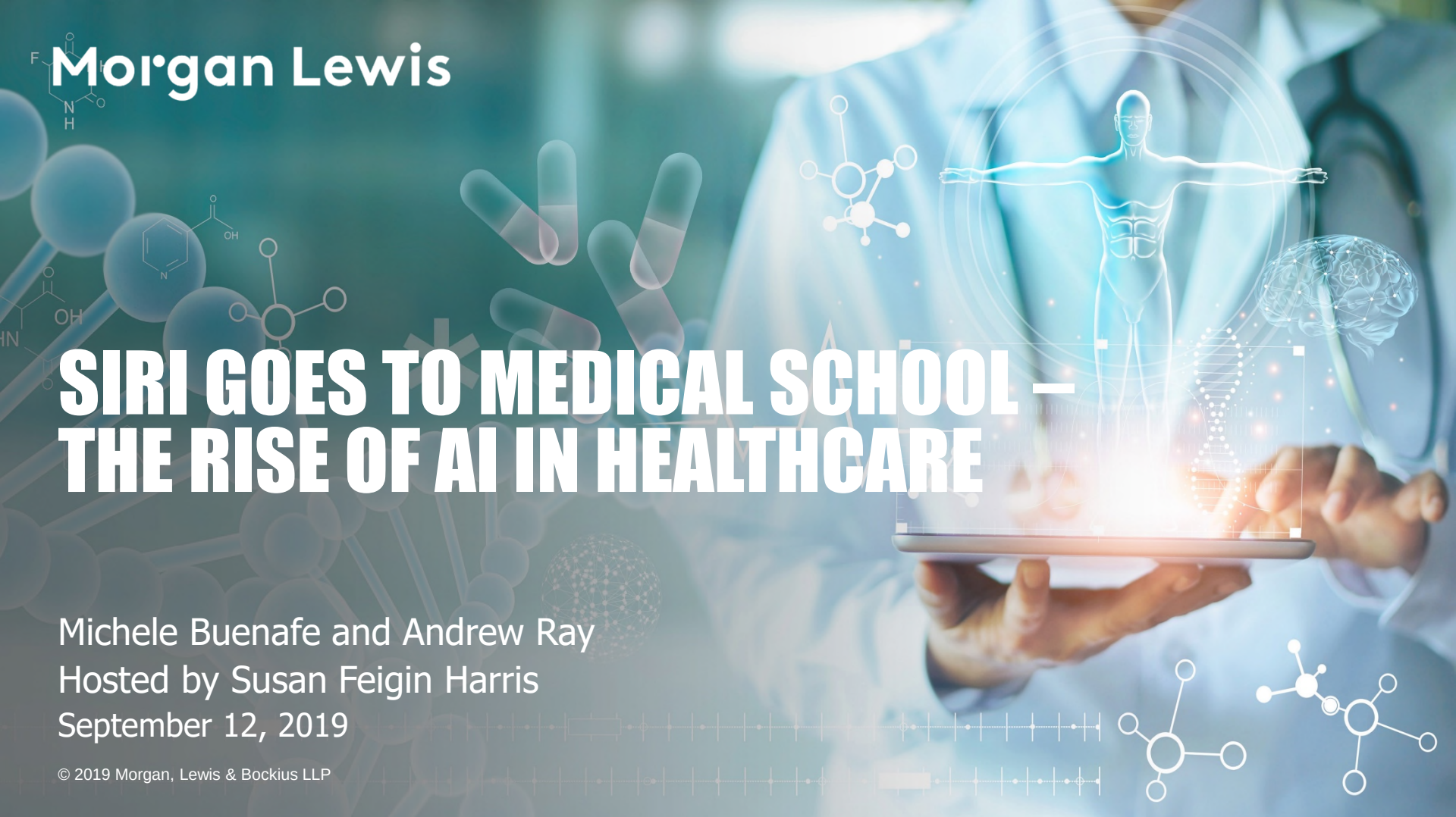

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SIRI GOES TO MEDICAL SCHOOL – THE RISE OF AI IN HEALTHCARE

Michele Buenafe and Andrew Ray
Hosted by Susan Feigin Harris
September 12, 2019

DIGITAL HEALTH: CURRENT STATE OF PLAY

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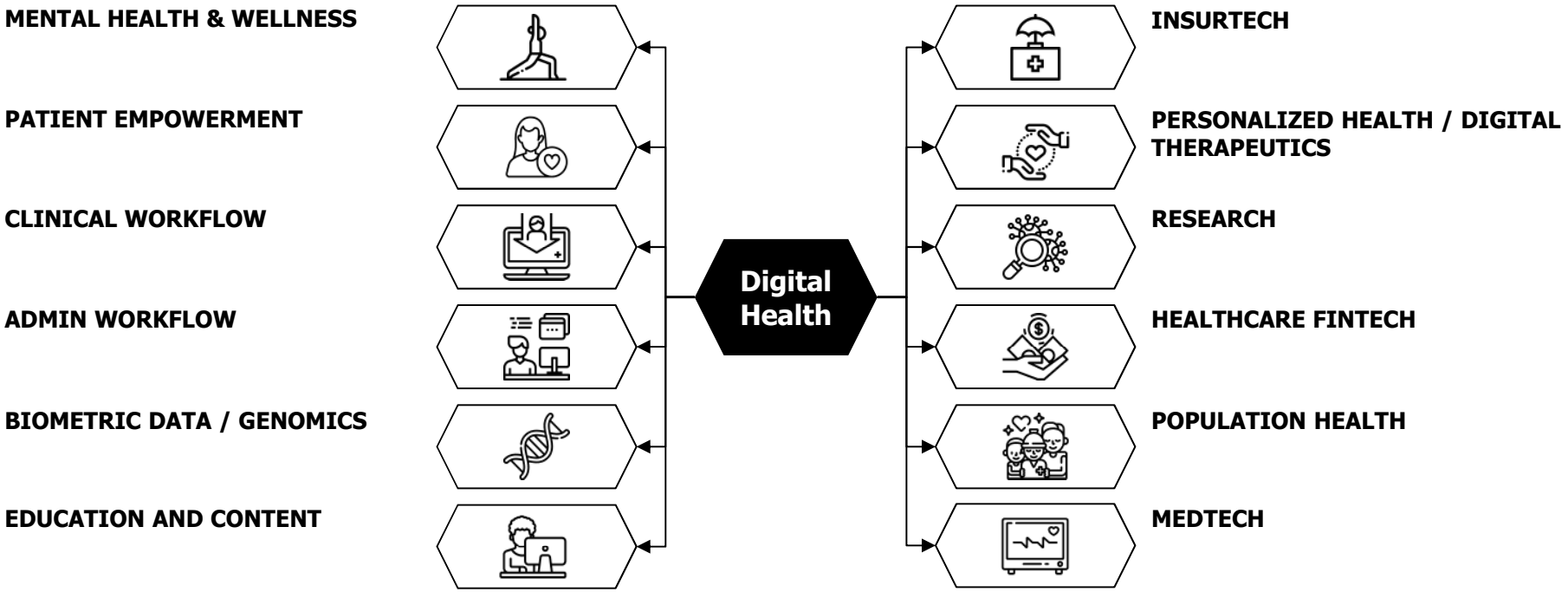
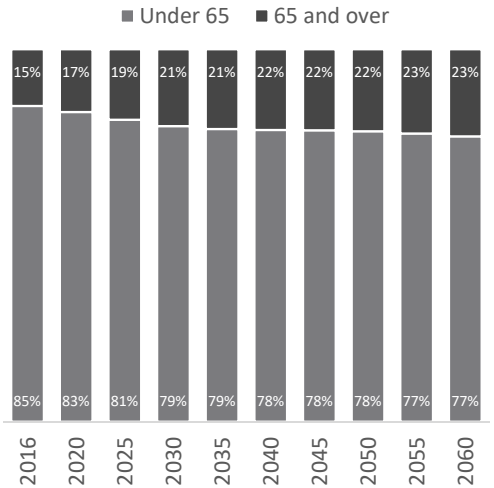
Digital Health Landscape



