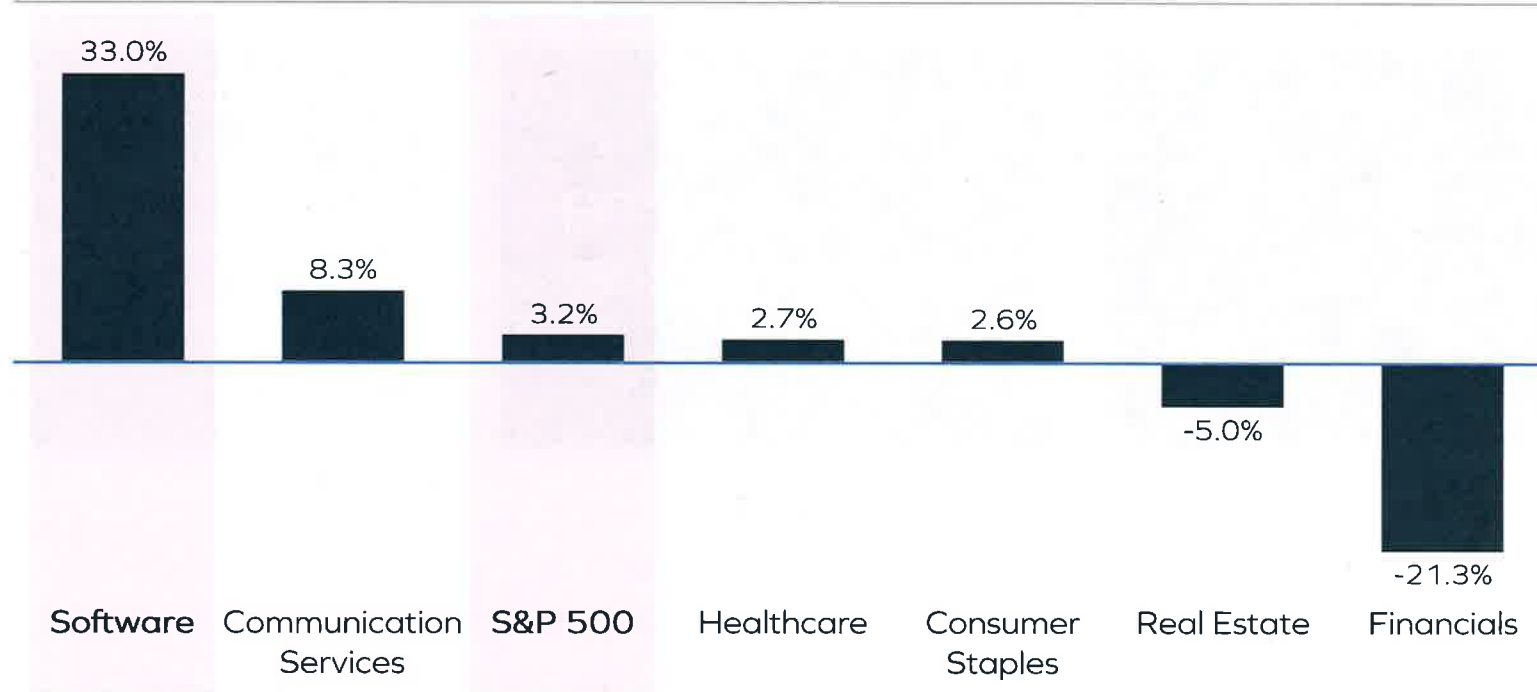
Projected YoY Revenue Growth, Forecasted Pre- and Post-COVID-19



Source: Capital IQ. Shows growth projections between the last fiscal year end (12 months ending 12/31/2019 or 01/31/2020) and the next fiscal year end. Projection estimates are shown based on initial guidance prior to COVID-19 and more recent guidance.

Strong public software returns YTD relative to other sectors

YTD Change in price return by industry



There are reasons to be optimistic...

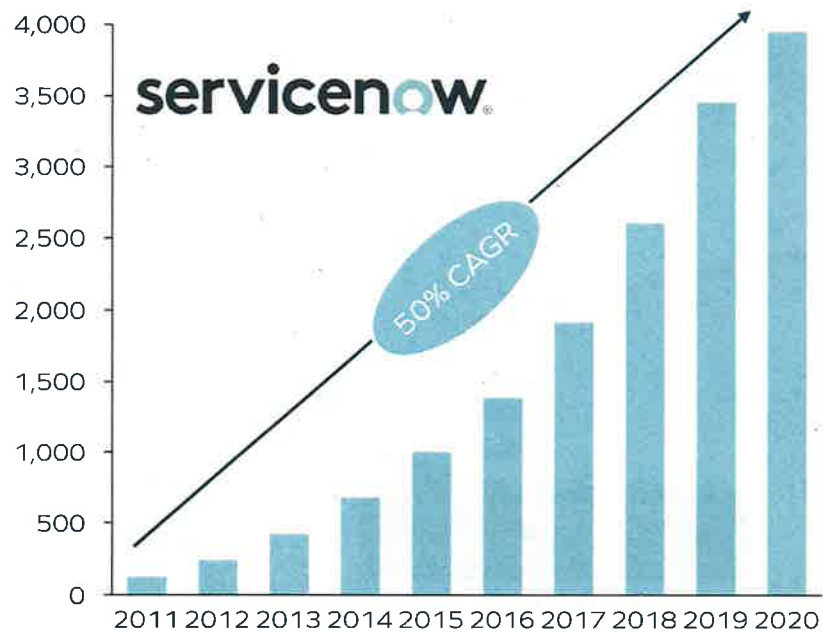
Digital
Transformation
Tailwinds

Solid Software
Business Model

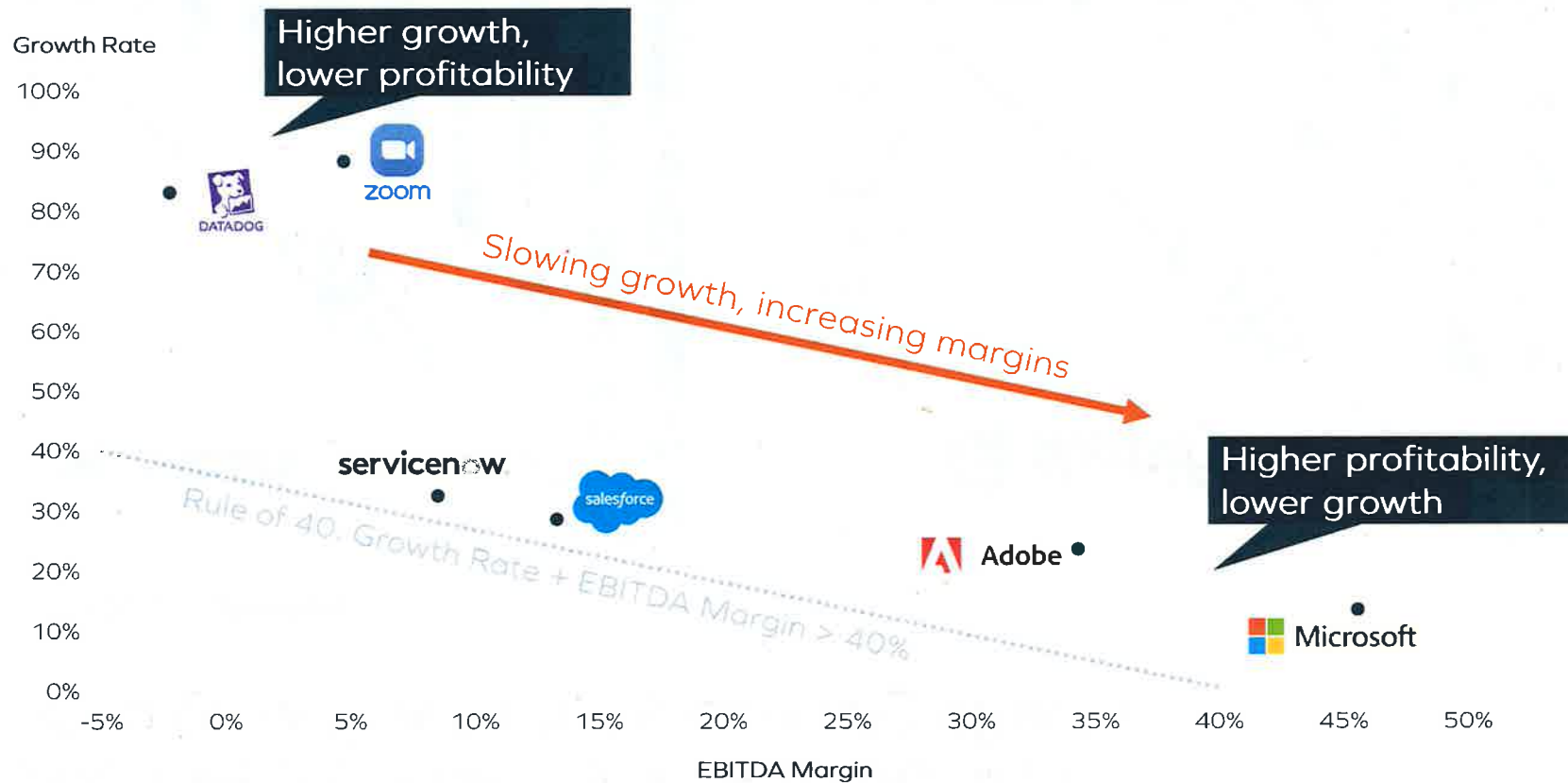
Federal Interest
Rate Policy

SaaS businesses have demonstrated high, sustained growth with compounding effects...

Annual Total Revenue, *millions of dollars*

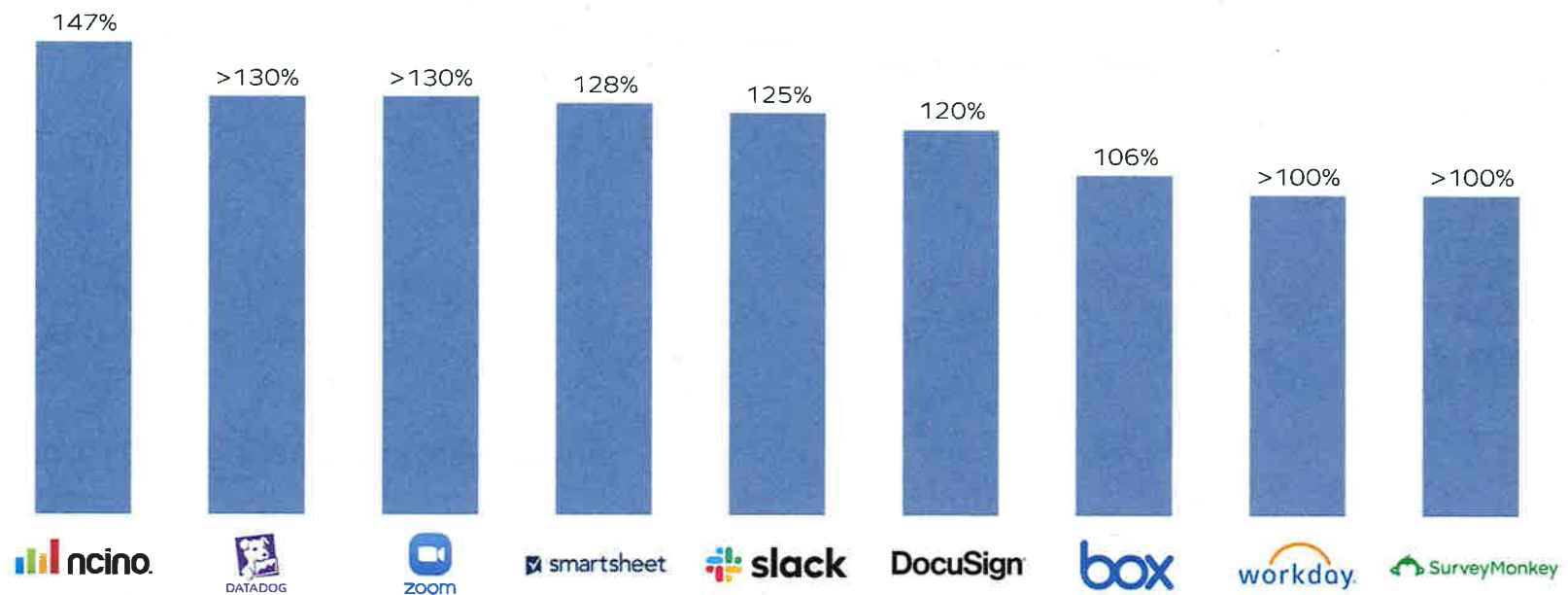


...And companies can scale margins over time as growth slows



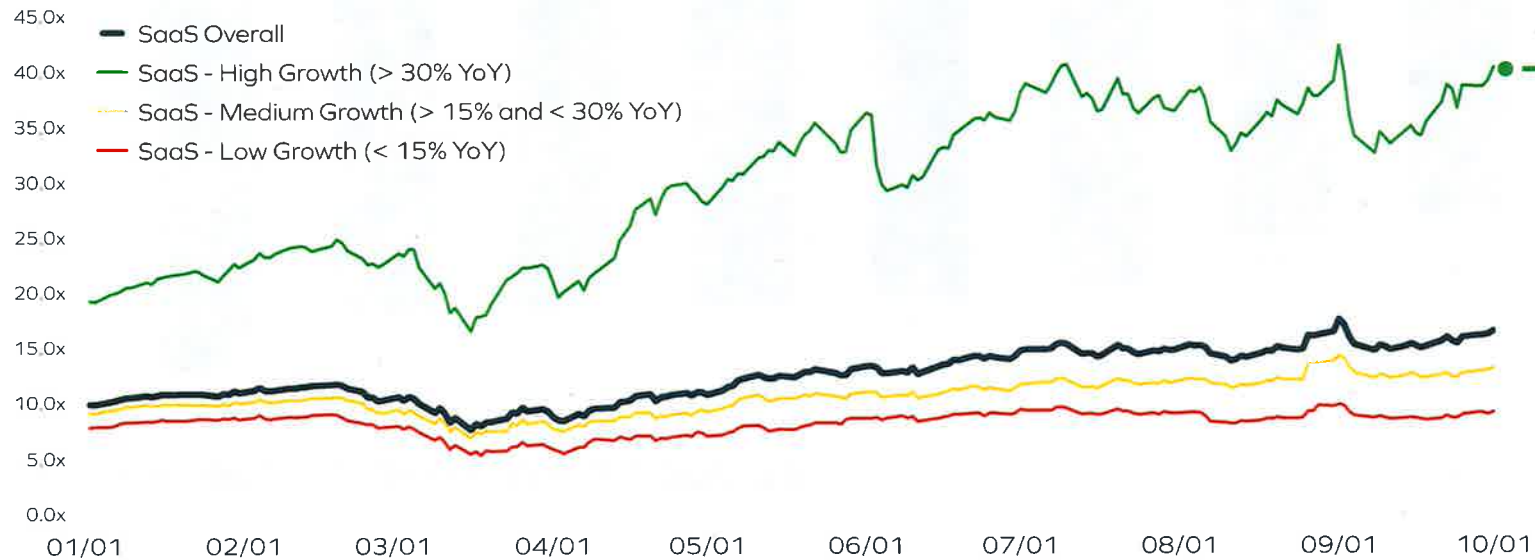
Software businesses are proving to be sticky despite a challenging macro environment

Net Dollar Retention During COVID-19, %



And while valuations are high, this is being led by hyper growth companies

Public SaaS TEV / Forward Total Revenue



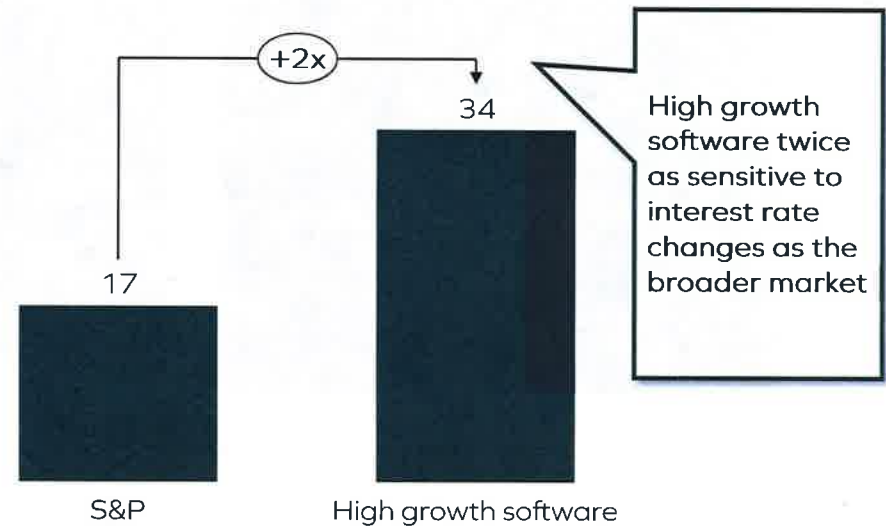
SOURCE: Capital IQ. Comp set includes: AVLR, AYX, BL, BOX, CDAY, CRM, CRWD, CSOD, DDOG, DOCU, ENV, HUBS, INST, LOGM, MIME, NEWR, NOW, PD, PFPT, PS, SHOP, SMAR, SPSC, SVMK, TEAM, TWLO, TWOU, VEEV, WDAY, WORK, YEXT, ZEN, ZM, ZUO. High growth defined as any company with NTM vs LTM revenue growth projections of 30%+, medium growth defined as 15-30%, and low growth defined as below 15%.

Federal policy and low interest rates likely account for part of the valuation increase

10-Yr Treasury¹, *daily yield curve rate*



Implied Equity Duration²



However, there are reasons to be skeptical...

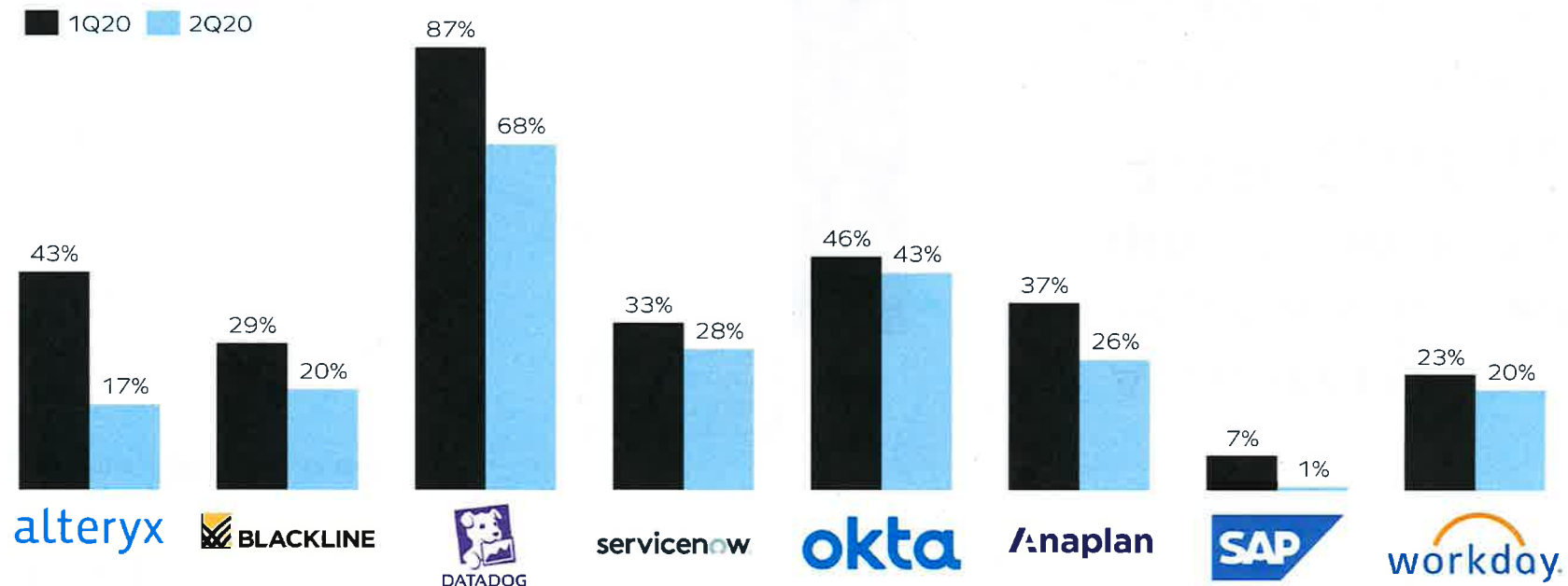
Headwinds in
Future Forecasts

Large Cap LBO
Targets Stretched
on Price

Over-Optimistic
Rebounds

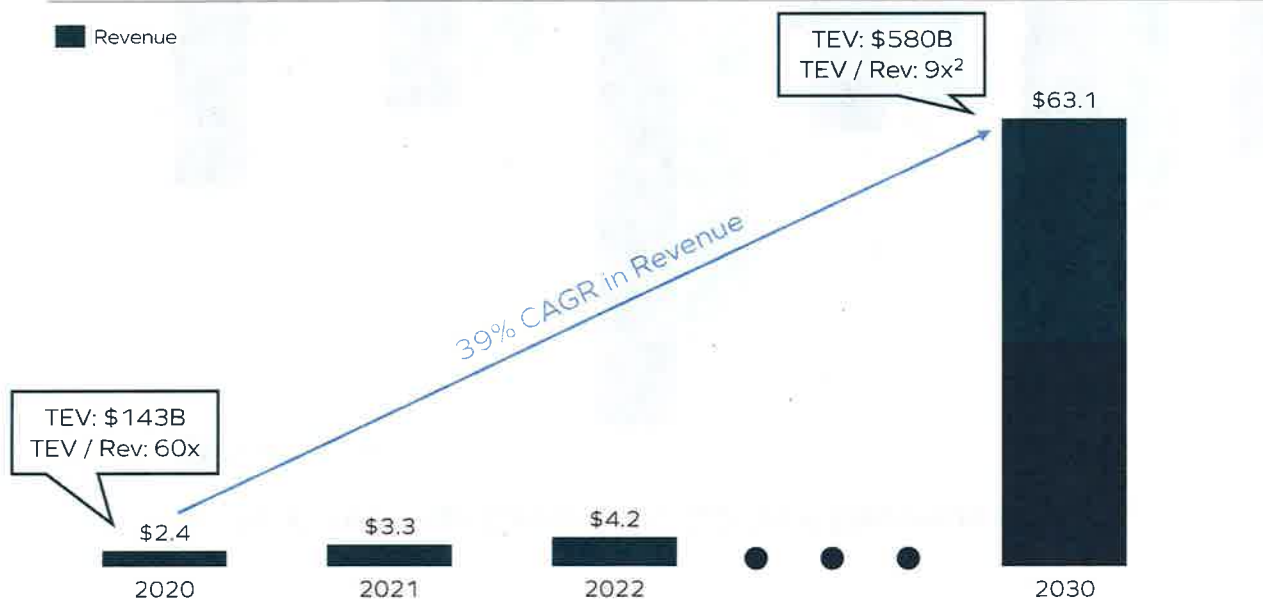
Digital transformation revenue bump did not materialize in Q2 as growth slowed