Healthcare Trends

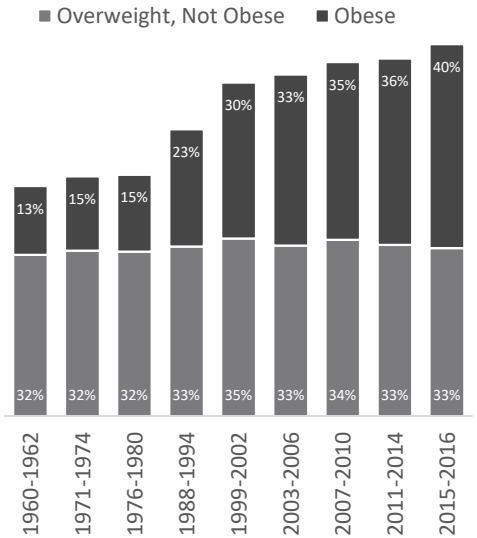
U.S. Population

Population Forecast by Age Group



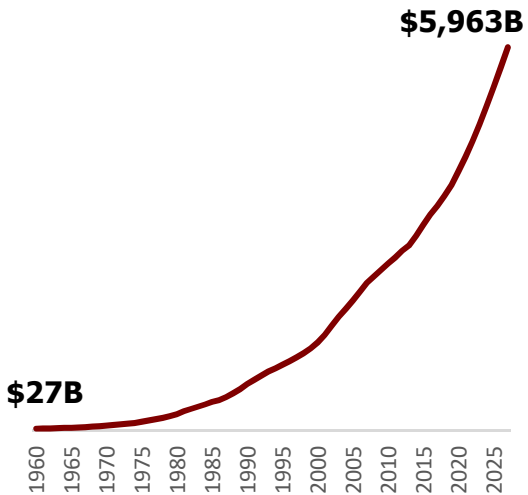
Obesity

Prevalence of Overweight and Obesity



U.S. Healthcare Spending

National Health Expenditure Forecast

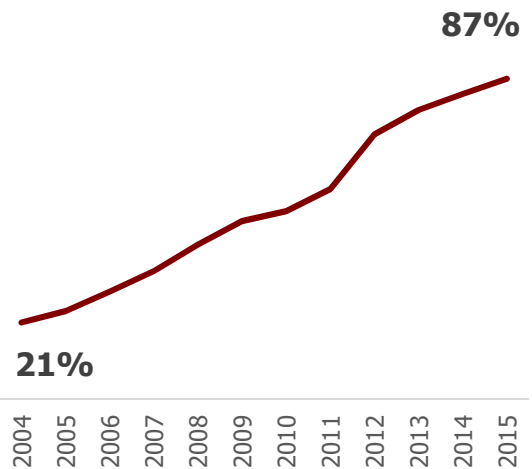


Sources – U.S. Census Bureau; Milken Institute; CMS

Adoption + Data + Tech ➔ Digital Health Growth

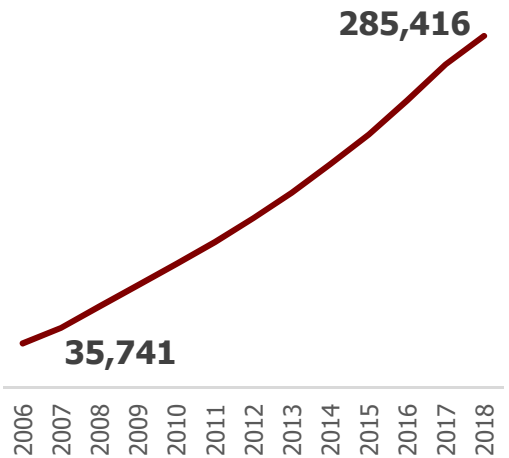
EHR Adoption

U.S. Physician EHR Adoption



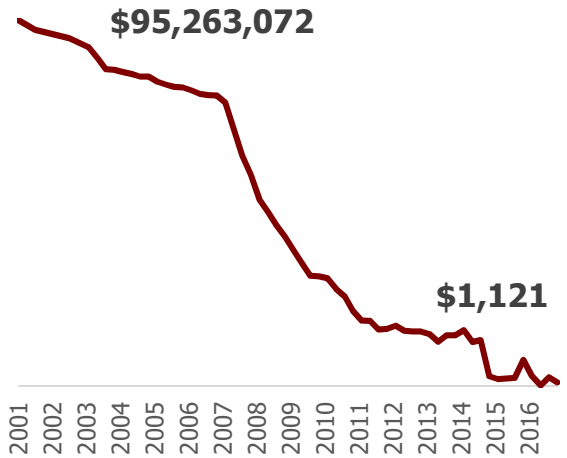
Clinical Trials Growth

No. of Registered Studies



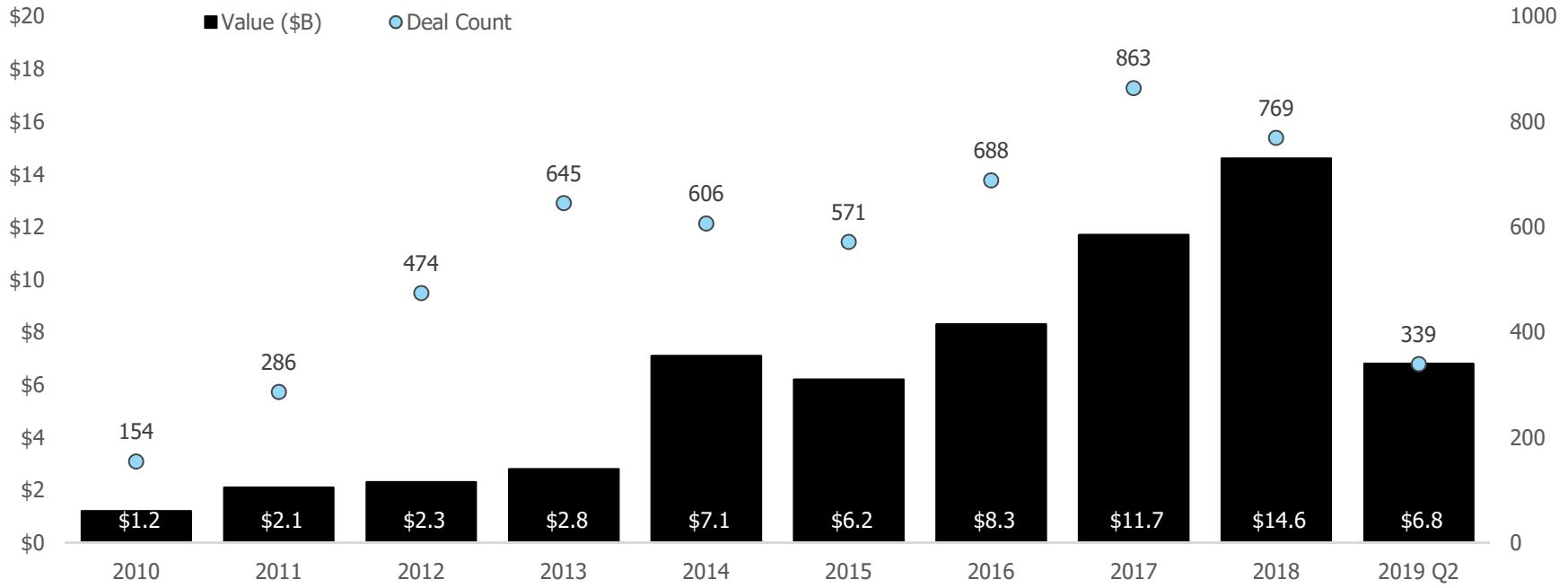