Q1 YoY Revenue Growth vs. Q2 YoY Revenue Growth, %



Top software companies are priced for best-in-class execution

Zoom revenue forecast model¹, USD billions



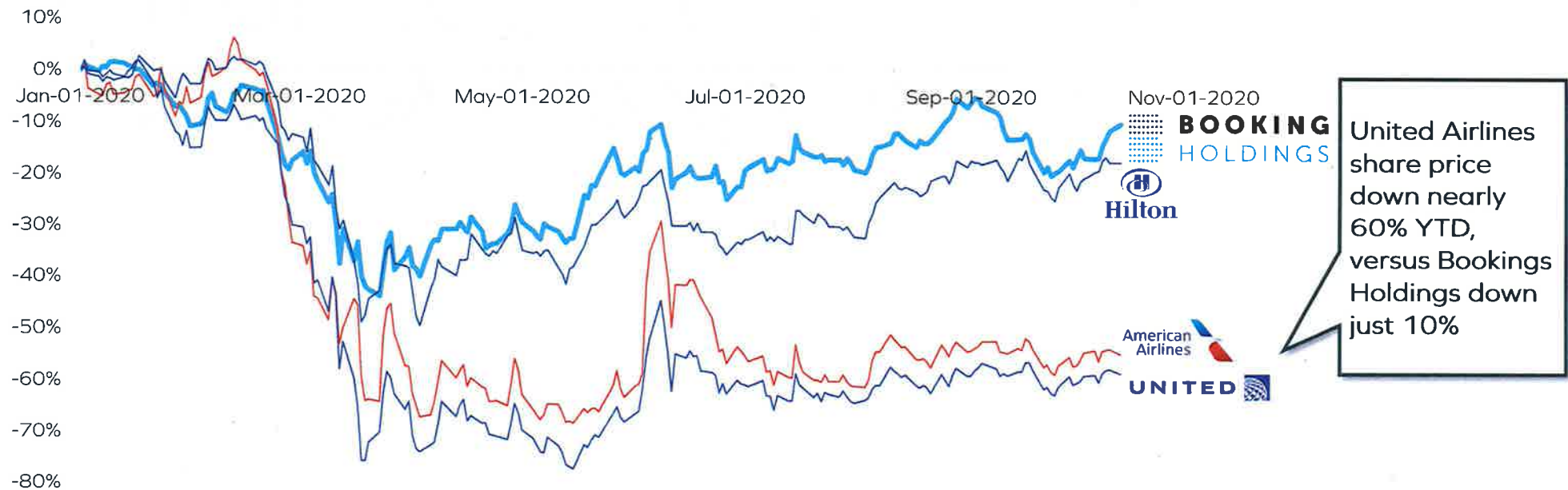
At current pricing, Zoom would need to grow revenue at a **39% CAGR** over a 10-year period for an investor to realize a 15% return

¹ SOURCE: 2020, 2021, and 2022 revenue projections from JMP Securities report on Zoom Video Communications, Inc. (ZM) as of October 15, 2020. Zoom fiscal year end of January 31. Revenue estimates by year use the projected revenue for the following fiscal year (e.g., 2020 revenue estimate based on projected revenue for fiscal year ending 01/31/2021, TEV of \$143.4 billion as of 10/14/2020. 2030 EV forecasted to deliver a 15% CAGR over a 10-year period between 2020 and 2030.

² SOURCE: Morgan Stanley "Has the Software Bubble Started to Deflate?", July 27, 2020. Estimate based on average EV/Rev multiple for incumbent software companies (Microsoft, Adobe, Oracle, SAP, Salesforce).

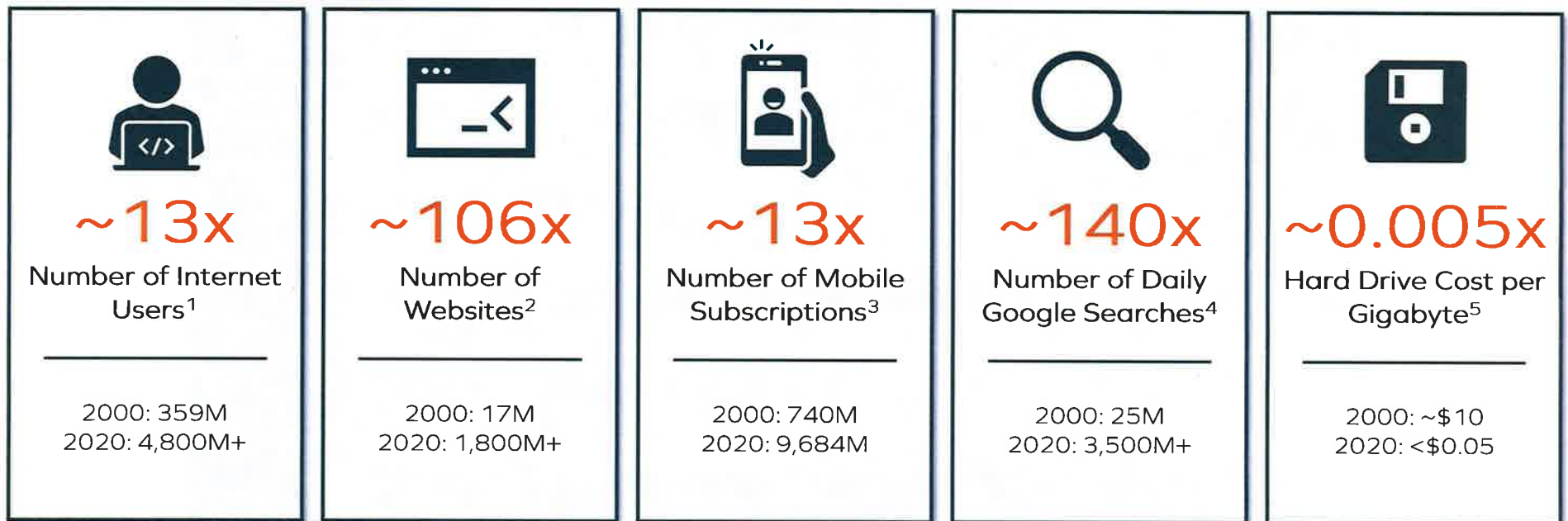
And in industries with no clear tailwinds, tech stocks continue to rebound

Daily change in public share price



So the key question is, do
current market **trends**
support future growth?

The world has changed rapidly in the past 20 years



Note: For illustrative purposes only.

1 SOURCE: Internet World Stats (). Internet users as of July 2000 and June 2020.

2 SOURCE: Internet Live Stats (). Number of websites as of June 2000 and September 2020.

3 SOURCE: Statista "Number of mobile (cellular) subscriptions worldwide from 1993 to 2019" () and "Number of mobile subscriptions (incl. M2M) worldwide from 2010 to 2020" ().

4 SOURCE: Internet Live Stats (). Daily Google searches for 2000 calculated as the total annual searches divided by 365.

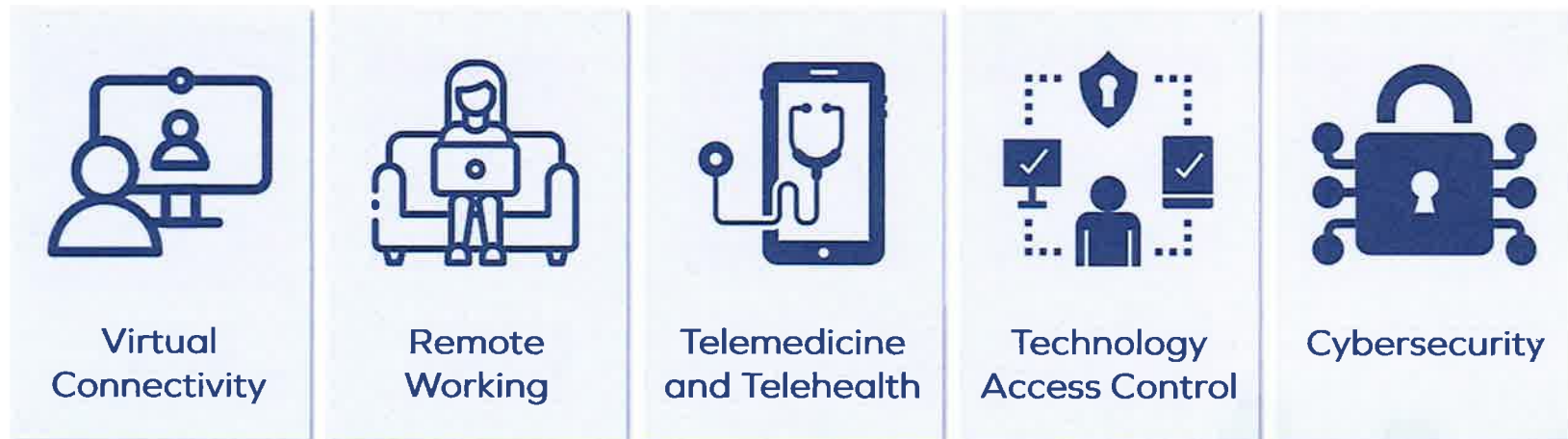
5 SOURCE: mkomo.com (), Backblaze ().

Cost per gigabyte approximation for 2000 based on hard drives ranging from \$6.90 to \$19.70 in cost.

What technology **trends** are driving change now?

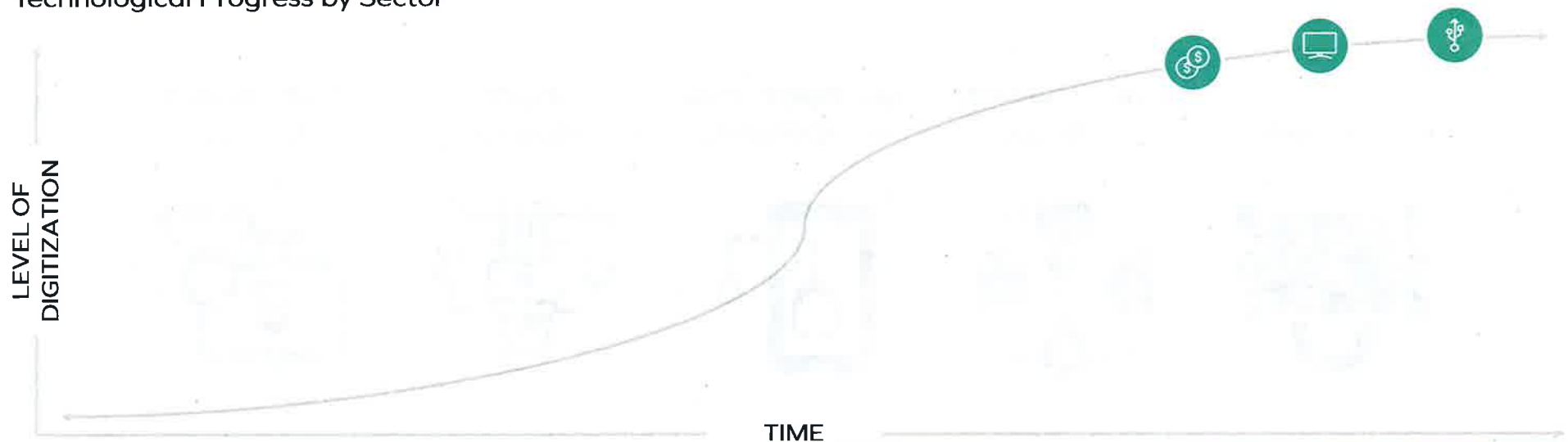
- 1 COVID-19 and Associated Virtual Connectivity
- 2 Digital Transformation
- 3 Artificial Intelligence and Machine Learning
- 4 Cloud Migration
- 5 Internet of Things
- 6 Mobile First Engagement
- 7 DevOps

1 COVID-19 | The COVID-19 pandemic has accelerated several trends



2 Digital Transformation | Some industries have invested heavily to digitally transform...

Technological Progress by Sector



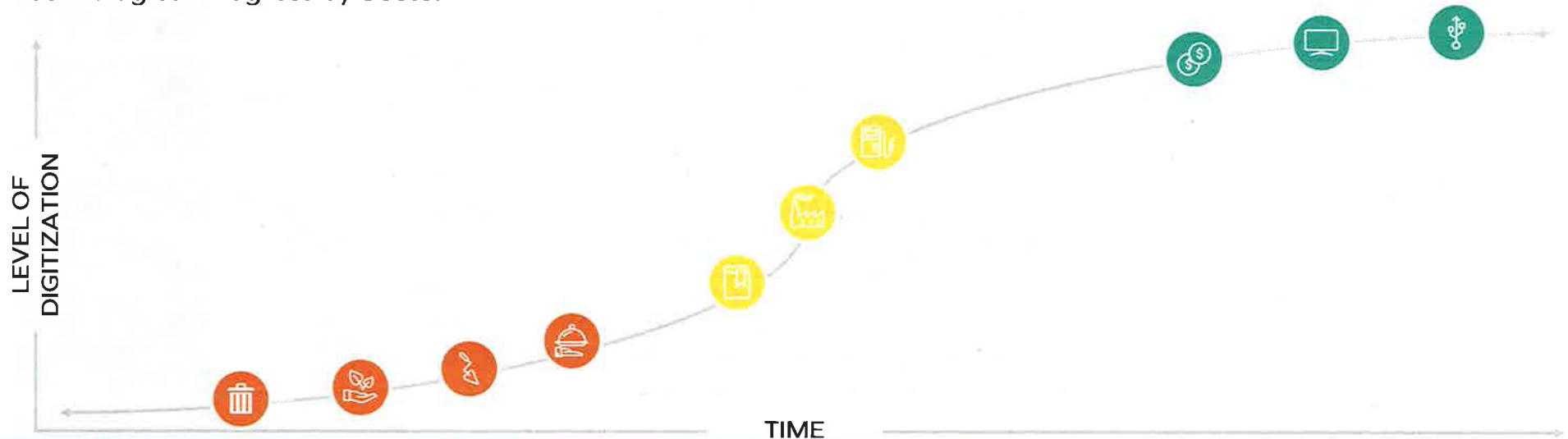
Relatively Low Digitization

Relatively High Digitization

Finance
Media
Technology

2 Digital Transformation | ...but there remains meaningful runway across the economy

Technological Progress by Sector



Relatively Low Digitization






Agriculture
Construction
Hospitality

Relatively High Digitization

Education
Advanced Manufacturing
Oil and Gas

Finance
Media
Technology

2 Digital Transformation | Large enterprises across industries are investing in digital

Retail		Integrated augmented reality into IKEA Place app to allow consumers to test furniture in their home; acquired TaskRabbit for seamless furniture assembly support ¹
Restaurant		Developed digital platforms to enhance ordering and operations; today, 65% of U.S. sales come from digital channels ²
Healthcare		Invested behind telemedicine; in 2016, 52% of the health system's 100 million primary care encounters were virtual ³
Finance		Released plan to hire 2,500 programmers in 2020 to support advances in automation; expects \$600M in savings in 2020 from its digital investments ⁴
Government		Launched its "Digital Growth Strategy" in 2018 to enhance Denmark's position as an attractive digital hub, allocating €134M to the effort ⁵

¹ SOURCE: Forbes "The Digital Transformation to Keep IKEA Relevant: Virtual Reality, Apps And Self-Driving Cars", October 19, 2018 (<https://www.forbes.com/2018/10/19/ikea-digital-transformation-vr-apps-self-driving-cars.html>).

² SOURCE: Domino's 101: Fun Facts (<https://www.dominos.com/101-fun-facts>).

³ SOURCE: Tennessean "Kaiser's Tyson to Nashville: Health care's future isn't in a hospital", April 21, 2017 (Based on interview with Bernard Tyson, chairman and CEO of Kaiser Permanente).

⁴ SOURCE: Bloomberg "Citi's Investment Bank Plans to Hire 2,500 Coders This Year", January 6, 2020 (<https://www.bloomberg.com/news/articles/2020-01-06/citi-plans-to-hire-2500-coders-this-year>).

⁵ SOURCE: Denmark Ministry of Foreign Affairs "The Danish Government Presents 'Digital Growth Strategy'", February 19, 2018 (<https://www.um.dk/en/news/2018/02/19/danish-government-presents-digital-growth-strategy>).

3 AI and ML | AI is creating headlines everywhere

Artificial Intelligence Nails Predictions of Earthquake Aftershocks
A neural-network analysis outperforms the method scientists typically use to work out where these tremors will strike

AI Art at Christie's Sells for \$432,500

NASA: AI Will Lead the Future of Space Exploration
It could be a giant leap for mankind

SOURCE: New York Times "AI Art at Christie's Sells for \$432,500", October 25, 2018 (<https://www.nytimes.com/2018/10/25/arts/ai-art-christies.html>); Futurism "NASA: AI Will Lead the Future of Space Exploration", June 27, 2017 (<http://www.futurism.com/2017/06/27/nasa-ai-will-lead-the-future-of-space-exploration/>); Scientific American "Artificial Intelligence Nails Predictions of Earthquake Aftershocks", August 31, 2018 (<https://www.scientificamerican.com/article/artificial-intelligence-nails-predictions-of-earthquake-aftershocks/>).

3 AI and ML | There are only a few basic functions that work well today

Examples

Text Analysis and Generation

Image and Video Recognition and Generation

Anomaly Detection

Nearest Neighbor / Recommendation Engines

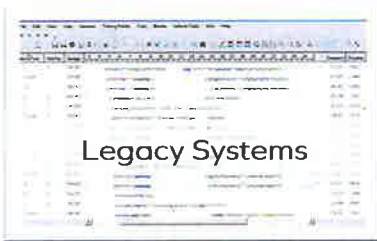
3 AI and ML | But these few skills can be applied to a multitude of use cases

- Validate whether term papers are original or plagiarized
- Organize photos by category and tag friends
- Detect payment fraud
- Suggest growth equity investment candidates
- Recommend pricing for loans
- Estimate insurance claims from photos
- Analyze legal documents
- Prepopulate customer support responses
- Write financial articles based on earnings reports
- Pre cache streaming TV content at the edge of the network to improve speed and responsiveness
- Recommend products to buy, shows to watch, or friends to connect with
- Block spam emails
- Detect malware
- Transcribe a conversation
- Trade equities
- Beat humans at video games and Go
- Recognize activities in video clips
- Predict machine failure
- Sort cucumbers
- Dispatch, navigate, and drive vehicles
- Predict hospital readmissions
- Distinguish chihuahuas & muffins
- Organize a news feed
- Recognize emotions in speech
- Fake a video of someone talking
- Turn a photo into artwork in the style of famous artists
- Generate photorealistic faces of fake celebrities
- Write poetry
- Speak naturally, pretend to be a human and make hair salon appointment
- Translate in real time

3 AI and ML | Case Study: AI is changing how mass transportation operates

Existing solutions fail to meet the needs of today's providers

Optibus leverages advanced optimization algorithms and AI to optimize every aspect of the transportation network



optibus

- Plans, optimizes, and operates all critical elements of a mass transit system
- Uses advanced optimization algorithms to evaluate and compare many operational scenarios to create an optimal transit plan
- Understands the costs of plan changes in real-time, generating cost savings of up to 15%
- Adapts to and ensures compliance with contractual, union, and regulatory requirements
- Leverages AI and historical data to predict and analyze on-time performance



Network and route plan



Bus stops and depot locations



Timetable



Vehicle and crew schedule



Electric Vehicle charging



Performance KPIs



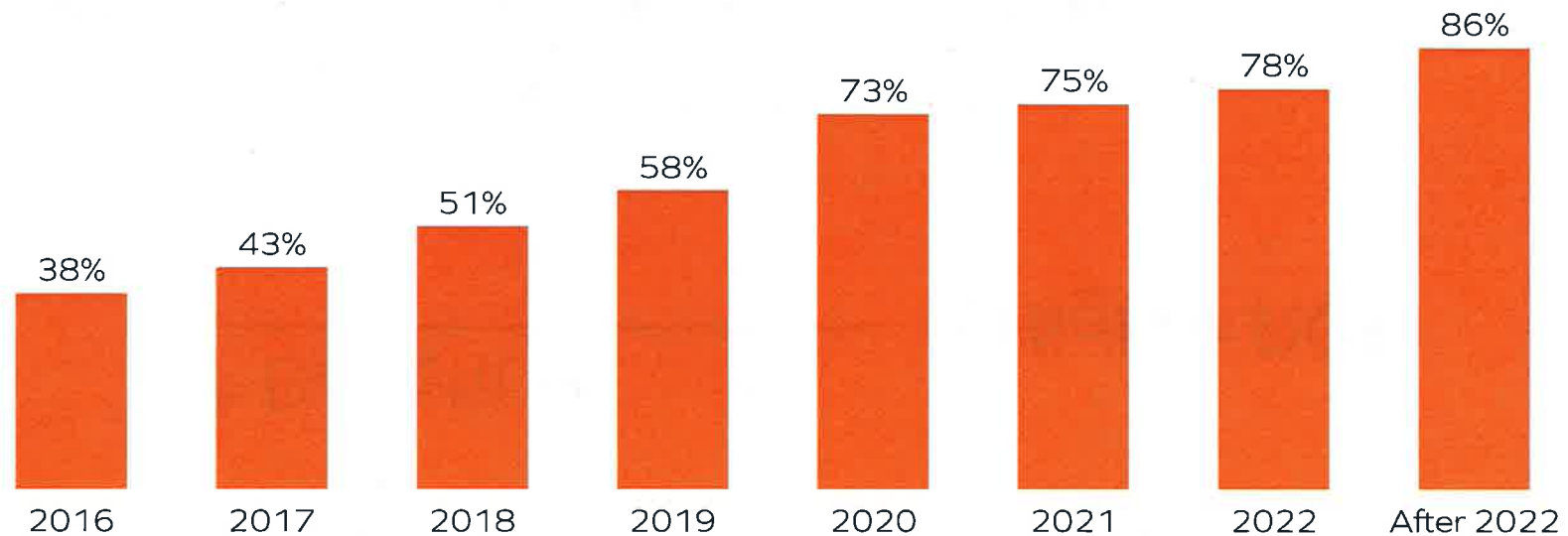
Drivers' shift preferences



Regulatory compliance

4 Cloud Migration | Cloud / SaaS adoption is accelerating

Percentage of organizations estimating when 80% of business apps will be SaaS



4 Cloud Migration | Cloud deployment (i.e., SaaS) can improve ROI on software implementations

$$\frac{\uparrow \text{Benefit} - \text{Cost}\downarrow}{\text{Cost}\downarrow} = \text{Higher ROI}$$

Key benefits of SaaS model



Faster ramp up
and quick
adoption



Improved
usage and
adoption



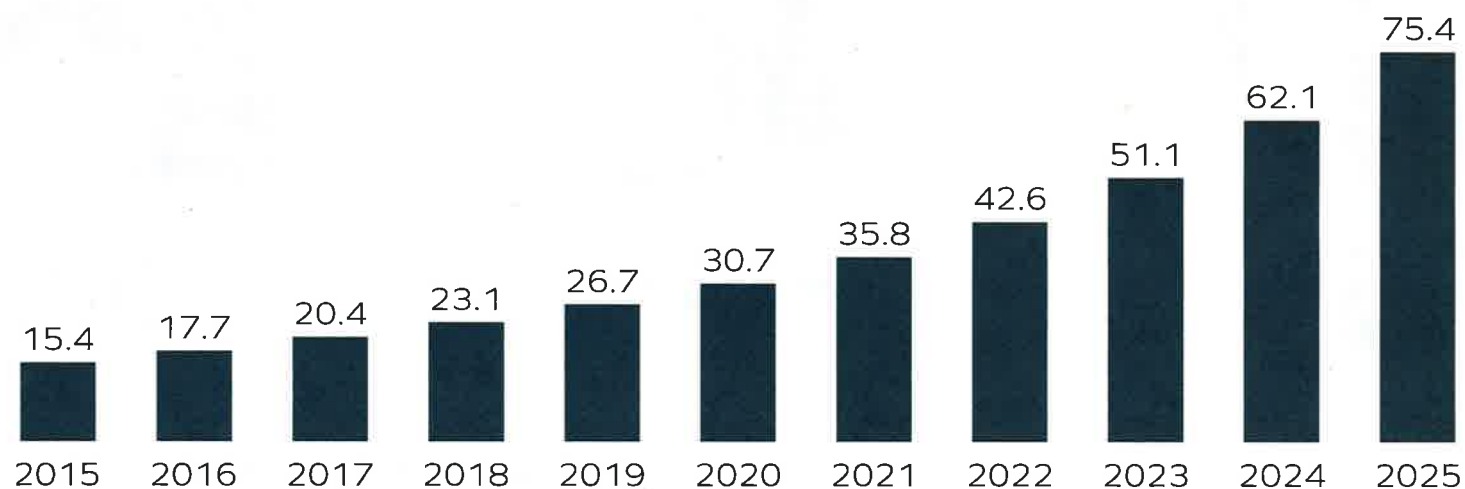
Lower
implementation
and activation cost



Reduced spend
on excess
capacity

5 Internet of Things | The number of connected devices is expected to steadily increase

Internet of Things (IoT) connected devices worldwide, *billions of devices*



5 Internet of Things | IoT devices have applications in a variety of use cases

ring



Ring has several home security IoT devices including doorbells that allow you to interact with guests from anywhere

 Propeller



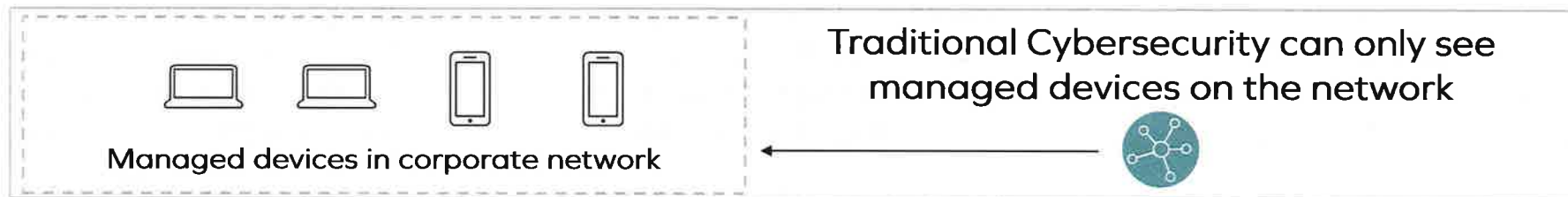
Propeller connects with inhalers to help individuals manage asthma or COPD and share important health information


JOHN DEERE

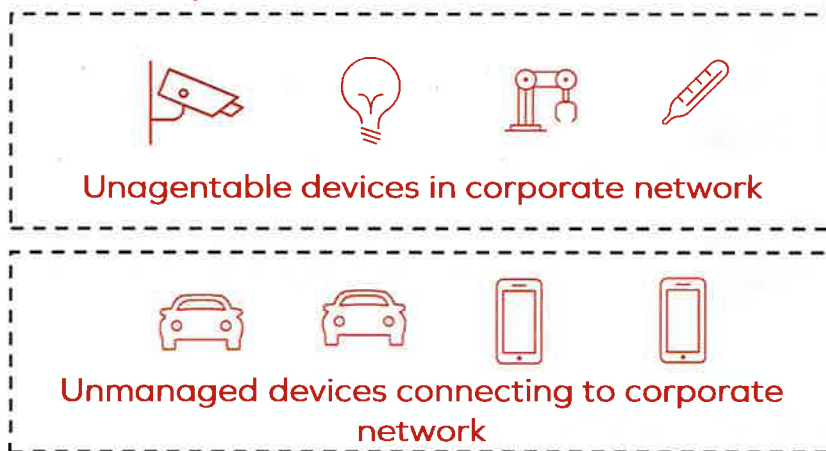


John Deere's precision ag technology enables better farm operations decision making to optimize productivity and efficiency

5 Internet of Things | Case study: Armis provides security for IoT devices in the enterprise



Previously not identifiable



Armis identifies all agented and unagented devices on the network and uses anomaly-based detection to automatically identify threats

6 Mobile First Engagement | The proliferation of mobile devices is changing how people engage

venmo



Venmo is a mobile payment solution that allows account holders to transfer funds to others via a mobile phone app

NIKE
TRAINING
CLUB



Nike Training Club is a handheld personal trainer for your mobile device, walking you through timed exercises and demonstrations

Diligent



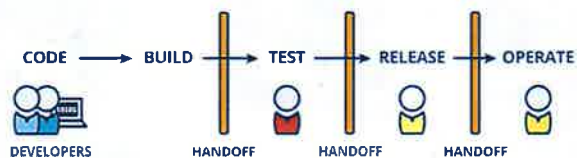
The Diligent Boards solution simplifies and improves how board materials are produced, delivered, and collaborated on across any device

7 DevOps | It used to take years to release new product versions, even for giants like Microsoft



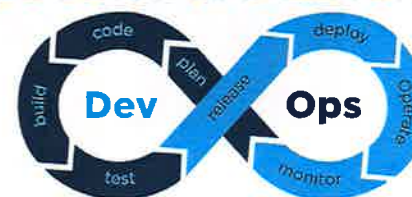
7 DevOps | The software “factory floor” is expanding and changing rapidly

Traditional software development¹



Teams responsible for various stages of software development are siloed, leading to an inefficient process as information breaks down across teams

DevOps software development²



Development teams and operations teams are integrated to promote collaboration, making the end-to-end process faster and more efficient

DevOps enables meaningful value³

100-200x

Increase in deployment speed

20%

Reduction in time spent on unplanned work

50-70%

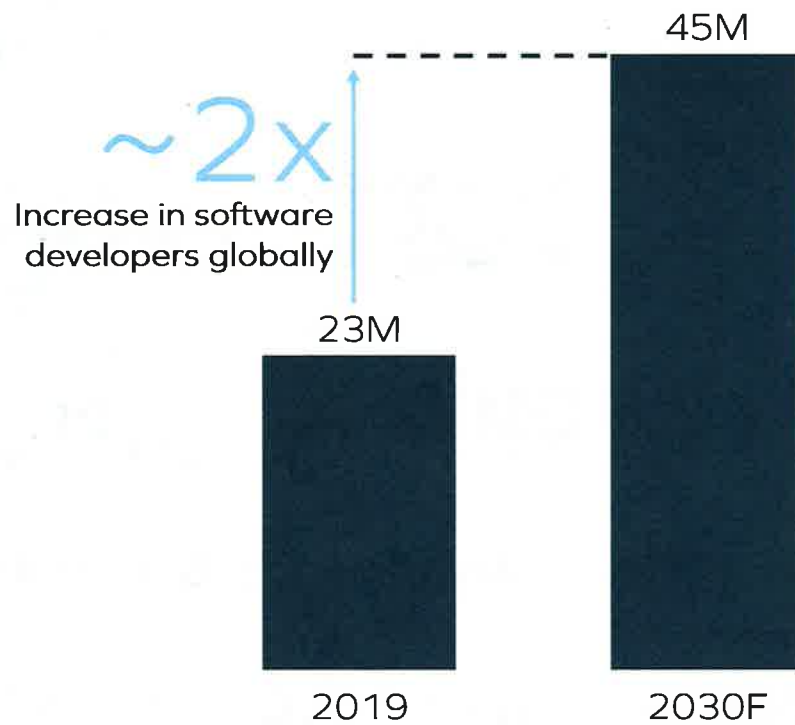
Reduction in change failure rate

¹ SOURCE: Medium "DevOps 101", October 22, 2018 (<https://medium.com/@mattiasw/101-devops-101-101c7d1c1c1c>).

² SOURCE: Medium "DevOps in a Scaling Environment", April 12, 2018 (<https://medium.com/@mattiasw/devops-in-a-scaling-environment-101c7d1c1c1c>).

³ SOURCE: BCG "The Value Unleashed by DevOps" (<https://www.bcg.com/publications/2017/devops>).

7 DevOps | The market for software development is rapidly growing and evolving



7 DevOps | This paradigm shift is making way for a new suite of tools that support DevOps

Legacy tooling is giving way...

...to the next-generation



Hewlett Packard
Enterprise



Development



Testing



Quality



Production



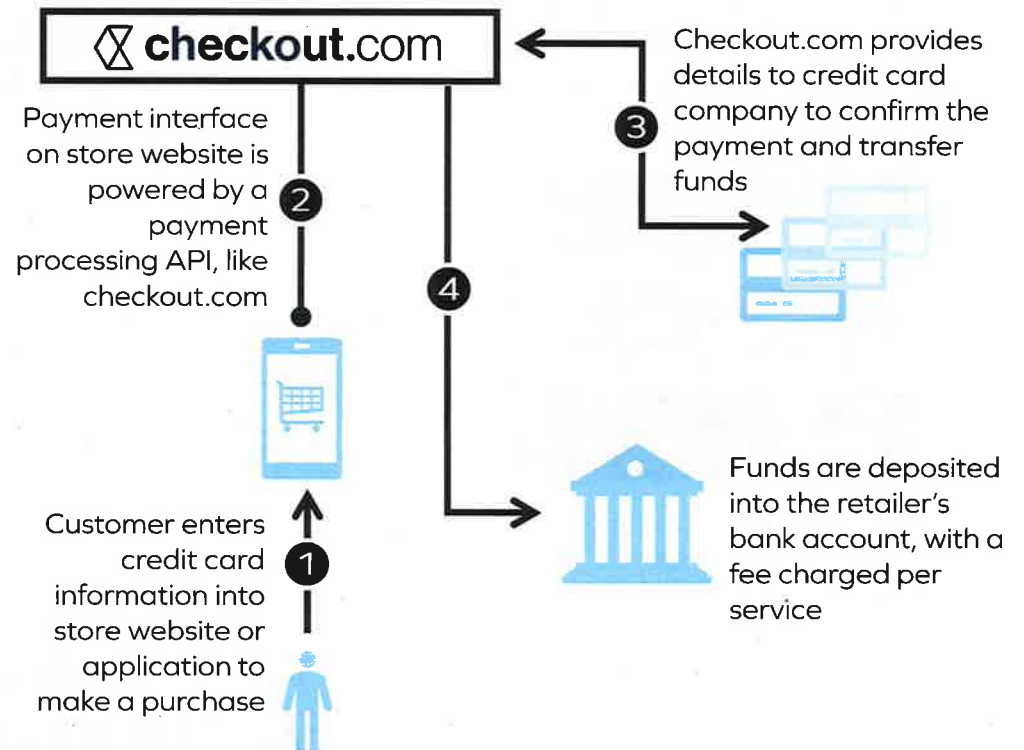
Insight Portfolio Examples

7 DevOps | API proliferation is accelerating innovation

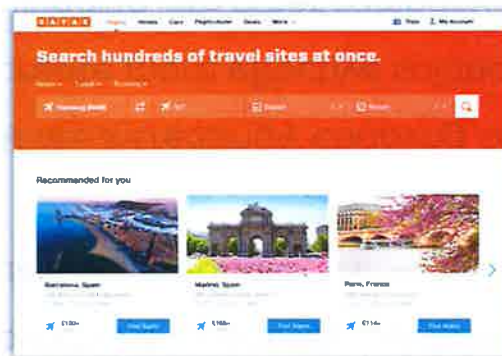
APIs (Application Programming Interfaces) are a new **standard building block for software** - an API is an interface on the applications we access that links to an underlying database

APIs are increasingly **enabling companies to create more effective solutions, faster**, by plugging into other company's core competencies for services such as payments, video streaming, and mapping and location services

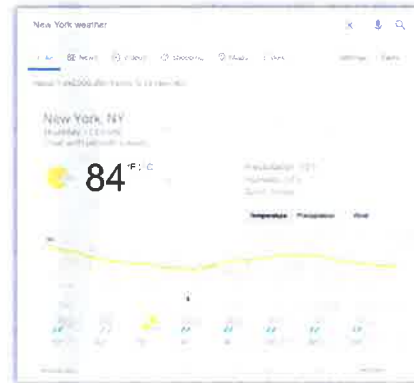
Example - How a payment processing API works:



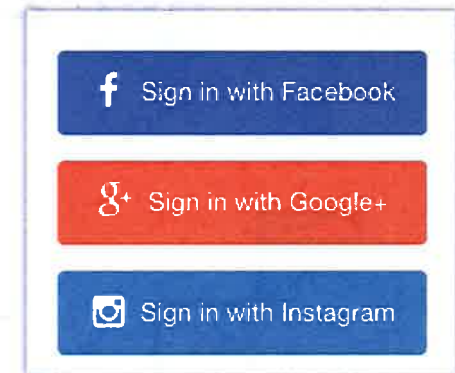
7 DevOps | APIs power the websites and applications we interact with daily



Travel aggregators use an API to pull information from individual travel sites to identify options that meet a customer's search criteria and book travel plans

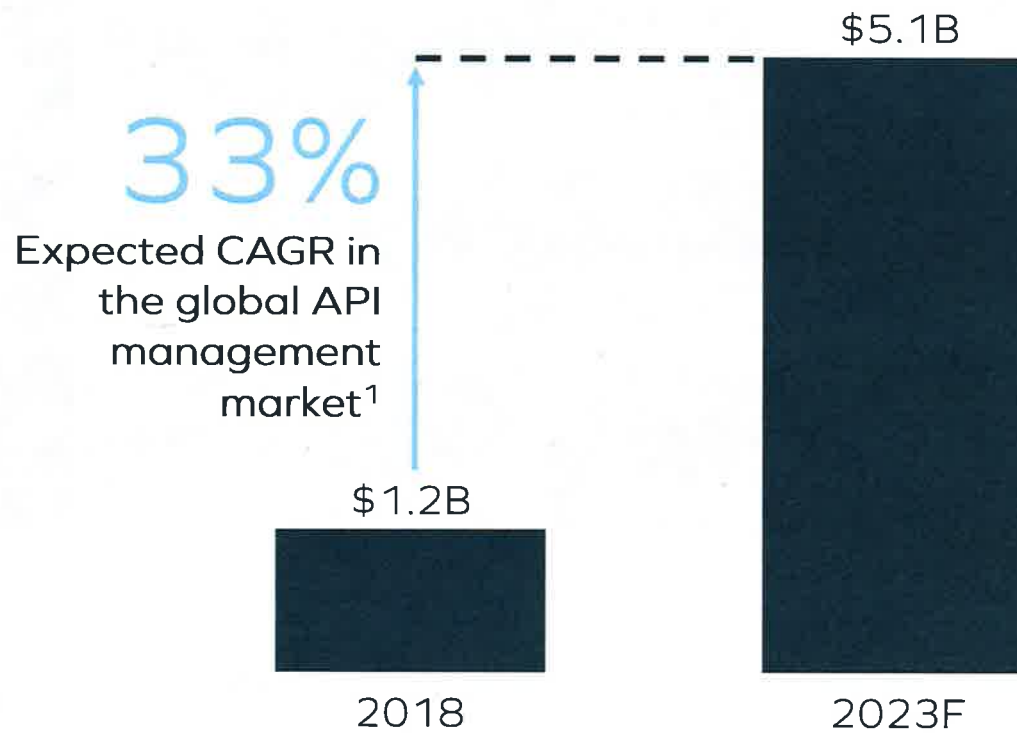


Weather widgets on various applications generally source data from a weather provider (e.g., The Weather Channel) using an API



Sites that allow users to sign in using various social media platforms like Facebook access the APIs for these platforms to validate log-in information

7 DevOps | As companies expand their digital footprints, the use of APIs is expected to grow



What technology trends are emerging and how will they impact future growth?

- 1 Blockchain and Cryptocurrency
- 2 Augmented and Virtual Reality
- 3 Autonomous Driving

What categories are we investing in right now? (1/2)

Next-Generation IT Management

Fund XI Investments



IT & HR Help Desk Automation



Improve Employee Support



Reduce IT Ticket Volume



Boost Productivity

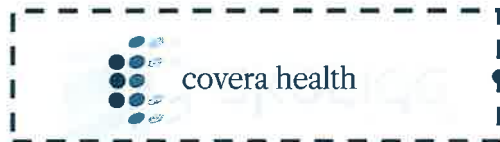


Case example: Espressive Barista (AI-based virtual support engine) was able to quickly ingest and process materials on a company's employee self-service portal to provide immediate answers to inbound employee questions that are personalized based on criteria like employee location¹

What categories are we investing in right now? (2/2)

New Wave of Vertical Solutions

Fund XI Investments



Elevating clinical accuracy through rigorous data science



Advanced Clinical
Analyses



Improved Patient
Outcomes



Reduced
Healthcare Costs



Case example: a peer-reviewed study of MRI exams uncovered a 43% average diagnostic error rate across MRI centers¹ – Covera Health uses advanced data science to connect employees with local radiologists proven to deliver the most accurate diagnoses

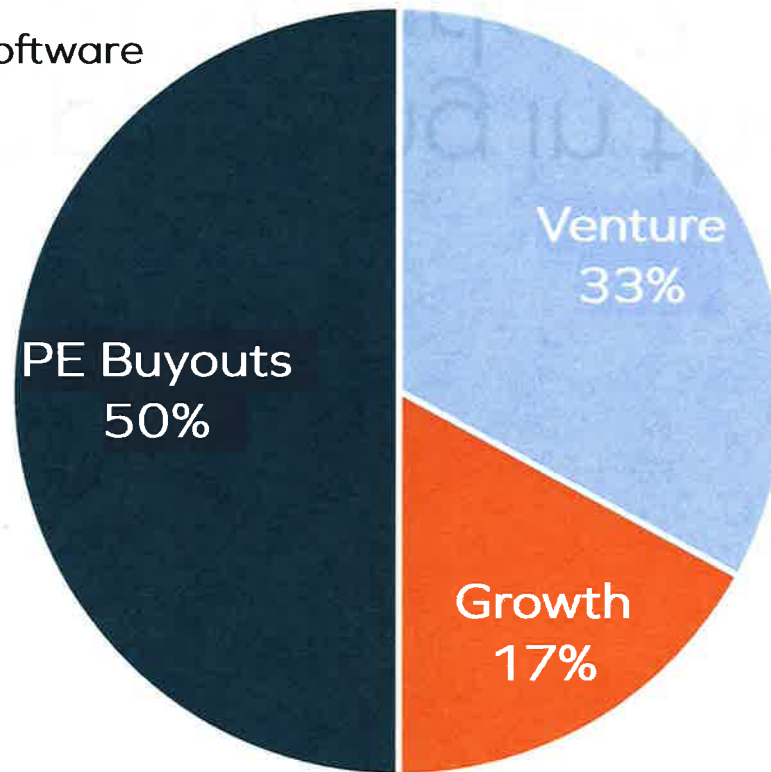
¹SOURCE: "Variability in diagnostic error rates of 10 MRI centers performing lumbar spine MRI examinations on the same patient within a 3-week period" by Herzog R, Elgort DR, Flinders AE, Moley PJ, The Spine Journal. 17 (2017) 554-561

Note: For illustrative purposes only. For a listing of all of Insight's portfolio companies, please visit [insightpartners.com](#)

What is happening in the
software **LBO** market?