Technological Innovation

Cost to Sequence (p/Genome)



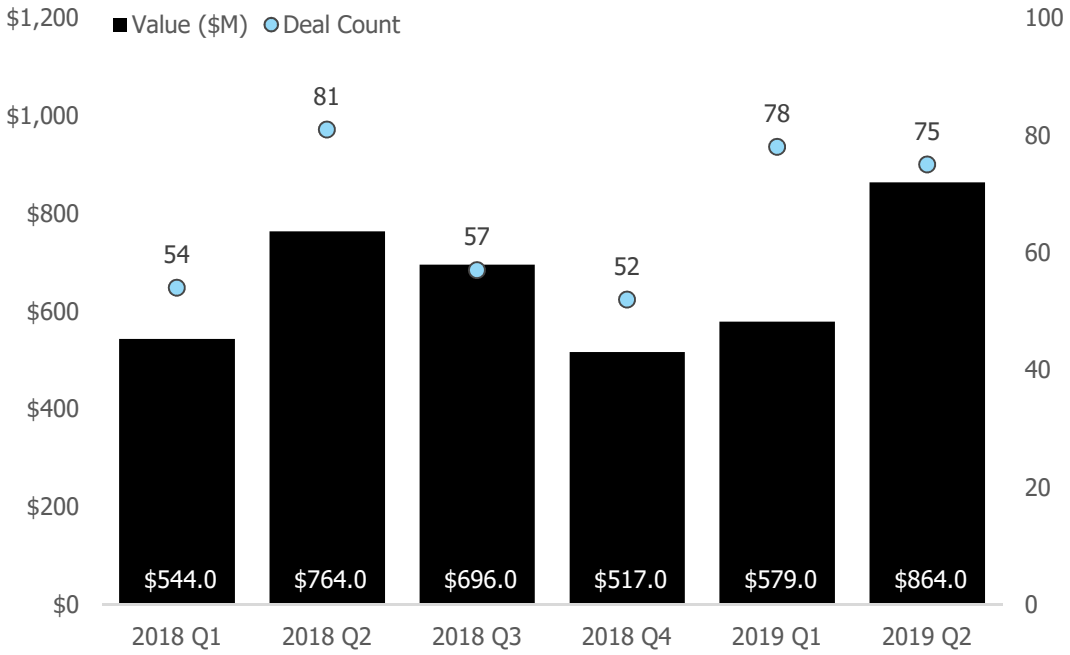
Sources – ONC HIT Health IT Dashboard; U.S. National Library of Medicine (ClinicalTrials.gov); National Human Genome Research Institute

Digital Health Funding Holding Steady in 2019



Source – 2019 Mid-year StartUp Health Insights

Digital Health AI Funding Reaches Peak in Q2



Source – CB Insights Global Healthcare Report Q2 2019

PathAI

Raised $60M in April '19
Developer of an AI-powered research platform intended to improve the accuracy and efficiency of cancer diagnosis and treatment.

Frontier MEDICINES

Raised $67M in June '19
AI platform that integrates advanced computational approaches and machine learning to develop medicines for disease-causing proteins

Digital Health Focused Hospital Corporate VCs

- UPMC Enterprises
- Ascension Ventures
- Kaiser Permanente Ventures
- Providence Ventures

Source – PitchBook Database

2019 Digital Health Financing Headlines

- Alphabet-backed Medicare Advantage startup Clover Health raises $500M
- Tencent-backed online healthcare platform Trusted Doctor secures $250M
- Enterprise healthcare platform Collective Health raises $205M led by SoftBank
- Precision medicine startup Tempus raises $200M to reach $3.1B valuation
- Doctolib is now a unicorn with new $170M round

Source – 2019 Mid-year StartUp Health Insights

Most Active Digital Health Investors

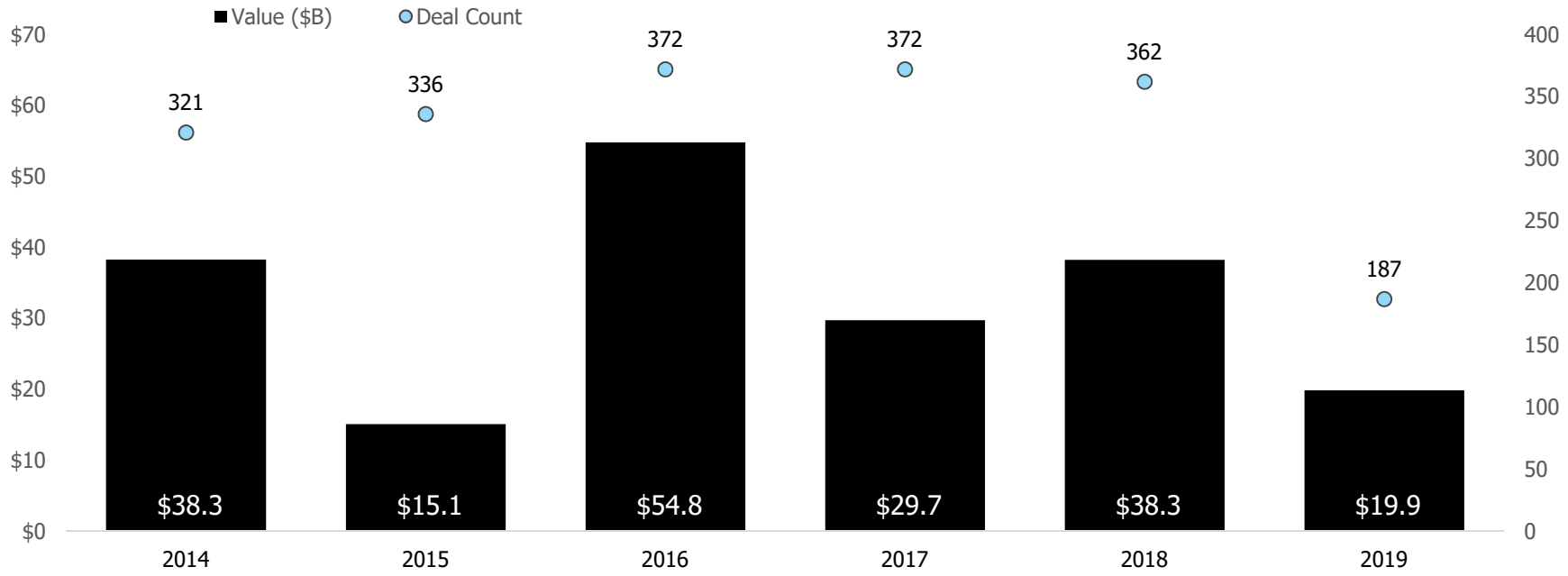
	2018 Deal Count	2019 Deal Count
STARTUP HEALTH	10	8
G/	6	6
F/PRIME	11	5
SEQUOIA	4	5
khosla ventures	14	5
echo HEALTH VENTURES	6	5
NEA	12	5

Other Active Investors

FOUNDERS FUND
THRIVE CAPITAL
OAK HC/FT
Y Combinator
GENERAL CATALYST
BOX GROUP
KLEINER PERKINS
Ben Franklin Technology PArtners
First Round
JUMPSTART FOUNDRY

Source – 2019 Mid-year StartUp Health Insights

Digital Health M&A Activity Remained Healthy



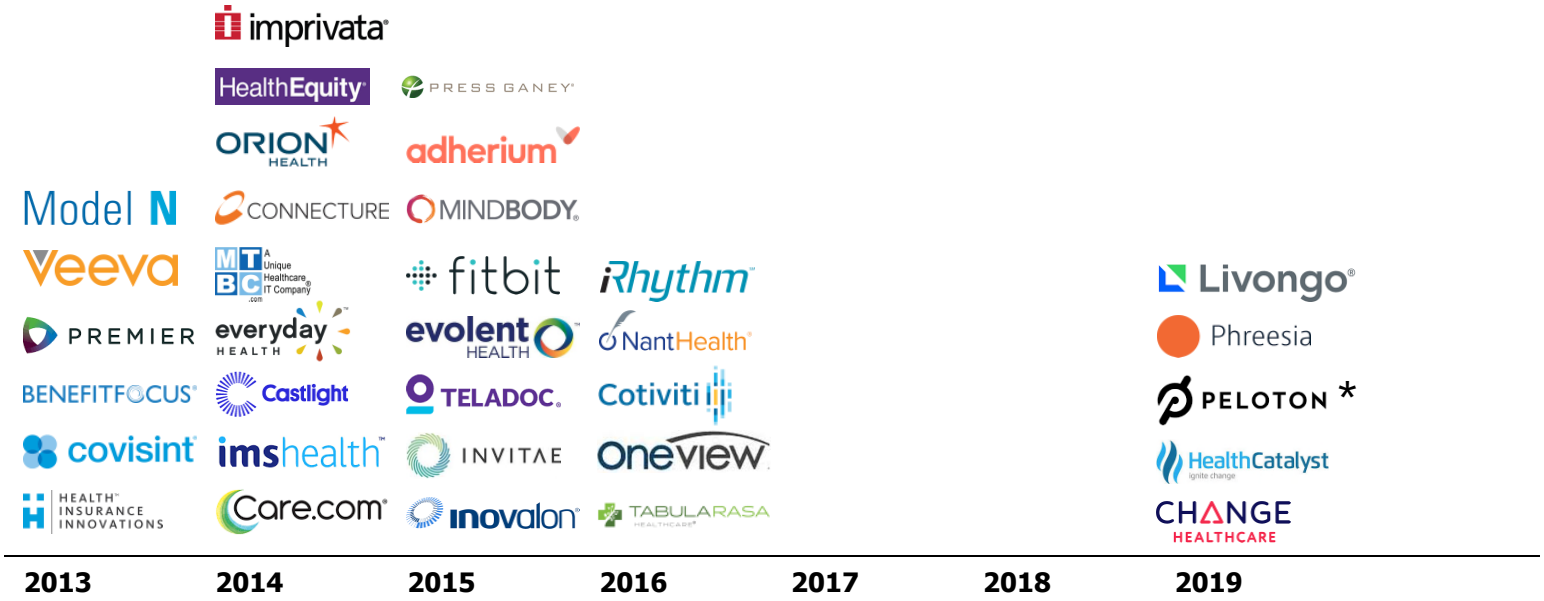
Source – 2019 Health Growth Partners Semi-Annual Market Review