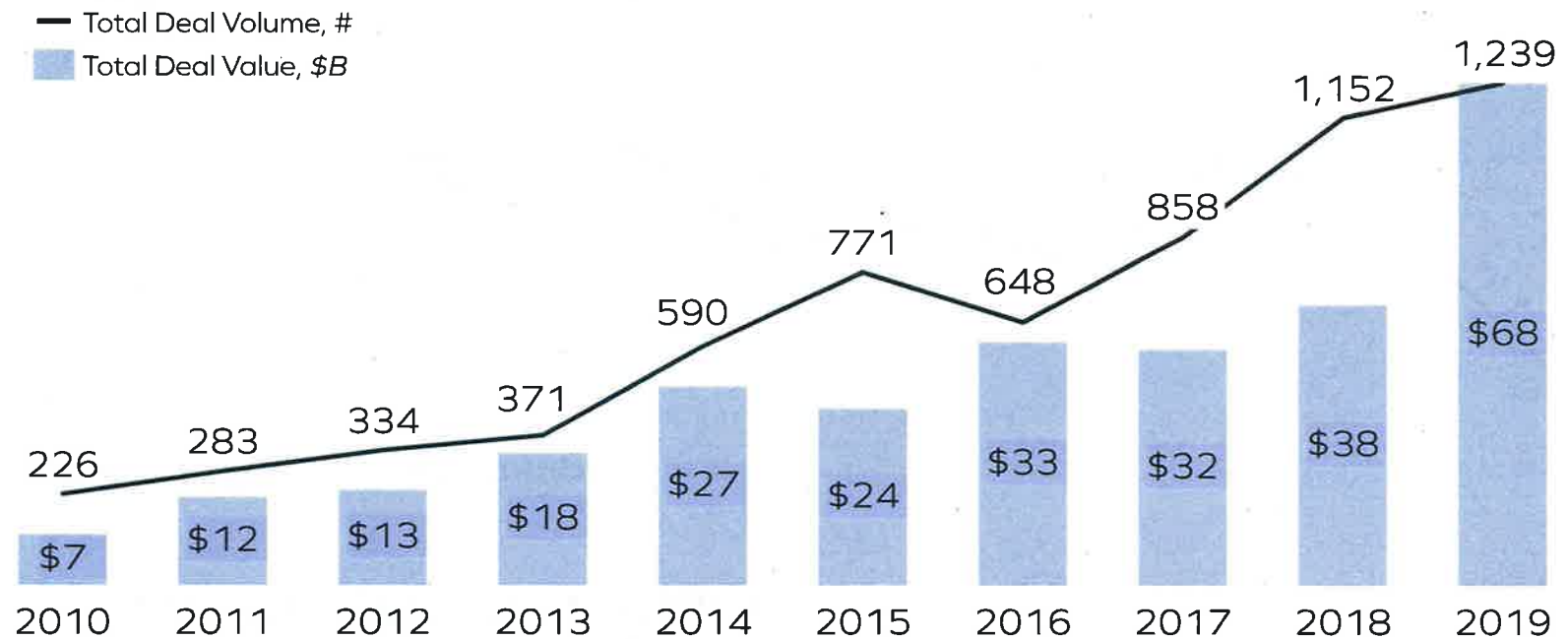
Most capital deployed to software is in the buyout space

Capital Invested in Software
in the U.S. in 2019,
Estimated dollars



An increasing number of PE dollars are going to the software sector

2010 - 2019 Annual Software Deal Value and Volume



SOURCE: Evercore analysis, "Software LBOs By Year 2010-2019 - Value & Volume" (April 2020); Pitchbook-NVCA Venture Monitor, July 13, 2020 (<https://pitchbook.com/resources/reports/venture-monitor/>).
Note: For illustrative purposes only.

EBITDA multiples on software deals in the LBO market have increased steadily

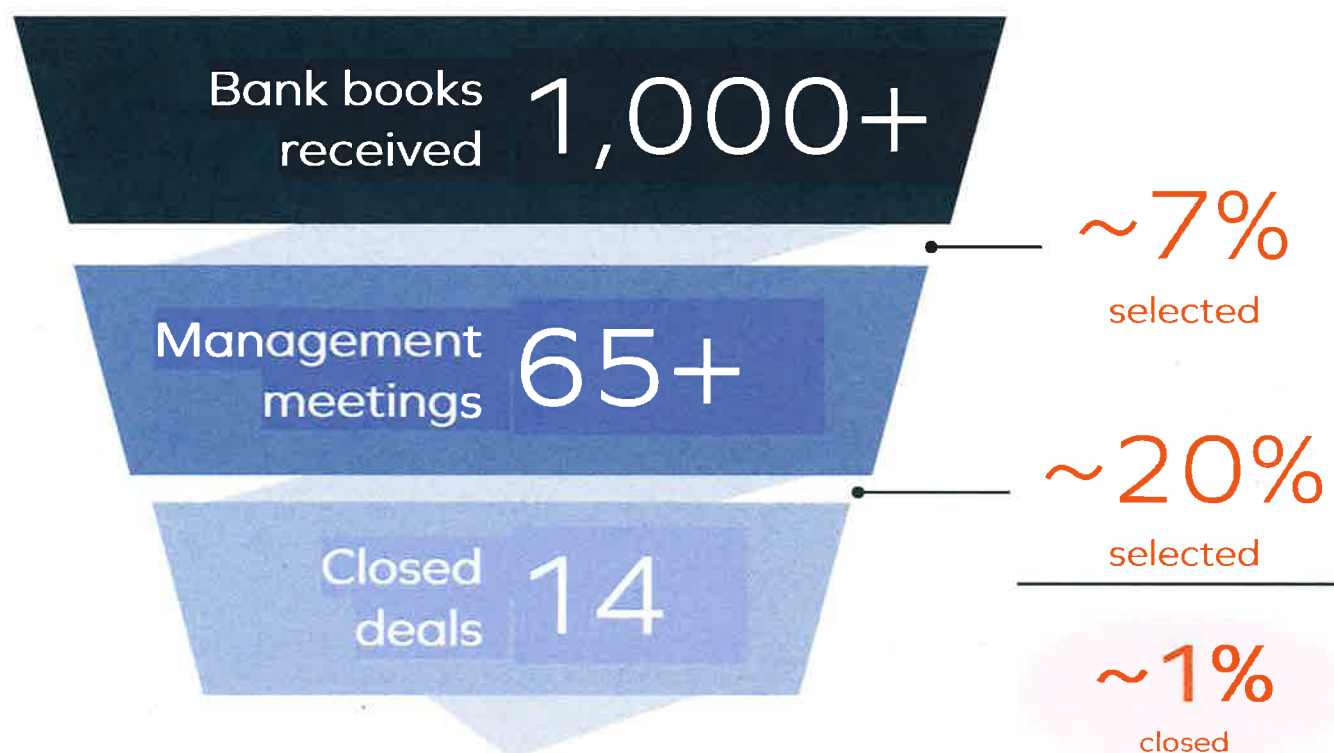
Software LBO EBITDA multiples



SOURCE: For data from 2009-2017, Source: RBC Capital Markets analysis, "Summary of Historical Leveraged Buyouts in the Software Sector Over the Last 10 Years." Data as of 10/18/2018. For data from 2018-2019, Source: Jefferies analysis, "Software M&A Deals." Data as of 9/14/2020. Analyses exclude deals under \$100 million and deals with EV / LTM EBITDA greater than 50.0x.
Note: For illustrative purposes only.

Insight's banked deal funnel is highly selective

Banked deal funnel, *Jan 2019 - Dec 2019*^{1,2,3}



¹ Includes all logged prospective banked deals, not just leveraged buyouts.

² May include deals provided by an investment bank for companies with which Insight had an existing relationship.

³ Insight participated in at least 65 management meetings with companies undergoing a banked sale process in 2019. However, the actual number is likely higher due to certain deals not being logged in Insight's banked deal database.



MATRIX CAPITAL

San Francisco Employees' Retirement System (SFERS) Presentation

Feeder Entities

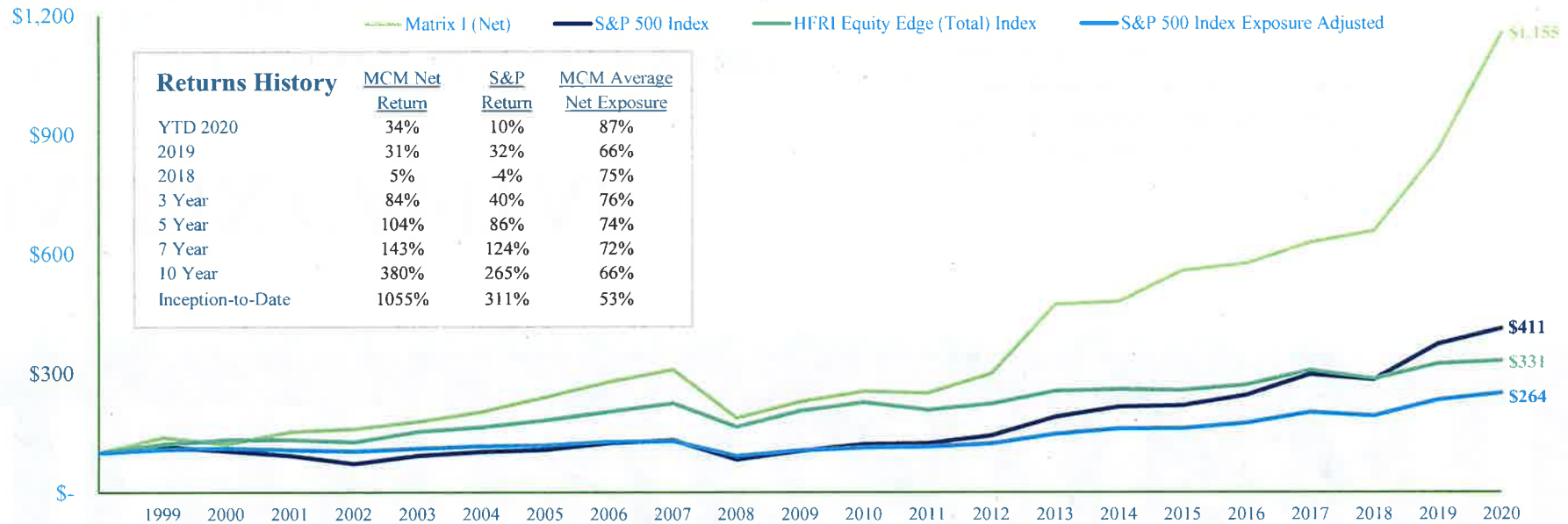
Matrix Capital Management Fund, L.P.

Matrix Capital Management Fund (Offshore), Ltd.

(collectively with Matrix Capital Management Master Fund, L.P., "Matrix Funds" and "Matrix Capital")

November 2020

Matrix Capital Returns Over Time



*Please see end notes on final page of this presentation for additional details on performance data. Unless otherwise specified, the information described herein is as of November 5, 2020. The HFRI Equity Hedge (Total) Index (HFRIEHI) value is based on the most recently released data as of September 30, 2020.

**The HFRIEHI is an index maintained by Hedge Fund Research, Inc. that aggregates the performance of investment managers who maintain positions both long and short in primarily equity and equity derivative securities.

The Fund has achieved meaningful absolute and exposure-adjusted outperformance of the S&P 500 through significantly better stock selection without the use of leverage

Our Strategy To Drive Returns

Invest As An Owner

- Founded in 1999 by David Goel and Paul Ferri
- GP represents ~38% of AUM
- Current assets are ~\$6B
- We invest capital as if it were our own because a substantial portion of it is
- Because Matrix was created to generate investment returns, not fee income, the firm has raised ~\$1B in capital, over 21 years, and generated ~\$5B in gains

Manage A Differentiated Portfolio Concentrated In Our Best Ideas

- Our U.S.-oriented portfolio is focused by sector
 - Life Sciences / Healthcare Tech
 - Software
 - Internet / Payments
 - Semiconductors
- We concentrate in our best ideas
 - 15-20 long ideas, 10-20 short ideas
 - Achieves portfolio diversification and maximizes our intense research efforts
 - Long positions are typically 3%-15% of equity and short ideas 0.5%-5%
- This focused approach is what enables us to operate our differentiated idea generation/diligence model

Operate A Sustainable Platform For Innovation

- Starts with our internal team
 - 9 research analysts in Waltham, MA
 - 5 research analysts in Palo Alto, CA
 - Focused talent development model
- Operations team of 11 people
- Incorporates external expertise, including > 500 Matrix Institute members and broader entrepreneur/industry veteran advisors
- Leverages proprietary data analytics
 - Proprietary data sets and creative approaches to broader data sets
- Unified with our investment processes and internal software platforms
 - Matrix Research Portal
 - Customized relationship management

The Matrix Institute

A Unique Diligence Model

INSIGHT

- A core premise from our founding was that entrepreneurs and private business executives could help identify and assess both technology disruption themes and specific investment opportunities, which lead to greater depth of understanding

NETWORK

- We began over twenty years ago with a portfolio of exceptional executive relationships, and have been expanding this relationship base over time
- We have formalized our approach to working with executives through the Matrix Institute
- We invest actively in expanding our portfolio of Matrix Institute relationships across our sectors of expertise
 - We actively recruit as we diligence investment ideas
 - We hire experienced talent who bring their own relationship base

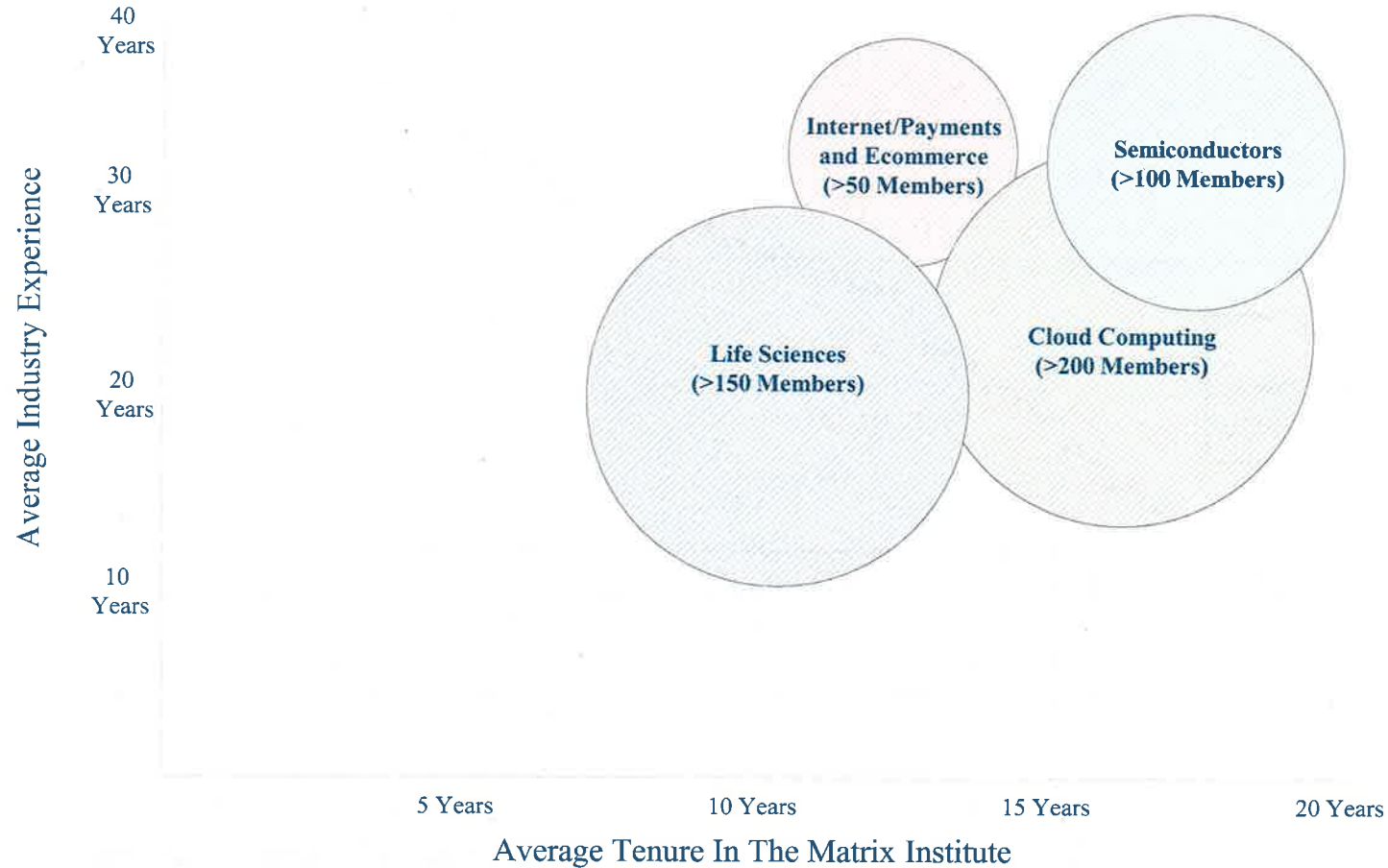
DIFFERENTIATION

- Our expansive global network across our portfolio sectors sets us apart
- We maintain deep focus across multiple vantage points, including competitors, implementation partners, technology partners, API partners, start-ups, large enterprise technology buyers, and private investors
- We assemble unmatched human capital, with titles including: Founder, CEO, CFO, CIO, CISO, Product Development Exec, Business Development Exec, Sales Exec, Procurement Officer, Regional Implementation Partner, Seed Investor, Early Stage Investor, Board Member

DURATION

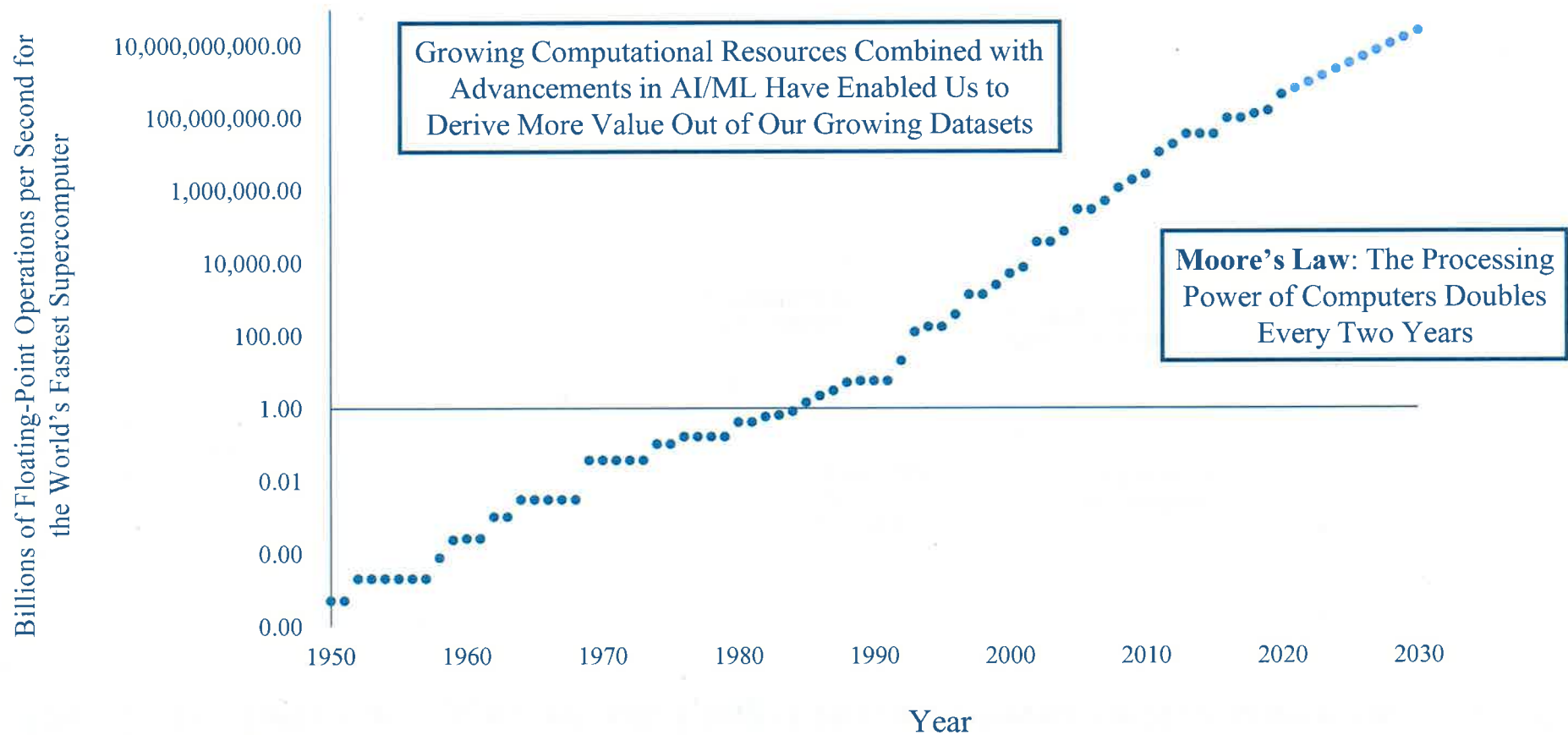
- Our relationships are developed over time to support our ability to invest over a multi-year period, as opposed to transactional relationships used elsewhere