2019 Digital Health M&A Headlines

- Dassault Systemes SA acquires Medidata Solutions for $5.8B
- Ares Capital Management and Leonard Green & Partners acquire Press Ganey Associates for $4.2B
- UnitedHealth Group acquires Equian for $3.2B and PatientsLikeMe
- HealthEquity acquires WageWorks for $2B
- Silver Lakes invests $1B in Verily Life Sciences
- JPMorgan Chase acquires InstaMed for $600M

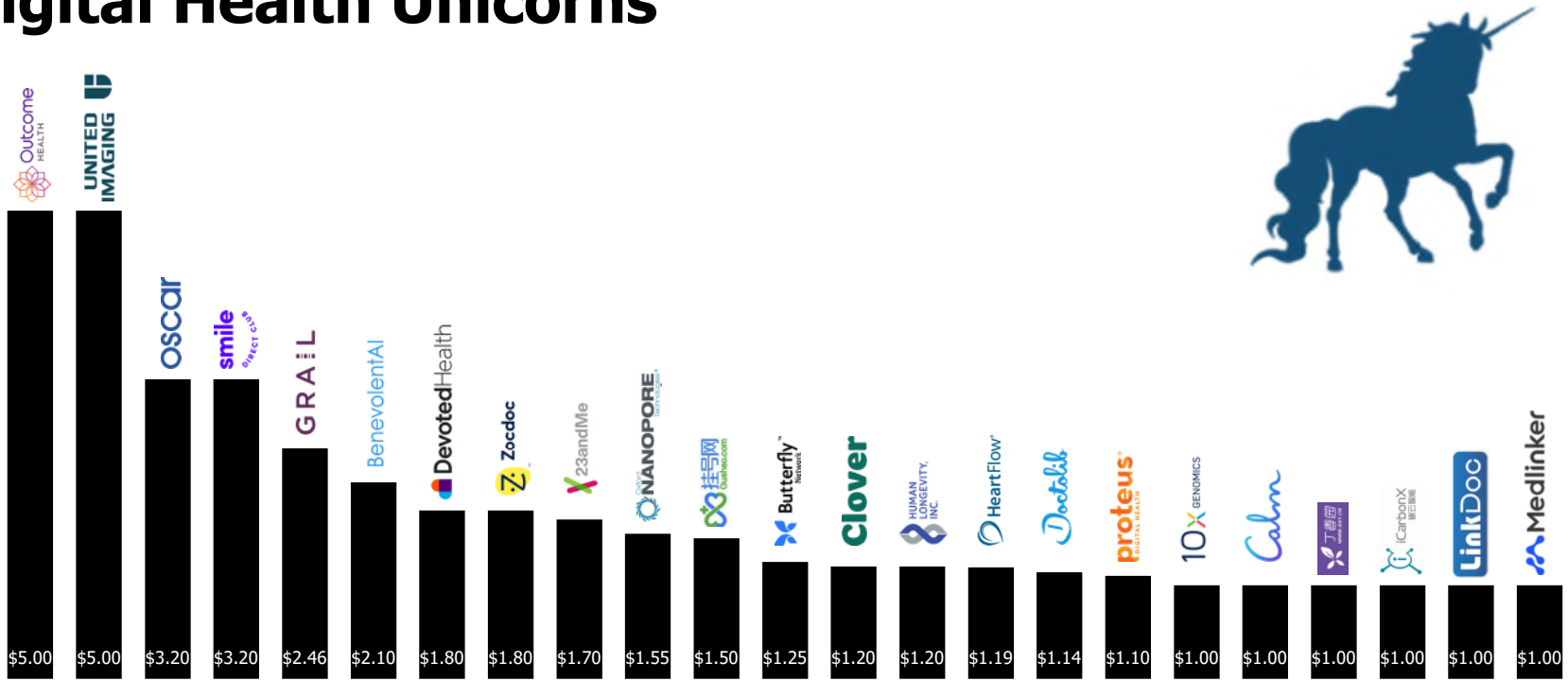
Source – 2019 Health Growth Partners Semi-Annual Market Review

Digital Health IPO Drought Ends



Source – 2019 Health Growth Partners Semi-Annual Market Review

Digital Health Unicorns



Source – CB Insights

Most Active Digital Health Hubs

	City / Region	Funds Raised	2018	2019
1	SF Bay Area	$2.0B	137	59
2	Boston	$669M	45	25
3	New York City	$559M	96	39
4	Chicago	$230M	13	9
5	Salt Lake City	$125M	3	2
6	Denver	$113M	7	9
7	Columbus	$75M	6	3
8	Seattle	$73M	13	10
9	Boulder	$60M	-	1
10	Phoenix	$48M	4	3