The Matrix Institute: Experienced, Long-Tenured Executive Relationships



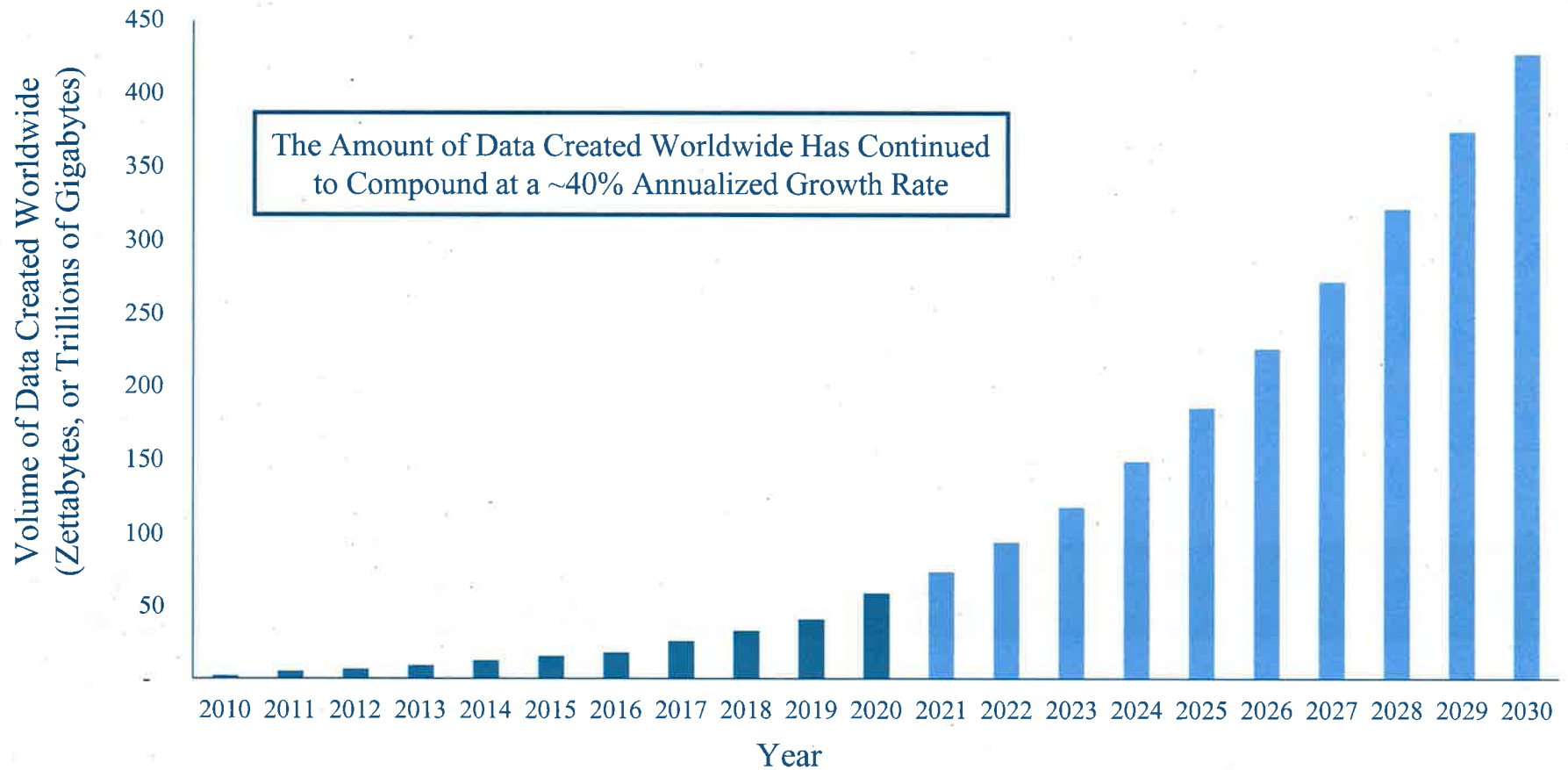
Global Computational Power Has Improved Dramatically

The Need To Analyze Large Datasets Has Spurred A Demand For Stronger Computing Engines



The Global Datasphere Has Rapidly Expanded In Recent Years

The Sheer Amount Of Data Generated And Recorded By Humanity Is Significant And Growing

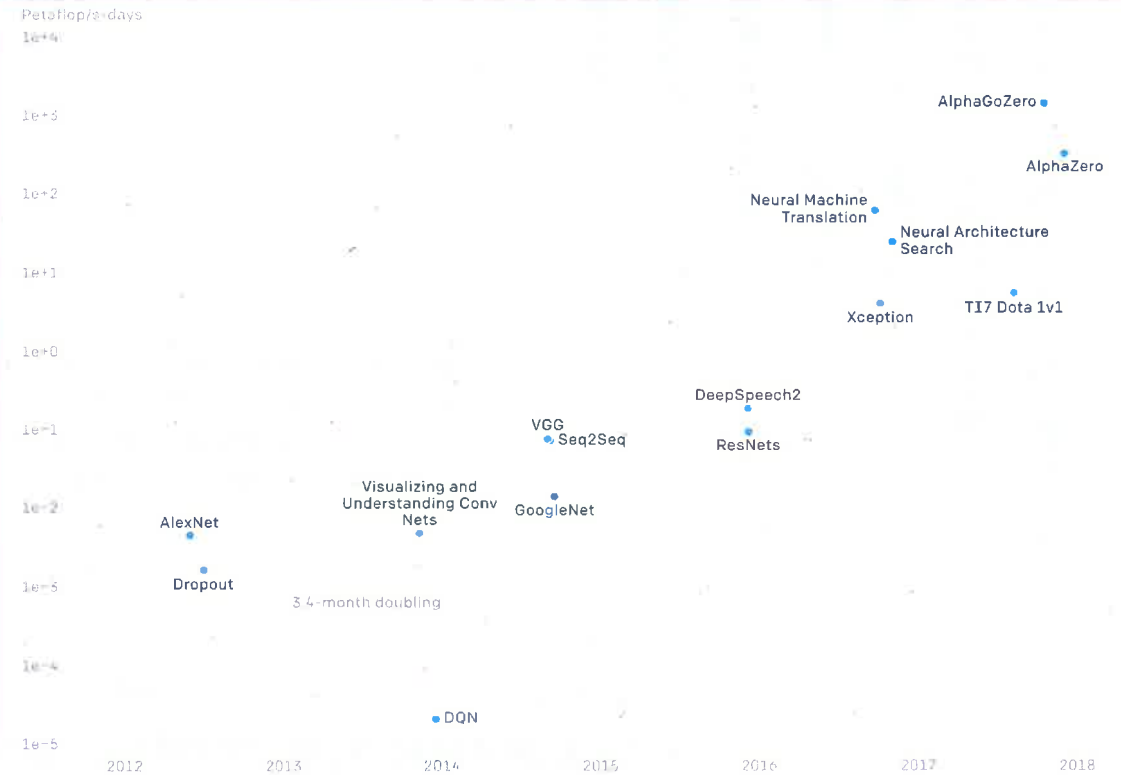
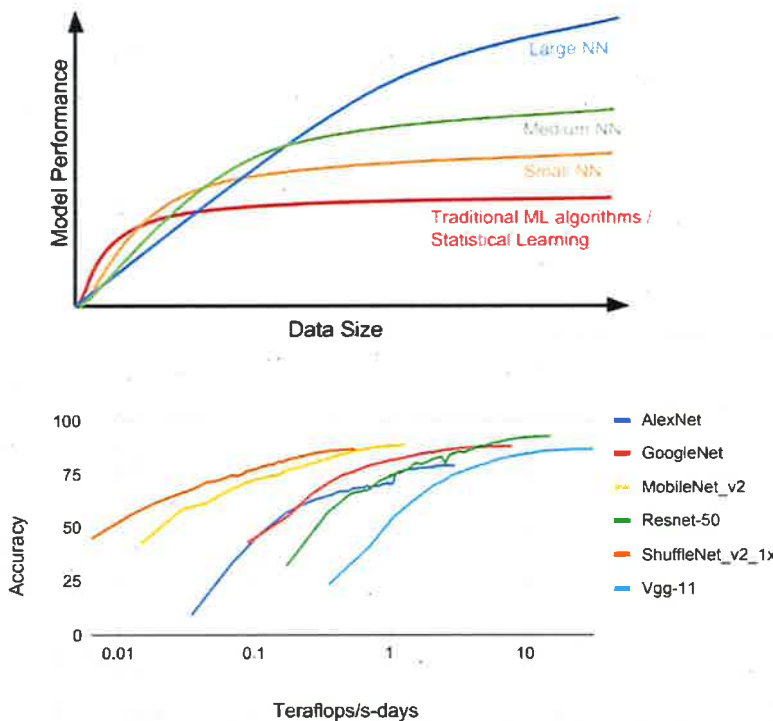


AI / ML Is The Inevitable Consequence Of The Emerging Data Economy

These Technologies Are Only Possible With Large Data Sets And Strong Computing Power

ML Model Performance and Accuracy Are Heavily Tied to the Size of the Training Dataset

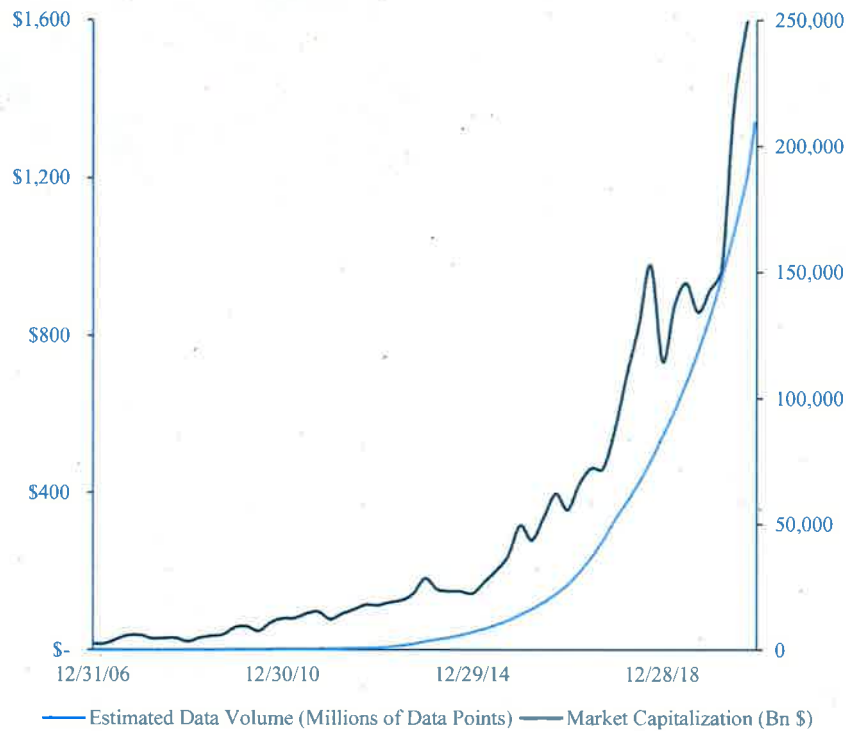
The Amount of Computational Infrastructure Required to Train High-Quality AI Algorithms is Doubling Every 3.4 Months



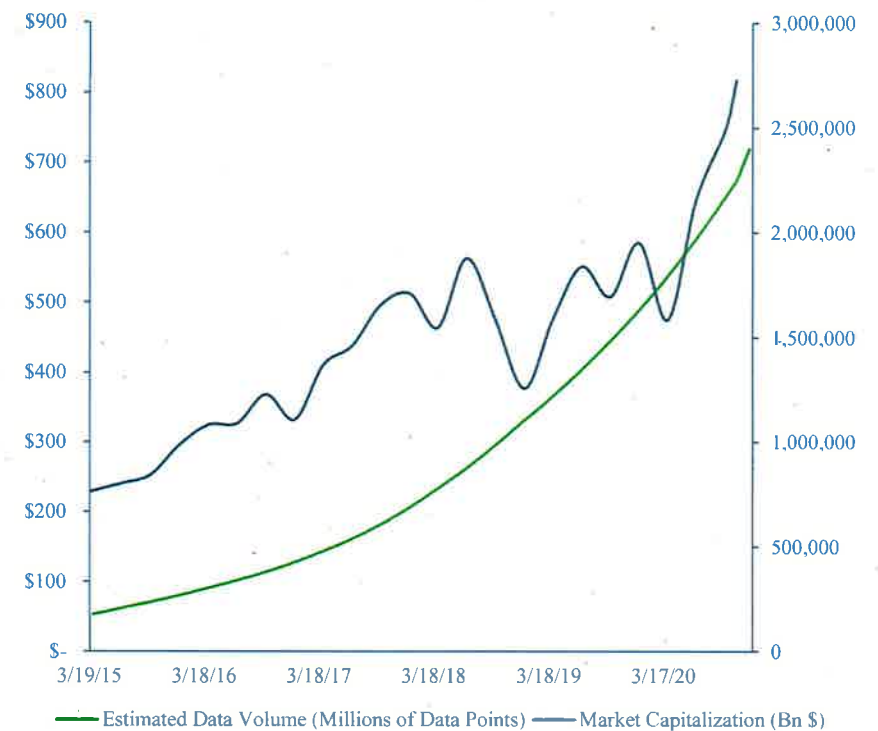
The Explosion of Data Has Fueled Significant Economic Value Creation

Trillion-Dollar Businesses Are Built On Massive Data Sets

Amazon's Market Capitalization and Estimated Data Volume Growth



Facebook's Market Capitalization and Estimated Data Volume Growth



AI / Next-Gen Technologies Are Powering a Wave Of Bio-Innovation

The Industry Is Looking To Optimize Their R&D Processes Using These New Approaches

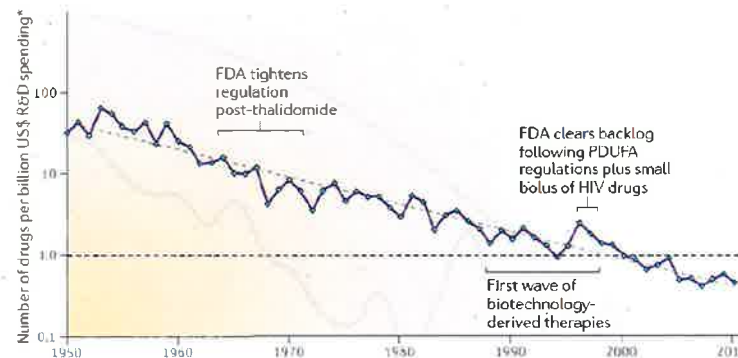
**Annual Worldwide Drug Spending
Will Continue To Increase...**

2021:
\$1.5T

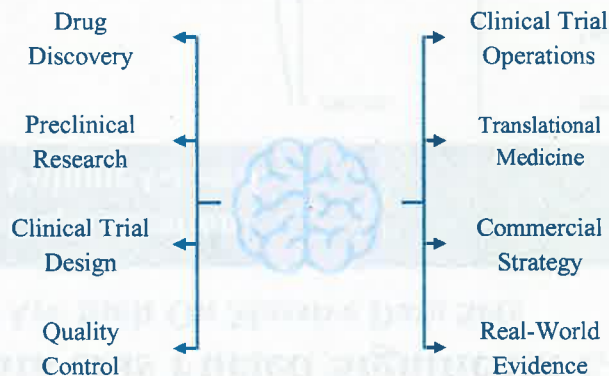


2024:
~\$2.0T

**...But
Biopharma R&D
efficiency has
declined
significantly over
the last 50 years**



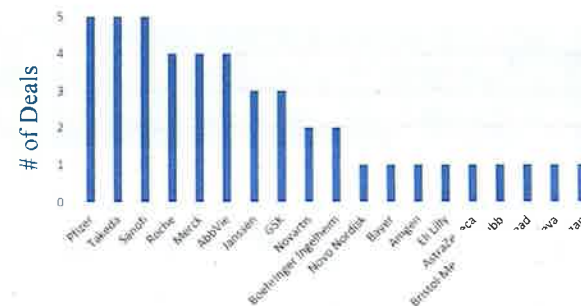
Artificial Intelligence and other emerging technologies are transforming nearly every component of the therapeutic development process, and attracting significant interest from large biopharma



AI/ML Drug Development Deals By Large Biopharma

>\$7B in Deal Value Signed to Date

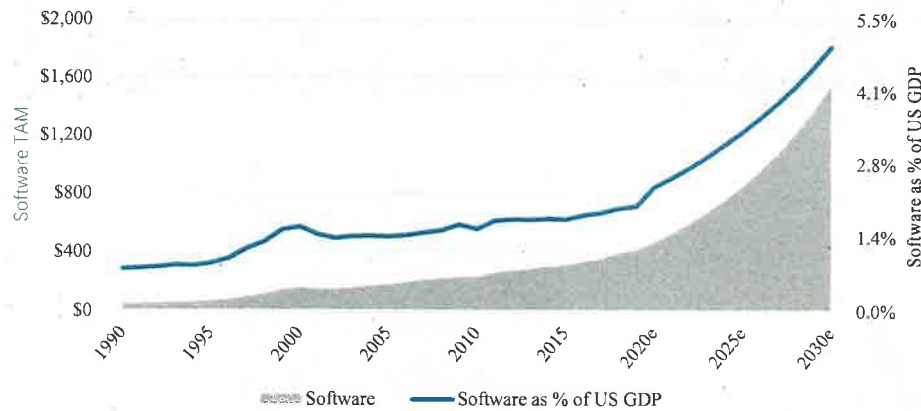
>> Est. >\$5T in Future Equity Value Creation



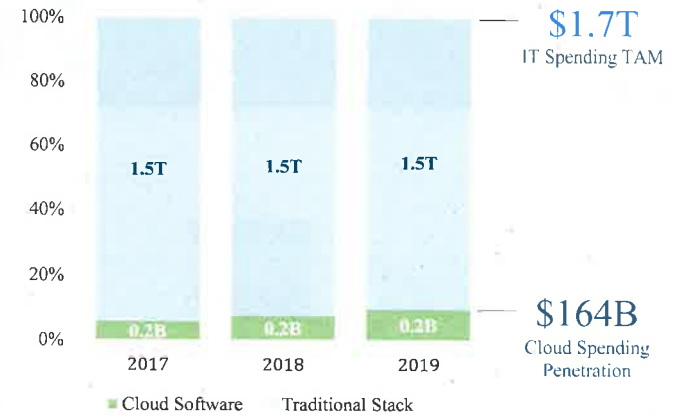
Explosion of Data / Compute Accelerates The Migration To Cloud Computing

The Shift to The Cloud has Created Several Emerging Opportunities Within Software

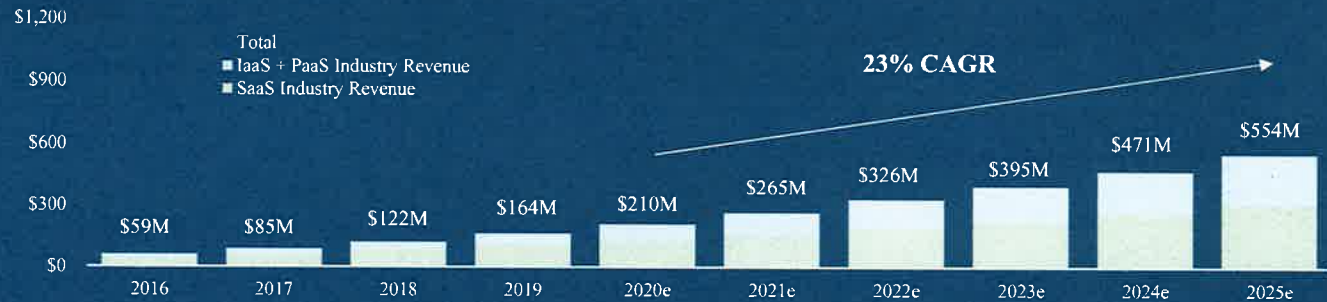
Software Is On Its Way To Doubling to ~5% of Global GDP by 2030



Today Cloud Spending Is Only <10% Of Total IT Spend



Cloud Spending Is On A Path To \$1T In 2030



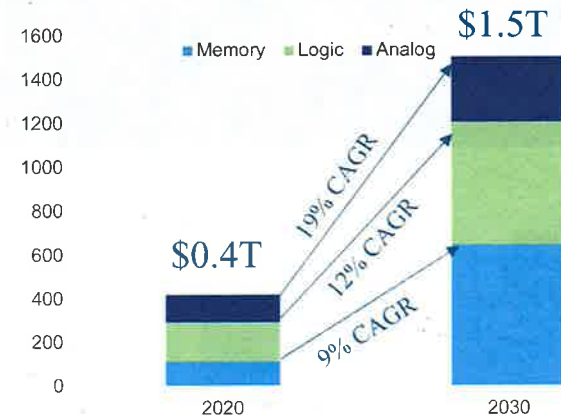
AI / ML Heightens The Strategic Importance Of The Semiconductor Industry

Key Area of Growth Aligned with Several Transformation Technology Themes

The \$420B semi industry is supporting \$5T in end-market industries, and a further \$50T in GDP – a 10x multiplier



The semiconductor industry is experiencing accelerating growth, driving a path to \$1T 2030 revenues



Improved Industry Economics



Insufficient Foundry Capacity



Slowing Moore's Law

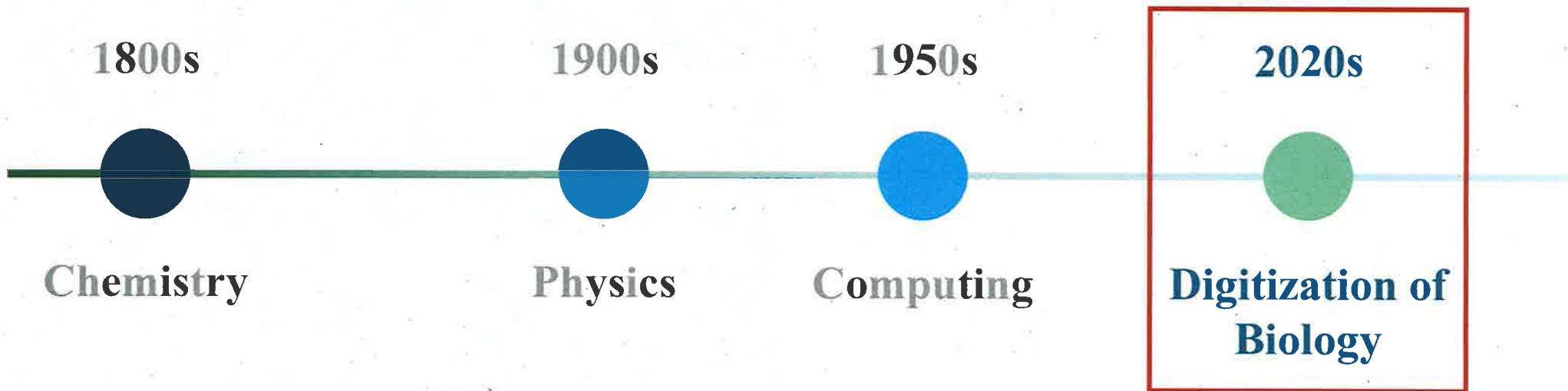


Secular Demand For Silicon



Commercial and Economic Power now resides in the hands of the scale semiconductor industry leaders