	City / Region	Funds Raised	2018	2019
1	Beijing	$486M	21	7
2	Paris	$321M	7	7
3	Tel Aviv	$182M	10	12
4	Bangalore	$178M	15	6
5	London	$130M	20	13
6	Guangzhou	$103M	3	2
7	Warsaw	$103M	-	2
8	National Capital Region, India	$85M	13	6
9	Zhejiang	$80M	1	1
10	Lausanne	$77M	1	1

Source – 2019 Mid-year StartUp Health Insights

REGULATORY HURDLES FOR AI IN HEALTHCARE

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Recent FDA Clearances for AI Imaging Technologies

- Zebra Medical Vision's HealthPNX tool
  - Scans a chest X-ray or digital radiography scan for signs of pneumothorax
- AiDoc's BriefCase software
  - Analysis of CT and CTPA images to assist radiologists by flagging and communication of suspected positive findings of intracranial hemorrhage and pulmonary embolism
- Viz.AI's Contact application
  - Analysis of CT images to notify providers of a potential stroke signs

FDA's Regulation of Artificial Intelligence

- FDA regulates software (including AI/ML software) and other technologies that meet the definition of a "device" under the Federal Food, Drug, and Cosmetic Act, which includes
  - Any instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar related article, including any component, part, or accessory
  - Intended for use in the diagnosis of disease or other conditions, or in the cure, treatment, or prevention of disease, or intended to affect the structure or function of the body
  - Which does not achieve its principal purposes by chemical action in or on the body of man or by being metabolized (*i.e.*, not a drug).
- VERY broad definition

FDA - Software Specific Exemptions

- 21st Century Cures Act
  - For *administrative support* functions
  - For *maintaining or encouraging a healthy lifestyle*
    - FDA Guidance – General Wellness: Policy for Low Risk Devices
  - To serve as *electronic health records*
  - For transferring, storing, converting formats, or displaying *medical device data or results* (including clinical lab test data)
    - Includes "medical device data systems" or "MDDS"






FDA - Software Specific Exemptions

- 21st Century Cures Act
  - For *clinical decision support* (CDS) functions – patient-specific recommendations or support about the prevention, diagnosis, or treatment of a disease or condition, provided that
    - The health care professional can independently review the basis of the CDS recommendations
    - The CDS function does not acquire, process, or analyze a medical image or a signal from an IVD device or signal acquisition system
    - The software is intended for use by a health care professional – not for consumer use
- 2017 Draft Guidance
  - To interpret the new statutory exemption for CDS software
  - Enforcement discretion for Patient Decision Support software

FDA - Software Specific Exemptions

- FDA Guidance – Mobile Medical Apps
  - Describes "FDA's intentions to focus its oversight on a *subset of mobile apps*," that "*pose[] the same or similar risks to the public health as currently regulated devices* if they fail to function as intended."
  - Identifies three categories of apps:
    - Apps that FDA intends to regulate as medical devices
    - Apps that may meet the statutory definition of a "device" but for which FDA intends to exercise enforcement discretion
    - Apps that do not meet the statutory definition of a "device" and which FDA will not regulate

What if My AI Product is Regulated?

Premarket Obligations

- Design controls
- Clinical testing compliance (if applicable)
- Premarket submission (if applicable)

Postmarket Obligations (aka General Controls)

- Establishment registration and device listing
- Good manufacturing practices (GMPs)/Quality System Regulation (QSR)
- Labeling
- Medical device reporting
- Reporting of corrections and removals

Recent FDA Developments for AI/ML Software

- Proposed framework to address how FDA would handle postmarket modifications to AI/ML software devices
  - Existing model for requires sponsors to evaluate all device software changes to determine whether the change requires a new submission to FDA
  - May not work for AI/ML software, because such software is intended to continuously evolve
- Under the proposed framework, AI/ML software developers would include in their initial FDA submissions a predetermined change control plan:
  - SaMD pre-specifications (SPS), which define the types of software algorithm changes that are covered/permitted under the plan
  - Algorithm change protocol (ACP), which defines methods to controls risks for the permitted changes and how the changes may occur
- May require statutory changes to fully implement proposed framework

Recent FDA Developments for AI/ML Software

- Changes that fall within the agreed upon SPS + ACP could be documented to file
- If outside the SPS + ACP and the change leads to a new intended use, change is subject to FDA premarket review
- If outside the SPS + ACP and no new intended use, change is subject to "focused FDA review"

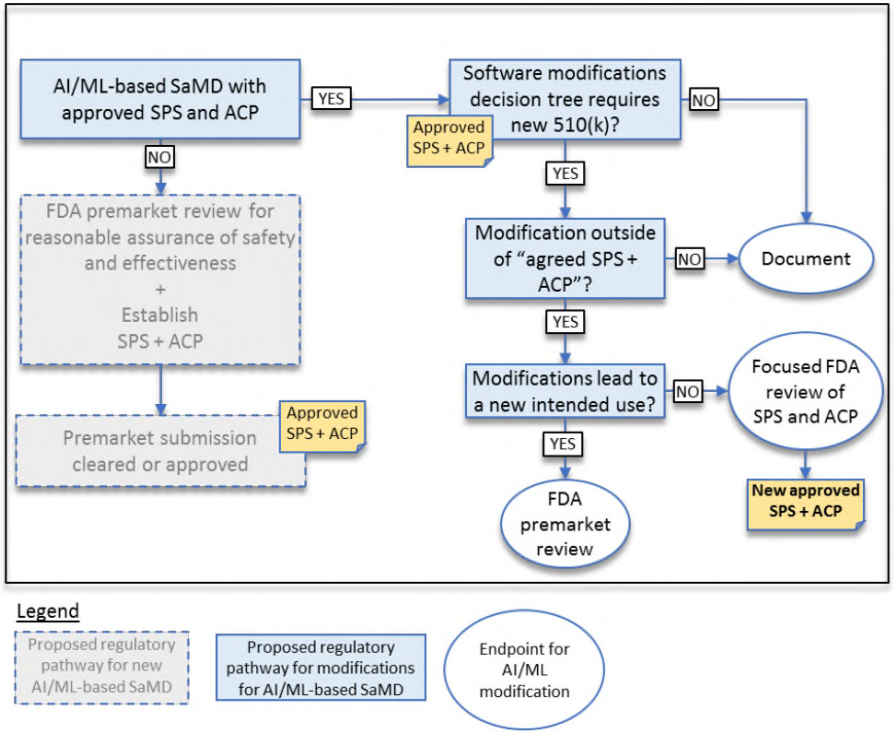

Figure 5: Approach to modifications to previously approved SaMD with SPS and ACP. This flowchart should only be considered in conjunction with the accompanying text in this white paper.