With These Technologies, We Are Entering The Next 'Epoch' Of Scientific Innovation **MATRIX**
AI/ML Is Allowing For Unprecedented Quantitative Precision In Analyzing Human Biology CAPITAL MANAGEMENT

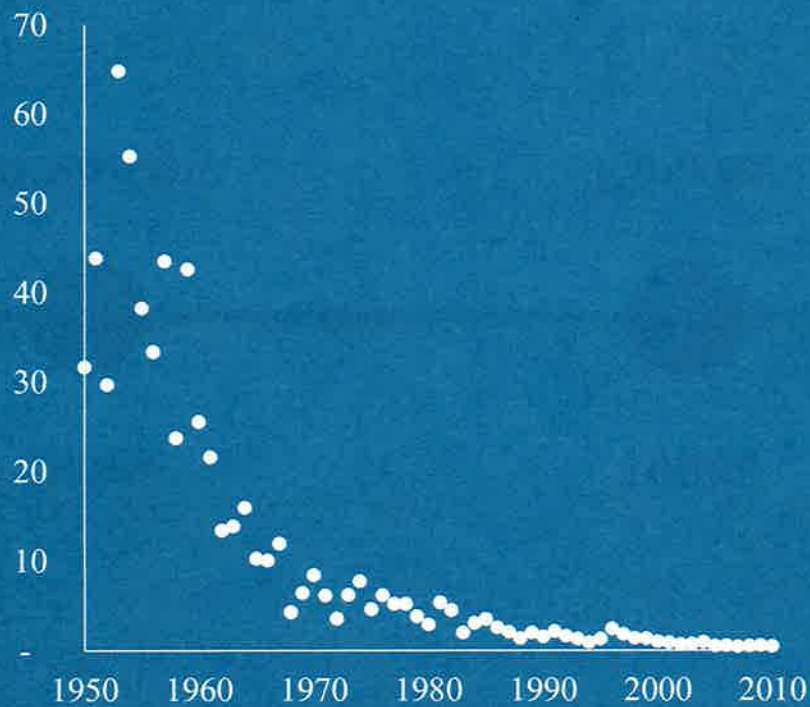


**The Convergence of Quantified Biology and Machine Learning
has Propelled us into the Next Generation of Discovery**

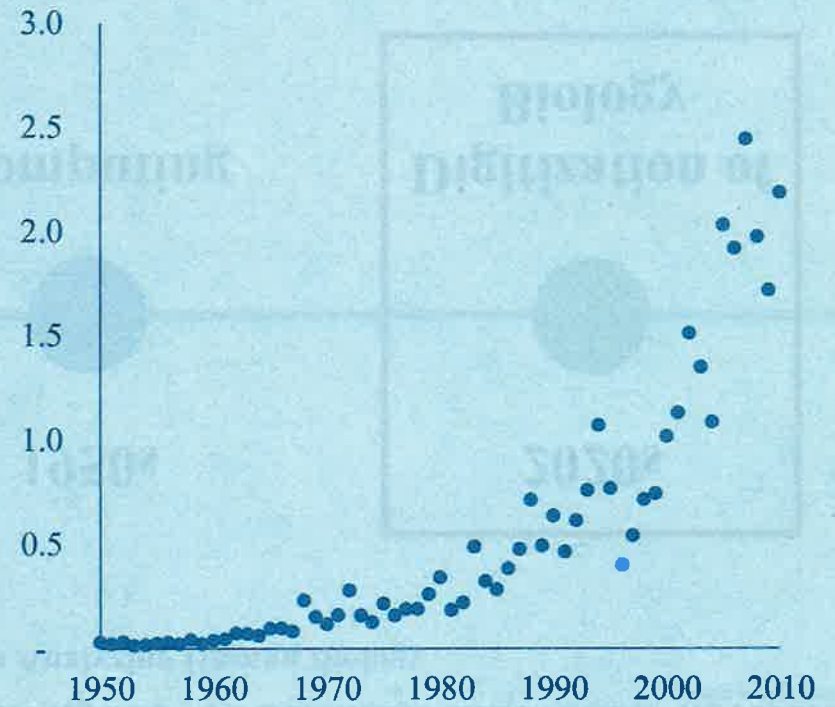
Eroom's Law: Drug Discovery is Becoming Slower & Less Efficient

This Trend Represents The Inverse of Moore's Law

New Drugs Developed Per \$Bn Of R&D Spend



Average R&D Cost For New Drug Development (\$Bn)



Eroom's Law Is Driven By Four Key Trends

Despite Improvements in Technology, Drug Development has Become More Challenging

MATRIX
CAPITAL MANAGEMENT

New Drugs Only Offer Modest Incremental Improvements over the Standard of Care

- As the standard of care improves over time it becomes more difficult to produce even more effective treatments

R&D Programs Have Become Larger and More Human Capital has Been Deployed to Projects

- Organizations tend to throw money and resources at a project in order to maximize the chance of success
- Project overrun has led to bloated R&D cost structures which have increased development costs

Government Regulators have Become Increasingly Risk Averse

- After several approved drugs were removed from market regulators have adopted more stringent requirements
- There has been a progressive lowering of risk tolerance

Changes to the Research Process Have Prioritized Brute-Force Discovery Techniques

- The field of drug discovery has transitioned from classic animal testing methods to target-based high throughput screening (HTS)
- HTS methods tend to be faster and cheaper, but often come with a lower probability of success

Rising Drug Development Costs Are Driven By A High Failure Rate

This Is Ultimately A Failure To Engineer And Develop Optimal Therapies

Over The Last 30 Years, The Cost of Drug Development has Increased ~25x

High Failure Rates Reduces The Return on R&D Investment in Drug Development Programs

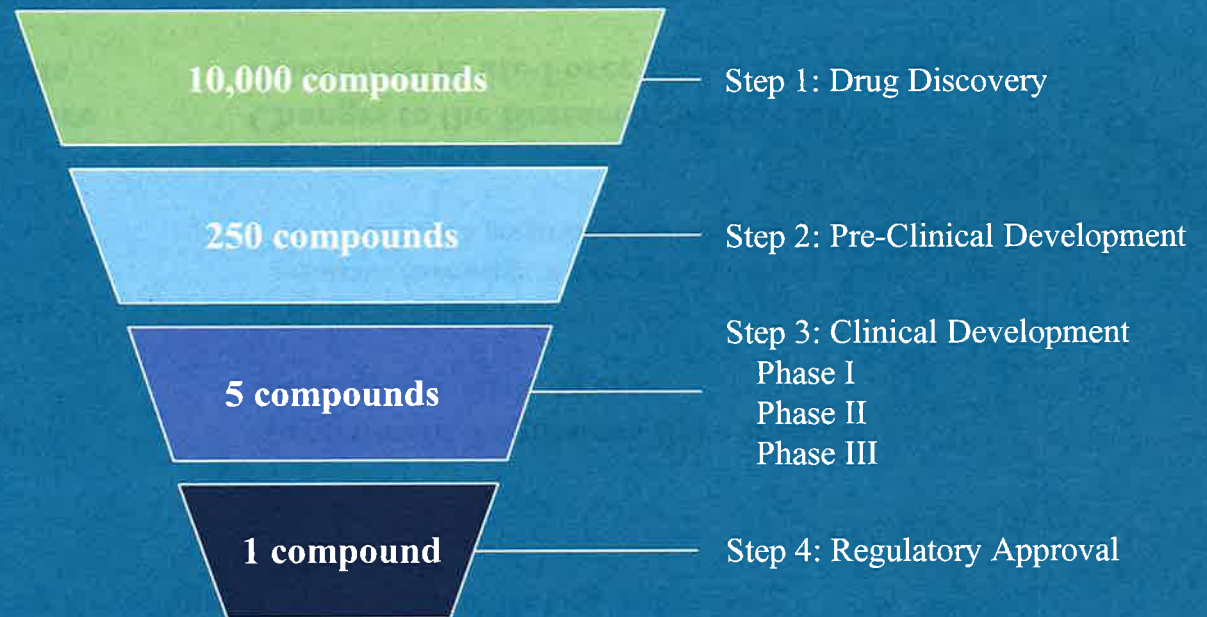
\$100M

1970s



\$2.5B

2000s



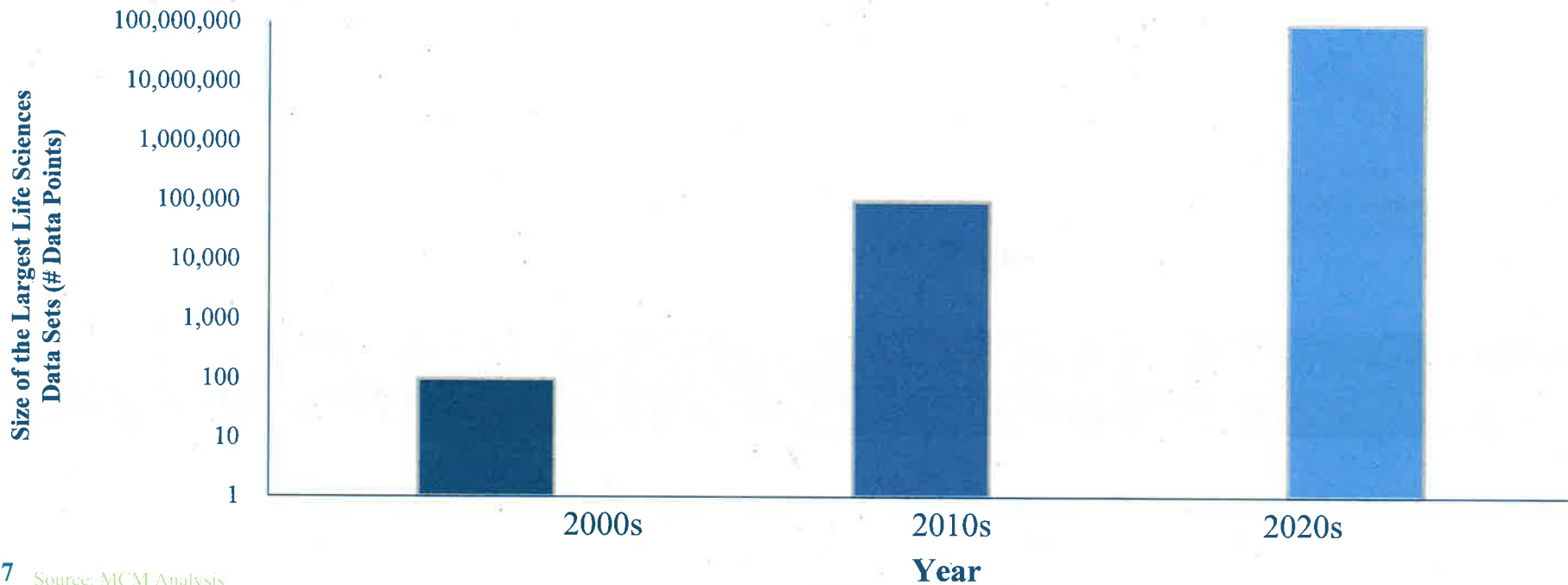
Life Sciences 'Digitization' Is Poised To Transform The Sector

Big Data is Poised to Revolutionize Pharmaceutical R&D And Other Essential Processes

Today, bio-data is difficult to generate, analyze, and share. 100,000 data points would be considered a 'large' dataset, and most companies struggle to gather data for more than a few hundred patients



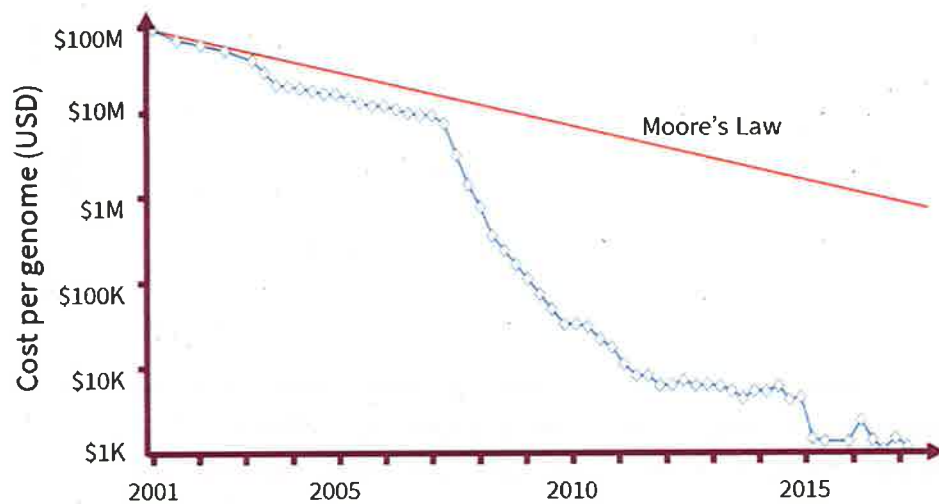
Over the next decade, we will witness a dramatic expansion of the data available to the life sciences industry



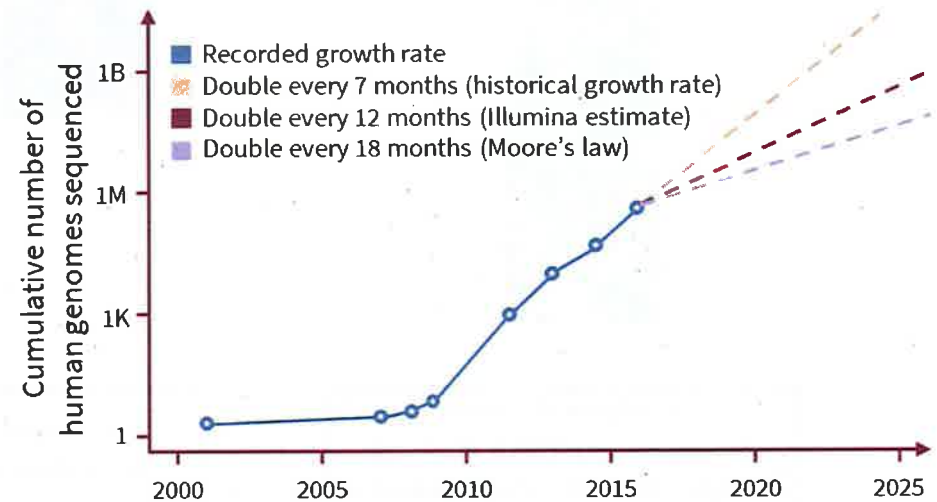
AI / ML Will Unlock Significant Value From Human Bio-Data

Given the Current Pace of Growth, There Will be Close to 2B Human Genomes Sequenced by 2025

Rapidly Declining Cost of Genome Sequencing



Exponential Growth in the Amount of Genomic Data



The Scale of Data Available for Biological Investigation is Expected to Grow Significantly

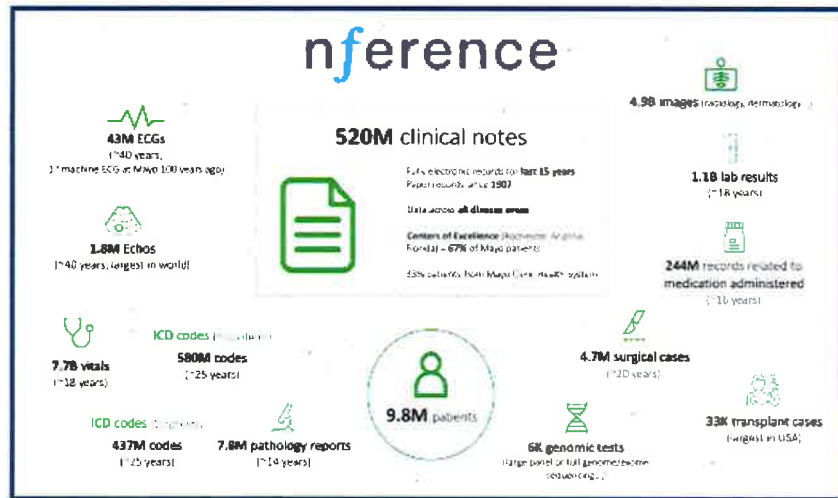


This Growth Will Enable Sophisticated Machine Learning Techniques to Unlock New Insights About Our Biology

Highlighted Investment 1: nference AI

Creating A Multi-Pronged Enterprise From One Centralized 'Big Data' Engine

Proprietary data via partnerships with Mayo Clinic and other institutions powers the nference platform, allowing the company to build a range of businesses and solutions



Comprehensive Data Science Solutions for Industry

nference uses its own proprietary database in conjunction with partner company data to extract key insights and guide R&D strategy

Ongoing projects include Pulmonary Hypertension, Multiple Myeloma, Amyloidosis

Data Lake / Sandbox offering for industry and academic partners

Research Software

Digital Pathology

Smart Sensors



Highlighted Investment 1: Inference AI – Pulmonary Hypertension

Inference's Platform Is Revolutionizing The Diagnosis And Management Of A Devastating Disease

MATRIX
CAPITAL MANAGEMENT

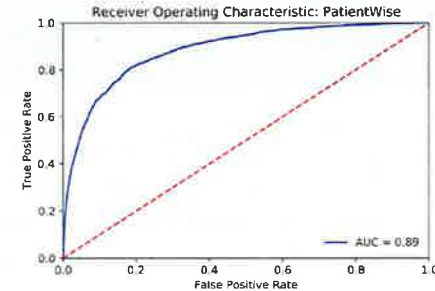
Pulmonary Hypertension Patient Journey

Global Pulmonary Hypertension Drug Market: \$6.3 Billion



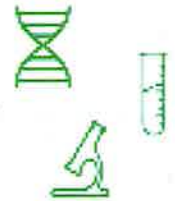
Inference is partnering with a large, global-scale pharma to determine early-stage biomarkers of Pulmonary Hypertension, a disease that has historically been difficult to diagnose – improvements in diagnostic accuracy can lead to longer duration of therapy, and therefore greater product sales

ECG and Heart Catheterizations are currently used in diagnosis, but are of mediocre efficacy



84% Sensitivity
83% Specificity

By applying AI / Machine Learning to its vast database of Mayo Clinic data, Inference has uncovered a set of genetic biomarkers that significantly improve upon existing diagnostic approaches and can direct patients toward the appropriate therapy earlier



Matrix has supported Inference from Seed Stage, and plans to continue helping the company achieve its longer-term potential

2017: Matrix makes initial investment in Inference's Seed Round

2018: Matrix funds Inference Series A

2019: Matrix funds Inference Series B

2020: Matrix funds Inference Series C

Total Invested At Cost: \$67m

Equity Ownership: 22%

Highlighted Investment 2: Encoded Therapeutics

High Throughput Genomic Screening + Machine Learning To Design Optimized Gene Therapies

Astellas' Audentes reports 3rd death in gene therapy trial

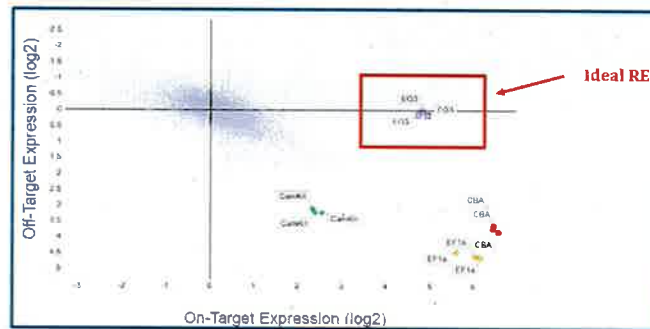
STAT+

Solid Biosciences' Duchenne gene therapy trial halted after patient suffers serious toxicity

Toxicity of dorsal root ganglia is widely associated with CNS AAV gene therapy

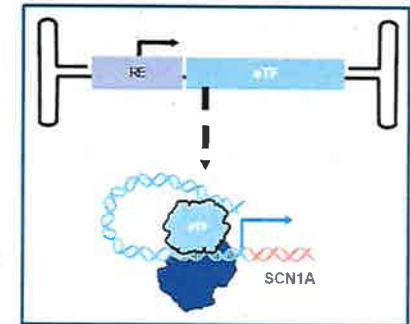
MARY ANN LIEBERT, INC./GENETIC ENGINEERING NEWS

First generation gene therapies suffer from a lack of cell type specificity, but figuring out how to achieve this specificity has traditionally been a slow, manual process



The Encoded platform applies machine learning to high-throughput screens of non-coding genomic regions, uncovering the most ideal biomarker 'tags' for their therapies

This type of design allows for significantly improved efficacy and safety



Encoded is using this technology to address severe, treatment-resistant diseases such as Dravet Syndrome, a devastating form of epilepsy

We have supported Encoded through each of its financing rounds, and believe the company will ultimately be a dominant player in the gene therapy landscape

2016: Matrix makes initial investment in Encoded's Series B Round

2019: Matrix funds Encoded Series C

2020: Matrix funds Encoded Series D

2021-22: Encoded's lead program to enter Phase 1 clinical trials

Total Invested At Cost: \$117m

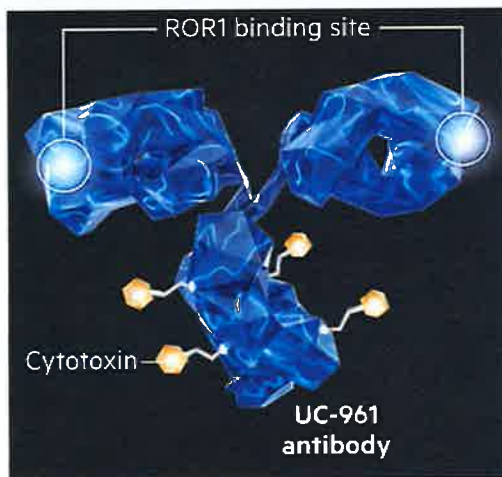
Equity Ownership: 26%

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Highlighted Investment 3: VelosBio (Sold The Company)

Acquired by Merck for \$2.75B (Nov 2020) | Matrix MOIC: ~7.7x

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VLS-101 Structure

VelosBio's lead therapeutic compound, VLS-101, is an antibody-drug conjugate (ADC) targeted against the ROR1 antigen

Historically, primitive chemical engineering methods resulted in disastrous toxicity profiles and underwhelming efficacy for these drugs – the entire class was poorly perceived by investors and the industry for many years

But recently, advancements in medicinal chemistry and protein engineering technologies have allowed biotechs to generate ADCs with unprecedented efficacy and tolerability – this has led to significant ROI for investors in best-in-class ADC companies

With recent advances in ADC technologies, Velos and other biotechs have begun to achieve impressive milestones and exits in 2020, bringing the entire class / modality into the spotlight


VELOS BIO

Acquired by Merck (\$2.75B)

 Seagen

✓ MCM investment 2017-20
✓ 3-Yr Stock ROI: +220%

 Immunomedics

Acquired by Gilead (\$21B)

Matrix's track record investing in Seagen and VelosBio are reflective of a broader interest in the ADC space, which we identified as undergoing a major secular inflection

2018: Matrix introduced to VelosBio via Zentalis (ZNTL) investment

07/2020: Matrix named co-lead investor in Velos Series B, granted larger allocation than Viking, Foresite, OrbiMed, and other participating firms

11/2020: Merck acquires VelosBio for ~\$2.75B

Total Invested At Cost: \$25m

Value at Exit: \$193m

Identifying New Areas Of Growth Applying AI In Life Sciences

We Aim To Make A Range Of Highly Compelling Investments Around This Theme

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Company	Total Cost Basis	Current Market Value*	Est. Return Multiple To Date	Current Company Valuation*	Expected Long Term Valuation	Est. Future Return Multiple
Adaptive	\$151M	\$769M	4.2X	\$6.7B	>\$10B	>6.3X
Encoded	\$117M	\$147M	1.3X	\$600M	>\$3B	>6.3X
Inference	\$67M	\$106M	1.6X	\$660M	>\$3B	>7.2X
Zentalis	\$38M	\$125M	3.3X	\$1.3B	>\$4B	>9.9X

* For now-public companies, values as of market close on 09/30/20

We believe the next wave of Artificial Intelligence enabled innovation in Life Sciences is just beginning, and plan to invest significant capital in these transformative companies

Company	Sub-Sector / Theme	Potential Capital Commitment	Expected Return Multiple
Target #1	AI in Drug Engineering And Development	>\$100M	>8X
Target #2	AI in Medical Procedures	>\$35M	>10X
Target #3	AI in Care Delivery And Workflow Optimization	>\$75M	>5X
Target #4	AI in Research Tools & Translational Medicine	>\$50M	>6X

Appendix

There is no guarantee that targets will be or may be achieved. The information herein is the opinion of Matrix Capital Management based on information obtained from sources we deem to be reliable but is not guaranteed by Matrix and is subject to change at any time based on unforeseen company events or market conditions.