Recent FDA Developments for AI/ML Software

- The Discussion Paper does not define when AI/ML software would be subject to FDA regulation
  - Suggests that certain types of AI/ML software would be regulated – e.g., AI/ML intended to "drive clinical management" or "inform clinical management" or intended for use as "an aid in diagnosis"
  - Specific AI/ML hypothetical examples in Appendix A
    - AI/ML that processes/analyzes physiological signals to detect patterns that occur at the onset of physiological instability and generate alarms
    - AI/ML that uses images taken by a smartphone camera to provide detailed info to dermatologists on physical characteristics of a skin legion
    - AI/ML that analyzes chest x-rays to evaluate feeding tube placement, detect incorrect placements, and triage for radiologists

FDA's Software Pre-Certification Program

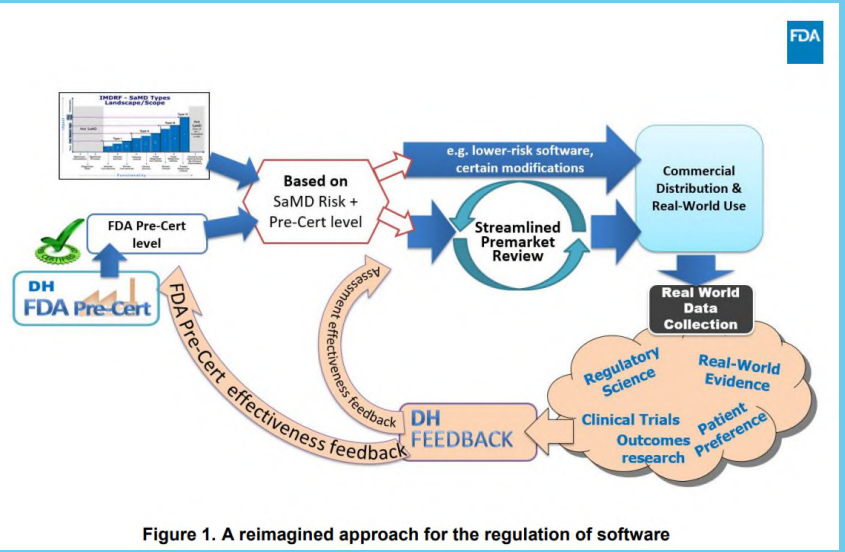

Figure 1. A reimagined approach for the regulation of software

- July 2017: Announce a voluntary pilot program
- April 2018: FDA issued Working Model (version 0.1) for the pre-certification program
- January 2019: FDA issues three new documents:
  - Version 1.0 of the Working Model
  - 2019 Test Plan to Test the Model
    - Internal testing by conducting retrospective tests of SaMD regulatory submissions that were previously reviewed
    - Prospective testing with pilot participants who volunteer to participate
  - Regulatory Framework for Conducting the Pilot Program

Pre-Certification Program – Working Model 1.0

- Four key components:
  - Excellence appraisal and precertification
    - Based on five excellence principles
    - Steps include
      - Pre-Cert Application
      - Appraisal
      - Pre-Cert Status Determination
      - Maintenance and Monitoring
  - Review pathway determination
    - FDA proposes to leverage the risk-category framework for SaMD developed by IMDRF
  - Streamlined premarket review
  - Real-world performance plan
    - Postmarket surveillance and feedback

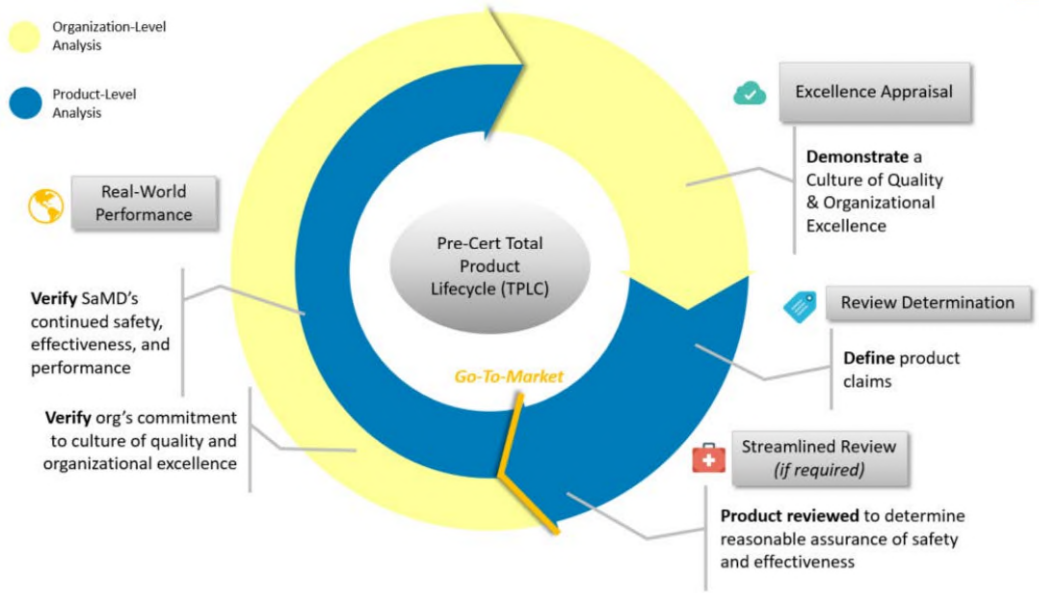

Figure 4. Total Product Lifecycle Approach of the Software Pre-Cert Program

Pre-Certification Program – Excellence Appraisal

Organizational Domains / Excellence Principles	Product Quality	Patient Safety	Clinical Responsibility	Cybersecurity Responsibility	Proactive Culture
1. Leadership & Organizational Support	X	X	X	X	X
2. Transparency	X	X	X	X	X
3. People	X	X	X	X	X
4. Infrastructure and Work Environment	X	X	X	X	X
5. Risk Management	X	X	X	X	X
6. Configuration Management and Change Control	X	X		X	X
7. Measurement Analysis, and Improvement of Processes and Products	X	X	X		X
8. Managing Outsourced Processes, Activities, and Products	X	X		X	X
9. Requirements Management	X	X	X	X	X
10. Design and Development	X	X	X	X	X
11. Verification and Validation	X	X	X		
12. Deployment and Maintenance	X	X	X	X	X

Federal Trade Commission

- FTC regulation and enforcement
  - January 2015 complaint against Focus Education, LLC
    - Claims that app permanently improves children's focus, memory, attention, behavior, and/or school performance
    - ADHD claims
  - February 2015 actions against MelApp and Mole Detective
    - Claims for analysis of pictures of moles and skin lesions taken with smartphones
    - Melanoma detection claims
  - January 2016 complaint against Lumosity
    - Claims to delay memory decline and protect against dementia and Alzheimer's disease
    - Claims to reduce the effects of ADHD and post-traumatic stress disorder
  - FTC enforcement thus far is generally consistent with FDA's policies for mobile medical apps and other digital health products

State Regulation

- Recent Actions by New York State Attorney General
  - Developers of three health-related apps
  - Allegations concerning misleading and unsubstantiated claims
  - Irresponsible privacy practices
  - Two of the apps involved were *exempt from FDA regulation*
  - The developers agreed to add new disclaimers, modify their claims, update their privacy policies, and pay a combined $30,000 in penalties

QUESTIONS?

Biography

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Michele L. Buenafe advises clients on regulatory, compliance, and enforcement issues related to the development, manufacturing, marketing, labeling, and advertising of medical devices, human tissue products, pharmaceuticals, controlled substances, listed chemicals, and combination products. She also advises clients on emerging legal issues relating to digital health platforms such as mobile medical apps, clinical decision support software, telemedicine systems, wearable devices, and other health information technology. Michele serves as the leader of the firm's digital health initiative and as co-leader for the firm's cross-practice healthcare initiative.

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Andrew Ray is the leader of the firm's interdisciplinary corporate practice in Washington, DC, where he represents public and private companies, financial sponsors, and management teams in a broad range of industries, including technology, financial services, life sciences, real estate, and the not-for-profit sector. Various industry publications recognize Andy as a leader in both M&A and in communications law, among other fields. He recently led the team representing Oculus VR in its $2 billion sale to Facebook, which was named the *M&A Advisor* M&A Deal of the Year.

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Named Texas' 2018 Lawyer of the Year, Susan Feigin Harris concentrates on the regulatory, business, corporate, governance, compliance, and contracting needs of a diverse group of healthcare clients. She regularly addresses federal and state healthcare regulations, and works with state and federal healthcare agencies involving Medicare and Medicaid licensing, certification, reimbursement, compliance, enforcement, and recoupment actions. Susan's clients include hospitals, physician groups, lab companies, post-acute providers, and healthcare innovations companies.

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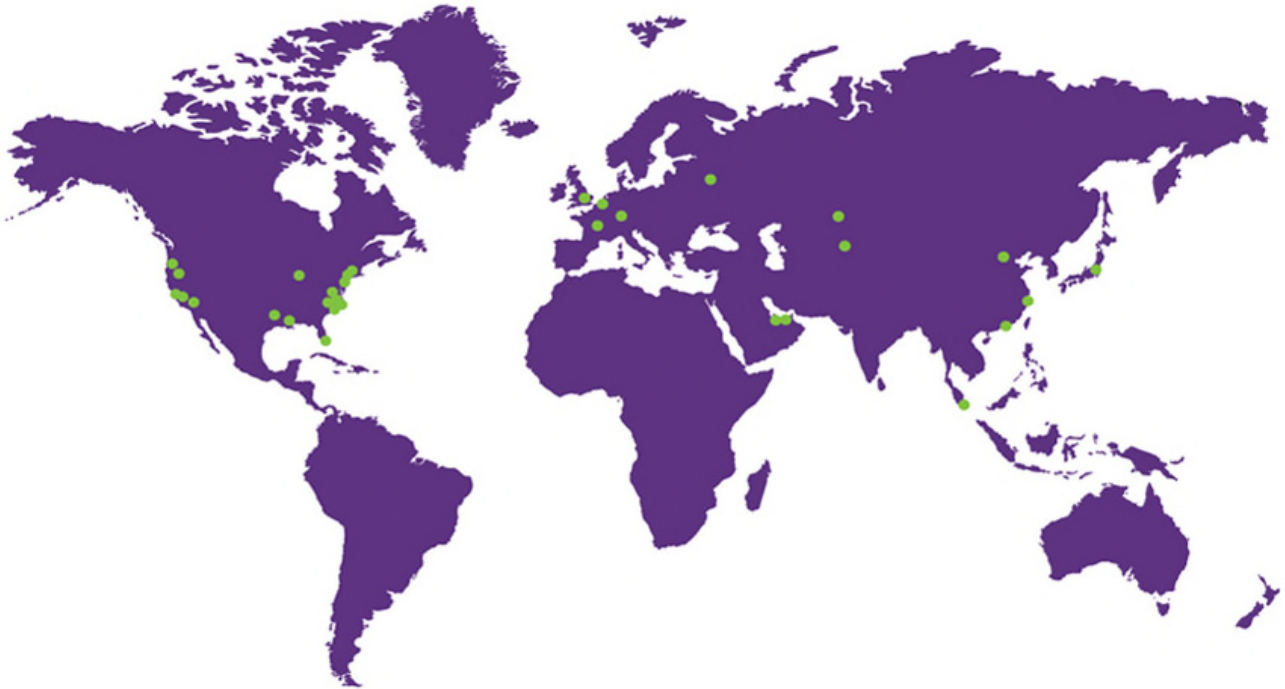

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