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Endnotes

1) Performance is audited for years 1999 to 2019 and unaudited through October 15, 2020. Actual returns may differ. Net Return includes all income and expenses. This includes the reinvestment of dividends, capital gains, 1.5% annual management fees (0.125% monthly), all other fund related income and expenses, and incentive fee. Net Return is the performance for an investor who has been invested since the October 1, 1999 inception date of Matrix; investors that invested subsequent to the investment date may have a different incentive fee rate which would affect the calculation of Net Return. The performance results are based upon the return of Matrix Capital Management Fund, L.P. Past performance is not a guarantee of future results. Net exposure data are attributable to holdings in public equity securities and do not account for investments in privately held companies.

2) The Standard & Poor's 500 Stock Index (the "S&P 500") is a market capitalization weighted index made up of the 500 U.S. companies with large market capitalizations. Performance is shown including the reinvestment of gross dividends. This index is unmanaged and therefore does not have any transaction costs, advisory fees or similar expenses that are associated with its performance. The performance of Matrix's funds is not comparable to this index because, among other reasons, the Matrix Fund may employ options, short sales, leverage, was not as diversified as the index, and experienced differing degrees of volatility. This index has not been selected to represent an appropriate benchmark to compare the performance of Matrix but rather is disclosed to allow for comparison of Matrix's performance to that of a well-known index. Matrix's holding may differ significantly from the securities held by the index.

**THANK
YOU**

MATRIX
CAPITAL MANAGEMENT





Presentation to San Francisco Employee Retirement System

OrbiMed Advisors LLC
November 18, 2020

This document does not constitute an offer to sell, or the solicitation of an offer to purchase, any security or fund, including interests in the OrbiMed Partners Funds. Any such offer may only be made by means of a confidential private placement memorandum, which is available to prospective investors upon request. This presentation is as of the date noted above and may be changed without notice, and nothing herein shall, under any circumstances, create any implication that there has been no change in the affairs of any fund referenced in this document since the date hereof.

OrbiMed Global Platform

Royalty & Credit

\$1.7

Public Equity

\$5.6

Private Equity

\$8.7

\$16 Bn Assets Under Mgmt.

~100 Total Professionals

~30 PhD or MD degrees

~15 Former CEOs or Founders

~190 Board Seats

~500 Portfolio Companies

Industry Experience

Leading Global Healthcare Platform...

- \$16 billion in assets under management
- 20-year track record in public and private funds
- Institutional infrastructure, strong governance

...with Deep Proprietary Resources...

- Venture Partners are proven company-builders
- 190 board seats provide networks for sourcing, diligence
- PhD/MD expertise in disease areas, biostatistics, etc.

...and Global Industry Coverage

- Investing from start-ups to large public companies
- Active across biopharma, devices, diagnostics, services
- Global network, professionals in 11 locations
- Synergies between public/private markets

Note: As of September 30, 2020. Board Seat, Portfolio Company and other data is estimated and is subject to change.

OrbiMed U.S Private Equity Leadership

Partners / Principals



Carl L. Gordon, Ph.D., CFA
Managing Partner
Prior: Imclone; Rockefeller Univ.



Jonathan T. Silverstein, J.D.
Managing Partner
Prior: Sumitomo



David Bonita, M.D.
General Partner
Prior: Morgan Stanley, UBS



Rishi Gupta, J.D.
Partner
Prior: Raymond James & Associates, Ventas Medicine



Chau Q. Khuong
Partner
Prior: Veritas Medicine, Yale



Peter Thompson, M.D.
Partner
Prior: Sexton-Dickinson, Chiron, Trubion



Mona Ashiya, Ph.D.
Partner
Prior: JPMorgan



Diyong Xu
Principal
Prior: Lazard

Venture Partners



Stephen Squinto, Ph.D.
Executive Partner
Prior: Alexion, Regeneron



Klaus Veitinger, M.D., Ph.D.
Venture Partner
Prior: Schwarz Pharma AG, PHARMA



Kevin Koch, Ph.D.
Venture Partner
Prior: Biogen, Amgen, Amgen, Pfizer



Iain D. Dukes, D. Phil.
Venture Partner
Prior: Merck, Amgen



Sevgi Gurkan, M.D.
Venture Partner
Prior: Merck, Rutgers



Dimitri Krainc, M.D., Ph.D.
Venture Partner
Prior: Northwestern, Lysosomal Tx.



Jim Sullivan, Ph.D.
Venture Partner
Prior: AbbVie

Overview

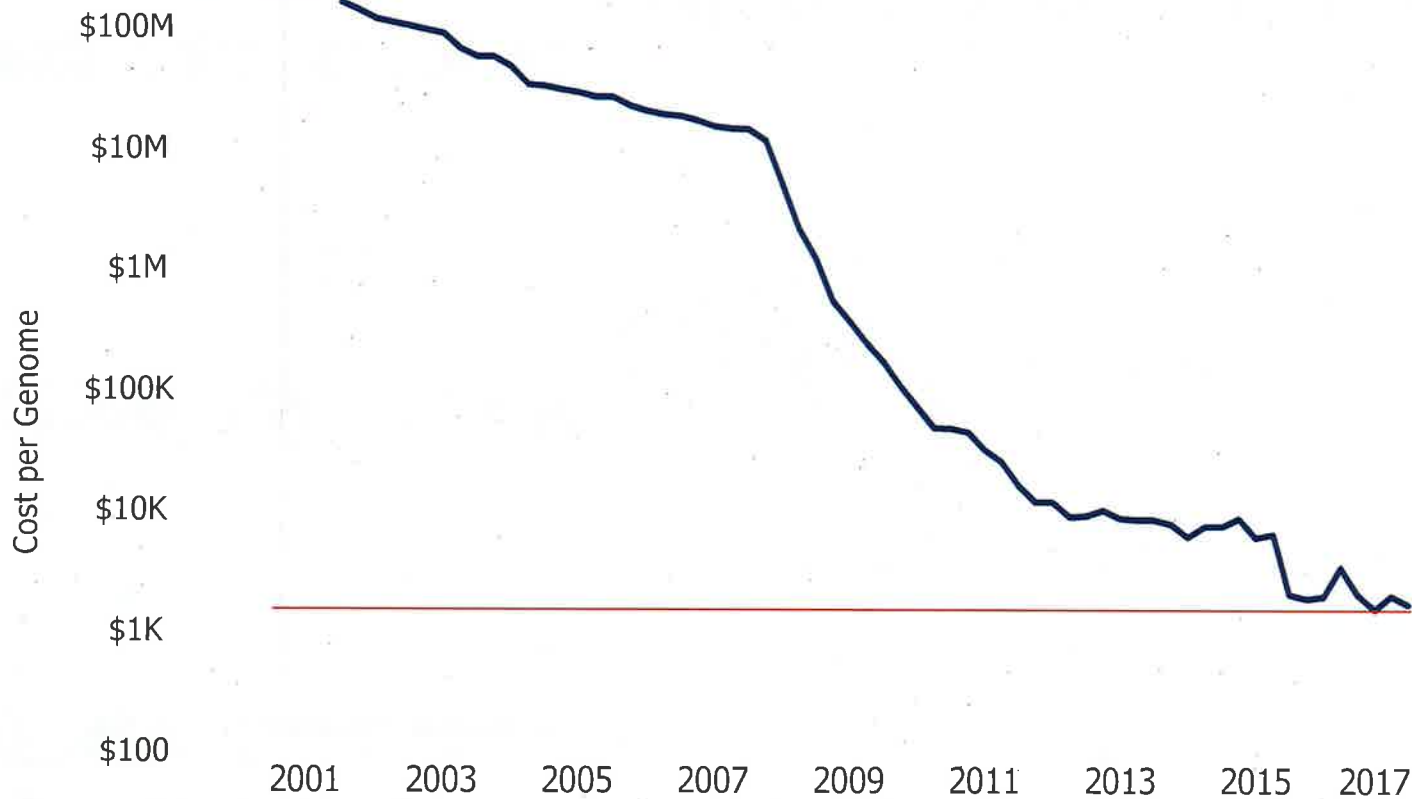
1 The last twenty years in biotech

2 The problem at hand - COVID-19

3 Future of our industry

Sequencing the Genome Ushered in a New Era

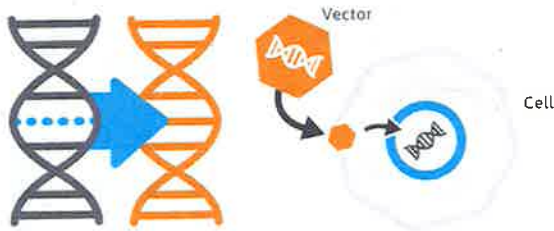
June 2000:
The Human Genome
Project publishes first
working draft of the
human genome sequence



2020: Currently costs
~\$700 to sequence a
genome

Witnessed First Approvals for Genetic Medicines

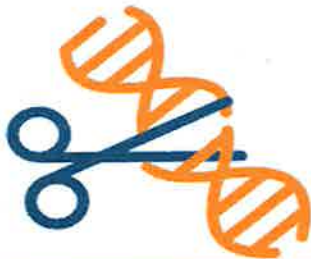
Gene Therapy



FDA NEWS RELEASE
FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss

FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality

Gene Editing

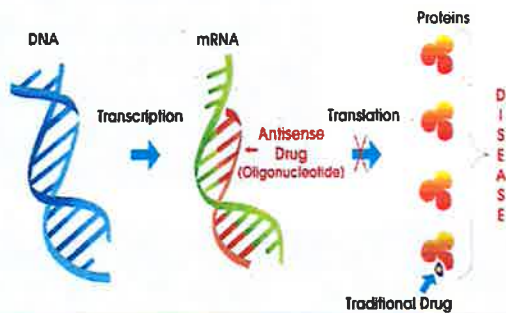


"It's a way to alter DNA with precision and accuracy...to control cells' fate. And even the properties of an entire organism." – Jennifer Doudna (Co-Recipient of 2020 Nobel Prize in Chemistry)

The New York Times
Chinese Scientist Claims to Use Crispr to Make First Genetically Edited Babies

Oligonucleotide Therapeutics

New Chemical Class • New Receptor • New Binding Motif



FDA approves first-ever RNAi therapeutic

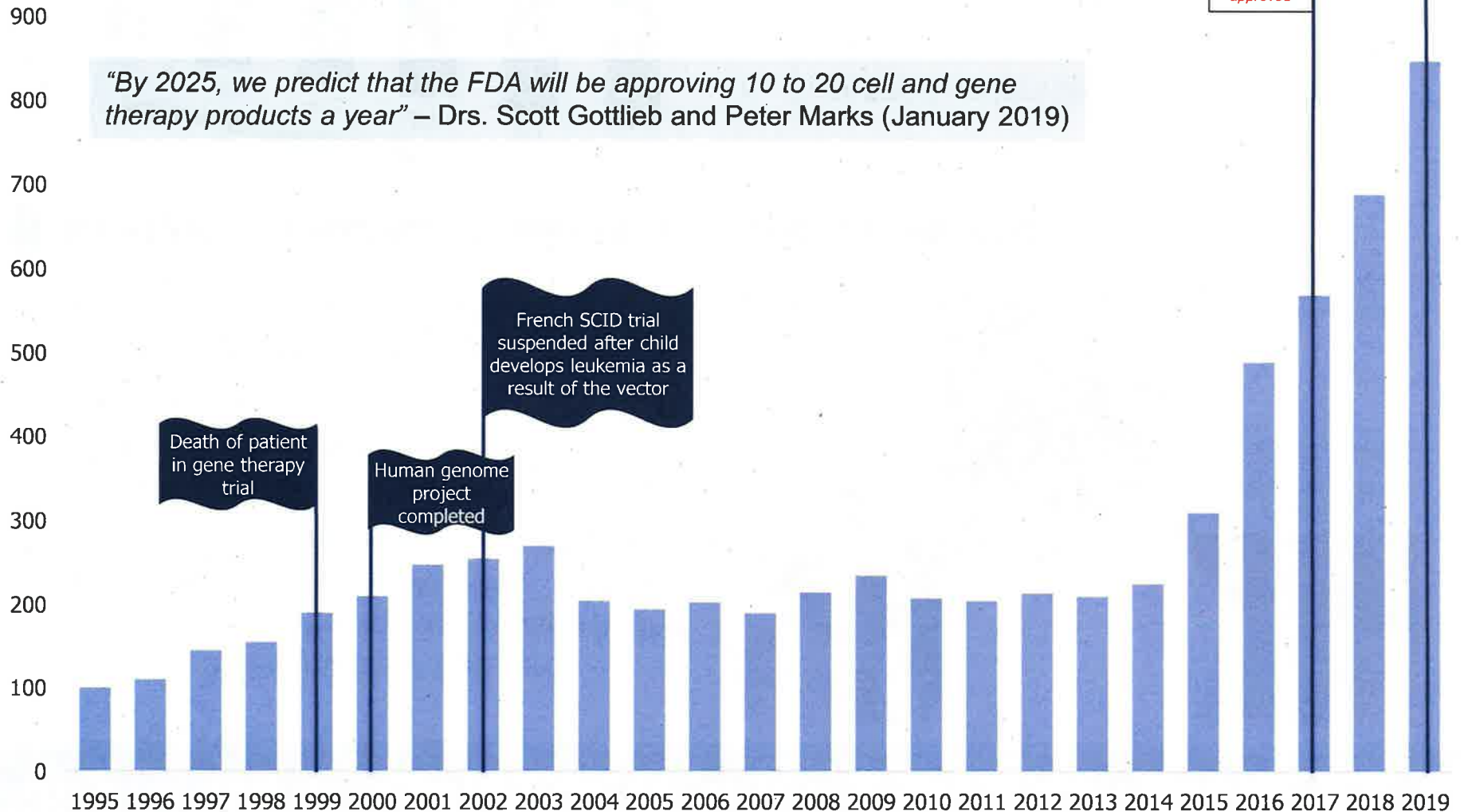
Nod for Onpattro caps two decades of academic and industry work to translate RNA interference from idea to drug

The challenge of delivering RNA-interference therapeutics to their target cells

Delivery difficulties brought the nascent research field to its knees, but approval of the first RNA interference drug offers hope.

Explosion of Genetic Medicines in the Last Decade

Genetic Medicines Pipeline Size⁽¹⁾



Source: Pharmaprojects, through January 2019, FDA press release. Zolgensma approval in May 2019.

Note: SCID = Severe combined immunodeficiency. (1) Genetic medicines includes gene therapy, gene editing, and CAR-T.

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Rare Disease Therapeutic Landscape Has Grown

- There are an estimated 7,000 rare diseases, most of which are caused by the altered function of a single gene
 - Two-thirds are serious and disabling
 - Three-quarters affect children
 - Over half are life-limiting
 - Most have no treatment
- Collectively, rare diseases are thought to affect >200mm people worldwide

Source: Boycott, 2017 Nature.



Source: Biogen, SpringWorks corporate presentation, Duchenne Family Support Group.

Steady rise in number of rare diseases under investigation



Source: Pharmaprojects 2019 Whitepaper.

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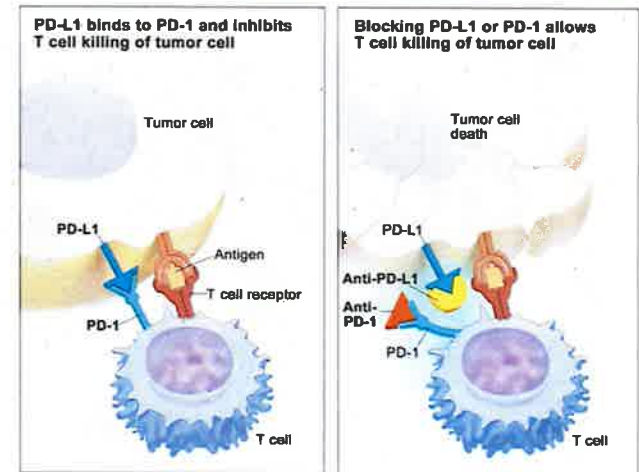
Over the past several years...

- ✓ Increased understanding of genetics
- ✓ Discovery of novel targets
- ✓ Development of new modalities

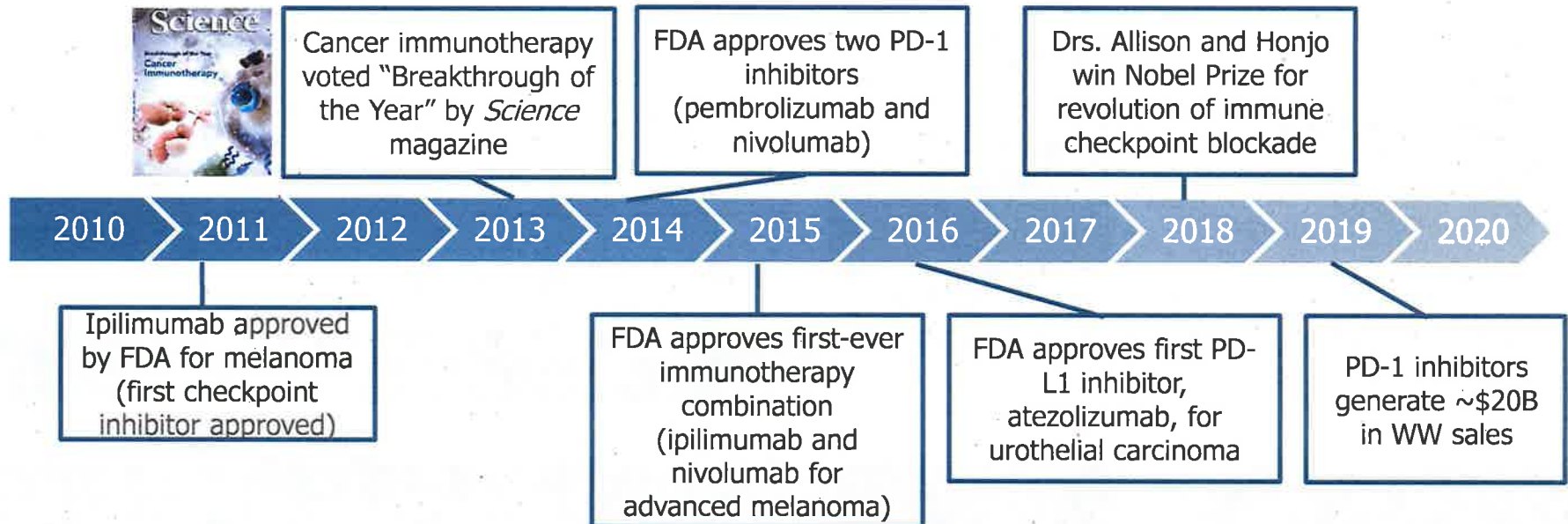
...have lead to higher success in targeting rare diseases

The Rise of Immune-Checkpoint Inhibitors

- A significant advancement for cancer treatment was the introduction of T cell targeted immunomodulators **blocking immune checkpoints, CTLA-4 and PD-1/PD-L1**
- The **growth in the number of active clinical trials testing anti-PD-1/PD-L1 agents has been dramatic**, increasing from 1 in 2006 to >2,000 in 2018¹
- The leading immune checkpoint inhibitors, Keytruda, Opdivo and Yervoy are **approved for a wide array of tumor types including, melanoma, lung cancer, renal cancer, and bladder cancer**



Source: J Adv Pract Oncol 2017;8:747-753



Source: MSKCC, Evaluate. ¹Nature, December 2018 Volume 17.

Treatment Paradigms Have Been Transformed

Combination Immunotherapy in Advanced Melanoma has ~60% Overall and 20% Complete Response Rate

Variable	Nivolumab plus Ipilimumab (N=314)	Nivolumab (N=316)	Ipilimumab (N=315)
Best overall response — no. (%)†			
Complete response	61 (19)	52 (16)	16 (5)
Partial response	122 (39)	88 (28)	43 (14)
Stable disease	38 (12)	31 (10)	69 (22)
Progressive disease	74 (24)	121 (38)	159 (50)
Unable to determine	19 (6)	24 (8)	28 (9)
Objective response‡			
No. of patients with response	183	140	59
% of patients (95% CI)	58 (53–64)	44 (39–50)	19 (15–24)

Source: Phase 3 CheckMate 067 Trial. Wolchok, 2017 NEJM.

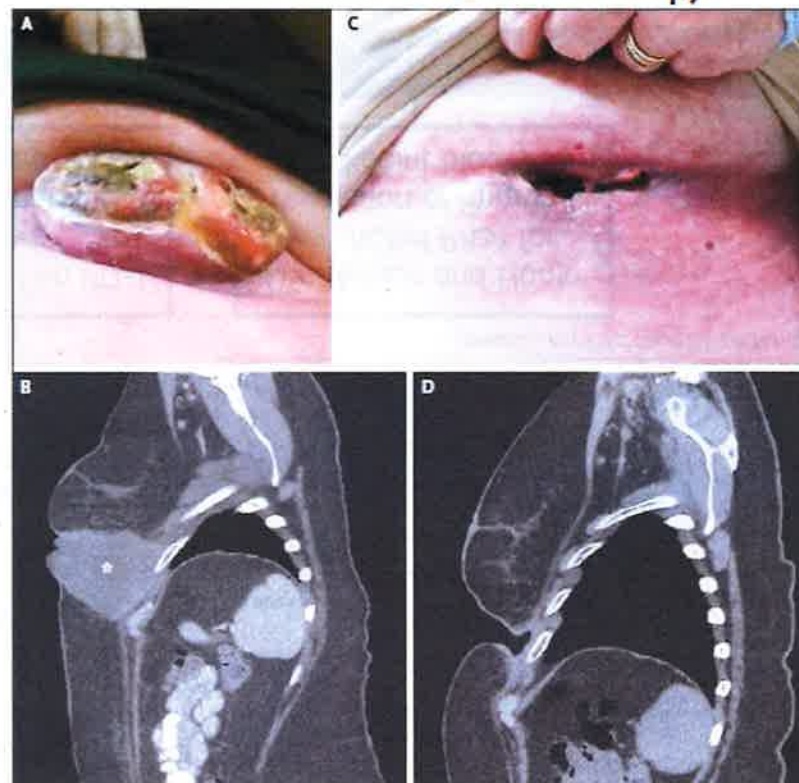
Immune checkpoint inhibitors approved for a variety of cancer types

- Breast cancer
- Bladder cancer
- Cervical cancer
- Colon cancer
- Head and neck cancer
- Hodgkin lymphoma
- Liver cancer
- Lung cancer
- Renal cell
- Skin cancer
- Stomach cancer
- Rectal cancer

Source: National Cancer Institute.

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THE NEW ENGLAND JOURNAL of MEDICINE Rapid Eradication of a Bulky Melanoma Mass with One Dose of Immunotherapy



2015: Image of a 49-year-old woman with a necrotic mass under the left breast. Tumor resolved three weeks after first treatment with ipilimumab and nivolumab.

Source: Chapman, 2015 NEJM,

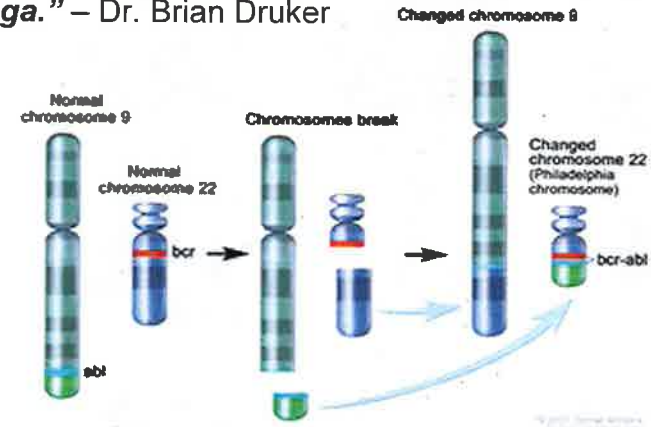
Emergence of Precision Oncology

Imatinib (Gleevec) Kickstarted Precision Oncology Field – Approved 2001

“Gleevec was a completely different class of drugs than what was used against cancer...“these once-dying patients were getting out of bed, dancing, going hiking, doing yoga.” – Dr. Brian Druker

Gleevec demonstrated a 100% response rate in Phase 1

DOSE (mg/DAY)	ALL PATIENTS	PATIENTS WITH RESPONSES	PATIENTS WITH COMPLETE RESPONSES
	no.	no. (%)	no. (%)
25 or 50	6	2 (33)	0
85	4	2 (50)	1 (25)
140	3	3 (100)	1 (33)
200 or 250	16	16 (100)	9 (56)
300-1000	54	54 (100)	53 (98)
Total	83	77 (93)	64 (77)



Researchers discovered for the first time that a genetic alteration could cause cancer. This translocation, resulting in a fusion gene (BCR-ABL) is found in almost all CML patients.

Since the first tyrosine inhibitor, Gleevec, was approved in 2001, there are now more than 50 FDA-approved kinase inhibitors approved mostly for various hematological and solid tumor cancers

Source: New York Times, 2009, Druker et al., 2001 NEJM, National Cancer Institute., equity research.
*\$7B total potential deal value.

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Jan. 2019: LLY acquired LOXO
Amount: \$8B

VITRAKVI
(larotrectinib)
400 mg/600 mg capsules

June 2019: PFE acquired ARRY
Amount: \$11.4B

BRAFTOVI
(brafatinib) 100 mg capsules

MEKTOVI
(meclofenoxolone) 100 mg capsules

March 2015: ABBV acquired Pharmacyclics
Amount: \$21B

Dec. 2015: AZN acquired Acerta
Amount: \$7B*

Retevmo™
selpercatinib capsules
40 mg - 80 mg

CALQUENCE
(acalabrutinib) 100 mg capsules

Note: Deals noted at date of announcement.

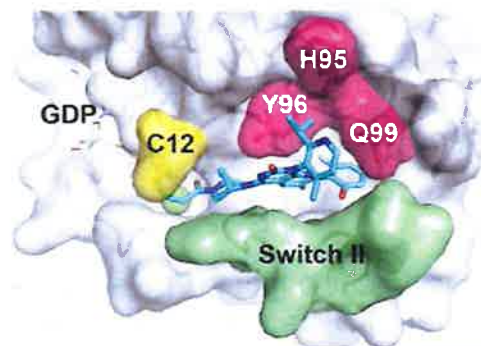


Case study: The previously “undruggable” KRAS

NEWS IN BRIEF • 10 JUNE 2019

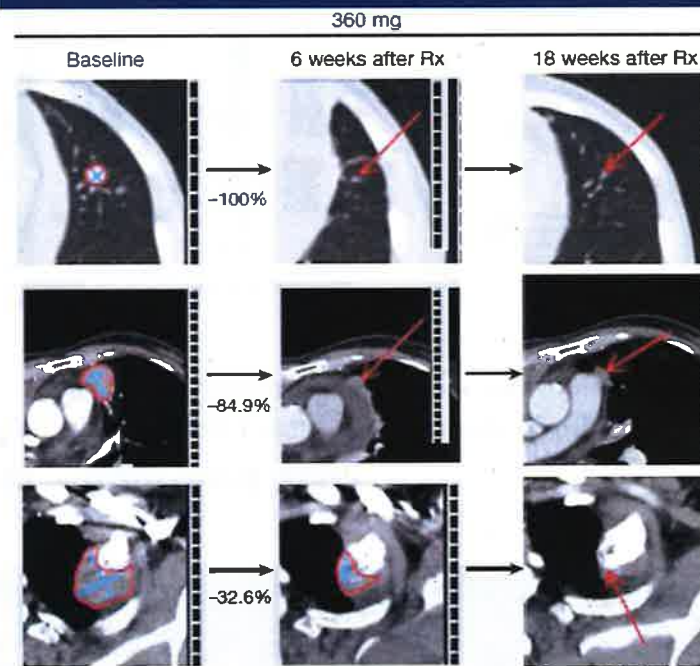
KRAS's undruggability cracks?

- KRAS is one of the most frequently mutated oncogenes in human cancer
- KRAS G12C mutation accounts for approximately¹:
 - ▶ **13%** of non-small cell lung cancers
 - ▶ **3-5%** of colorectal cancers
 - ▶ **2%** percent of other solid tumors
- Each year, *KRAS G12C* mutations are identified in about 23,000 NSCLC diagnoses in the United States²
- *KRAS* has previously been considered undruggable due to its small size, smooth surface, and rapid and tight binding to GTP in its active state
- OPI has invested in this space through a company called Kumquat Biosciences



Discovery of a covalent inhibitor of KRAS^{G12C} (AMG510)³

Effect of AMG510 in patient with lung cancer



Canon, 2019 Nature.



Source: ¹Canon, 2019 Nature, ²Amgen, ³Lanman, 2020 Journal of Medicinal Chemistry. AACR August 2019, Nature. NSCLC = Non small cell lung cancer.

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Different Approaches in the Fight Against COVID-19

Examples of Different Approaches Being Taken in the Fight Against COVID-19

Vaccines

- BioNTech/Pfizer – mRNA, Phase 3
- Moderna – mRNA, Phase 3
- Oxford/AstraZeneca – Adenovirus, Phase 3
- Johnson & Johnson – Adenovirus, Phase 3
- Novavax – Protein subunit, Phase 3¹

Antibodies

- Regeneron – combination of two mAbs targeting S protein epitope, Phase 3
- Eli Lilly / AbCellera – mono or combination of mAbs targeting S protein epitope, Phase 3²
- GSK / Vir Biotechnology – Phase 3

>700 therapies in development for COVID-19

Anti-virals

- Gilead – Remdesivir, FDA approved
- Roche / Atea Pharmaceuticals – Oral, direct-acting antiviral, Phase 2
- Anti-virals previously tested and subsequently halted use³
 - Hydroxychloroquine, lopinavir/ritonavir

Anti-inflammatories

- National Health Service (RECOVERY study) – dexamethasone (corticosteroid), Phase 2/3
- Acerta / AstraZeneca – Acalabrutinib (BTK inhibitor), Phase 1
- Eli Lilly – Baricitinib (JAK inhibitor), Phase 3
- Incyte / Novartis – Ruxolitinib (JAK inhibitor), Phase 3

¹In the UK, Phase 3 in U.S by end of November. ²LY-CoV555 and LY-CoV016 combination is in Phase 2. ³Stopped development in Solidarity trial in hospitalized patients. Source: BIO Industry Analysis as of 10/27/20..

First Interim Analysis of Pfizer COVID-19 Vaccine

More than 90% Effective

UPDATED: Pfizer says its Covid-19 vaccine is more than 90% effective, exceeding expert expectations and setting up an EUA submission late this month

“When we embarked on this journey 10 months ago this is what we aspired to achieve.”



Prof. Ugur Sahin,
BioNTech CEO

First interim analysis

- ✓ Pfizer and partner BioNTech reported on November 9th their first Phase 3 interim analysis conducted by an external, independent DMC¹
- ✓ Vaccine candidate was >90% effective in preventing COVID-19 in participants without evidence of prior SARS-CoV-2 infection
 - ✓ Study has dosed 38,955 participants and no serious safety concerns have been observed

Next steps

- Submit for Emergency Use Authorization in late November
- Continue clinical trial through final analysis to collect further data
- Examine potential to provide protection for those who have had prior exposure to SARS-CoV-2
- Produce 50mm doses by YE 2020 and up to 1.3B doses in 2021

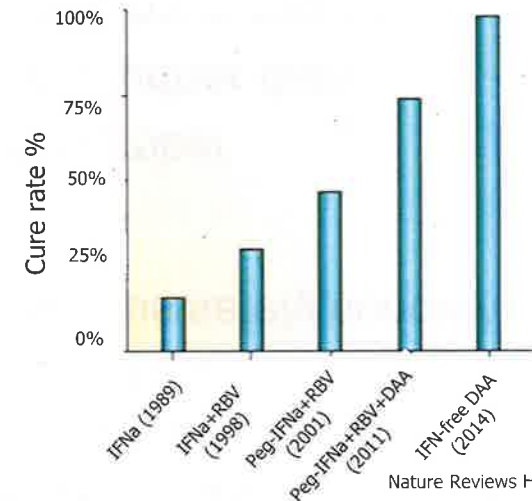
¹DMC = Data Monitoring Committee. Sources: Endpoint News, press releases.
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The Industry Has Handled Major Viruses Before

Hepatitis C and HIV

Hepatitis C (HCV) drugs today have over 90% cure rate

- The HCV treatment landscape for many years (2001-2011) was pegylated-interferon (IFN) in combination with ribavirin, which came with many adverse effects and low cure rates
- In the following years, direct-acting viral agents were approved >> treatment today with all-oral regimens demonstrates > 90% cure rate



HIV infection has been transformed from a fatal to a manageable, chronic disease

At the beginning of the AIDS crisis “median survival was anywhere from a year to a year and a half, a dreadful, dreadful prognosis” – Dr. Anthony Fauci

Antiretroviral therapy for HIV infection

In the 1990s



Up to 20 pills daily, taken at different intervals throughout the day

Today



As little as 1 pill per day, delivering multiple drugs



BIKTARVY®

bictegravir 50mg/emtricitabine 200mg/
tenofovir alafenamide 25mg tablets



dolutegravir 50 mg/
lamivudine 300 mg tablets

Source: Nature, March 2017, Reflections on 35 Years of AIDS, NIAID Antiretroviral Drug Discovery and Development, Fierce Pharma.

COVID-19 Has Modernized Clinical Development

"If there is a silver lining, it is that we are running a grand experiment concerning decentralized trials. We have been interested in this for a long time, because they can show us efficiencies and can be quite patient friendly." - Dr. Paul Kluetz, Deputy Director, Oncology Center of Excellence, FDA.

STAT Topics Coronavirus Opinion Podcast Newsletters Reports Events

As Covid-19 spreads, disruptions to clinical trial and drug development accelerate

by ADAM FEUERSTEIN @adamfeuerstein / MARCH 23, 2020



NEWS

CORONAVIRUS

NIGHTLY NEWS

Cancer patients forced to delay treatment over coronavirus concerns

How COVID-19 is Redefining Clinical Development

- **Decentralization of clinical trial sites**
 - ▶ Lab tests at local centers, facilitating patient recruitment
- **Telemedicine capabilities**
 - ▶ Electronic patient consent
 - ▶ Virtual patient assessments
 - ▶ Onsite visits limited to high-risk intervention and invasive monitoring
- **Direct-to-patient drug shipments**
 - ▶ Switch to home delivery for self-administered products
 - ▶ Optionality in alternative arrangements for infusion products

Source: FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, JAMA Oncology 2020, CEO Roundtable on Cancer.

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Artificial Intelligence Can Transform the Industry



"Artificial intelligence and machine learning have the potential to **fundamentally transform the delivery of healthcare**. These tools can provide more time for intervention, identifying effective therapies and ultimately saving lives."

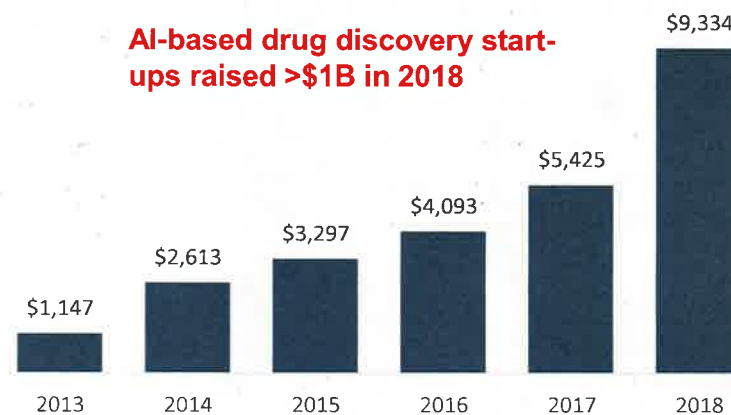
Seeking Insights into Rare Diseases, Pfizer Scales AI Analytics Platform

GSK puts faith in AI to make more successful drugs more quickly

Impact of AI on the Healthcare Industry

- ✓ **Improve speed in diagnosis**
 - Streamline processes to enable faster treatment (e.g., FDA approved software to alert for potential stroke)
- ✓ **Improve accuracy**
 - AI has shown potential to outperform doctors on detection of cancer
- ✓ **Aid drug discovery efforts**
 - Identify new drug targets
 - Examine millions of molecules and improve "hit rate"

VC Funding for AI Start-Ups (\$mm)



Source: Forbes, Nature.

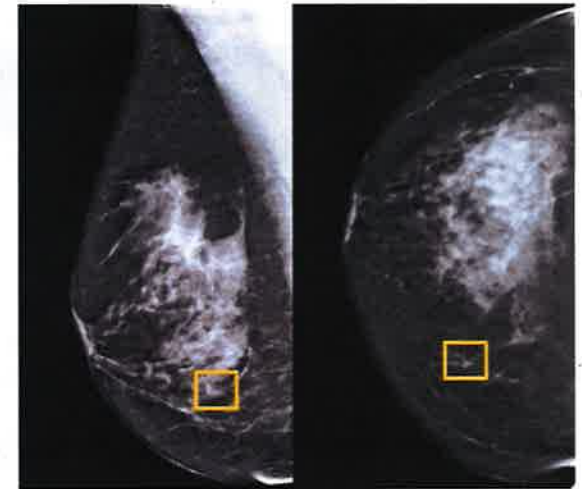
Source: NY Times, FDA Statement April 2019, Nature "Hunting for New Drugs with AI", WSJ, The Guardian.

Artificial Intelligence Has Begun to Flex its Potential

The New York Times

A.I. Is Learning to Read Mammograms

- In a paper published in Nature, Google Health tested an AI system on ~25,000 and ~3,000 mammograms in the UK and U.S where the outcome was known
- The AI system reduced the rate of false positives and false negatives by 5.7% and 9.4% respectively, compared to the radiologist's initial diagnoses
- In another test, 500 mammograms were presented to the AI system and 6 radiologists in the U.S, overall the AI outperformed the humans
- In some instances, AI missed a cancer all radiologists found, and vice versa



A sample cancer case that was missed by all six readers in the US reader study, but correctly identified by the AI system. McKinney, 2020 Nature.

Source: McKinney, 2020 Nature.

Diabetic retinopathy detection – approved 2018

- IDx-DR - medical device that uses AI to detect > a mild level of diabetic retinopathy
- First ever AI system cleared by FDA to provide a screening decision without need for clinician to also interpret image



Source: NY Times, FDA, Digital Diagnostics, Viz.AI.

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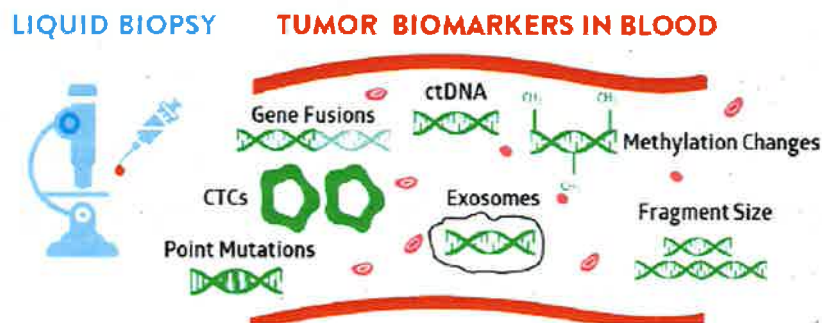
Stroke detection – approved 2018

- Viz.AI analyzes CT results and instantly alerts specialists to potential stroke
- Only clinically validated AI system to detect and triage large vessel occlusions (LVOs)
- In 95% of cases, Viz.AI alerted the specialist 52 minutes earlier than SOC



Liquid Biopsies Have Tremendous Market Opportunity

Liquid Biopsies – Blood Draw to Identify Cancer Signatures



Early Days

- Penetration of the therapeutic selection market is <10% and routine cancer screening is only available for ~5 cancers in the U.S

Selected Unscreened Cancers Today			Screen Available Today
Anorectal	Bile-duct	Renal	Breast
Appendix	Lymphoid neoplasm	Sarcoma	Cervical
Bladder	Melanoma	Seminoma	Colorectal
Urothelial	Myeloid neoplasm	Skin	Lung (limited)
Esophagus	Ovary	Testis	Prostate
Gastric	Lung	Thyroid	
Head & neck	Pancreas	Uterine	
Kidney	Gallbladder	Vagina	
Liver	Plasma cell neoplasm	Vulva	

Source: GRAIL, Thrive Earlier Detection, AACR Liquid Biopsy Meeting, Cowen

Liquid Biopsy Revenue Expected to Grow at Double-Digit Rates Through Most of Next Decade

U.S Liquid Biopsy Annual Total Addressable Market: \$30-130B




Asymptomatic Screening	High Risk Screening	Therapeutic Selection	Recurrence Monitoring	Biopharma Development
~\$5-50B	~\$2-5B	~\$2.5B	~\$20-75B	>\$1B

The Quest for Anti-Aging Medications

Anti-aging is a Field to Watch in the Future

- Anti-aging research has been growing steadily
- It has been discovered that the rate of aging is controlled to some extent, by genetic pathways and biochemical processes
 - ▶ E.g., mTOR, sirtuins, and NAD+ found to be important regulators of life span
- We now know of >2,000 genes that modulate longevity in model organisms, however, most have not yet been targeted pharmacologically

Biotechs are approaching anti-aging in a variety of ways

Company	Addressing?	\$ raised
	Cellular senescence	>\$200M in private funding, IPO'd in 2018
	Quantifying physiological decline, develop aging interventions	Stealth biotech, started by Google in 2013
	Use AI to track rate of aging and develop aging biomarkers	Spun off from Insilico Medicine in 2020



Nine candidate hallmarks generally considered to contribute to the aging process and together determine the aging phenotype. (Otin et al, 2013)

Bank of America has forecast the market will balloon to \$610 billion by 2025, from an estimated \$110 billion currently

Endnotes

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