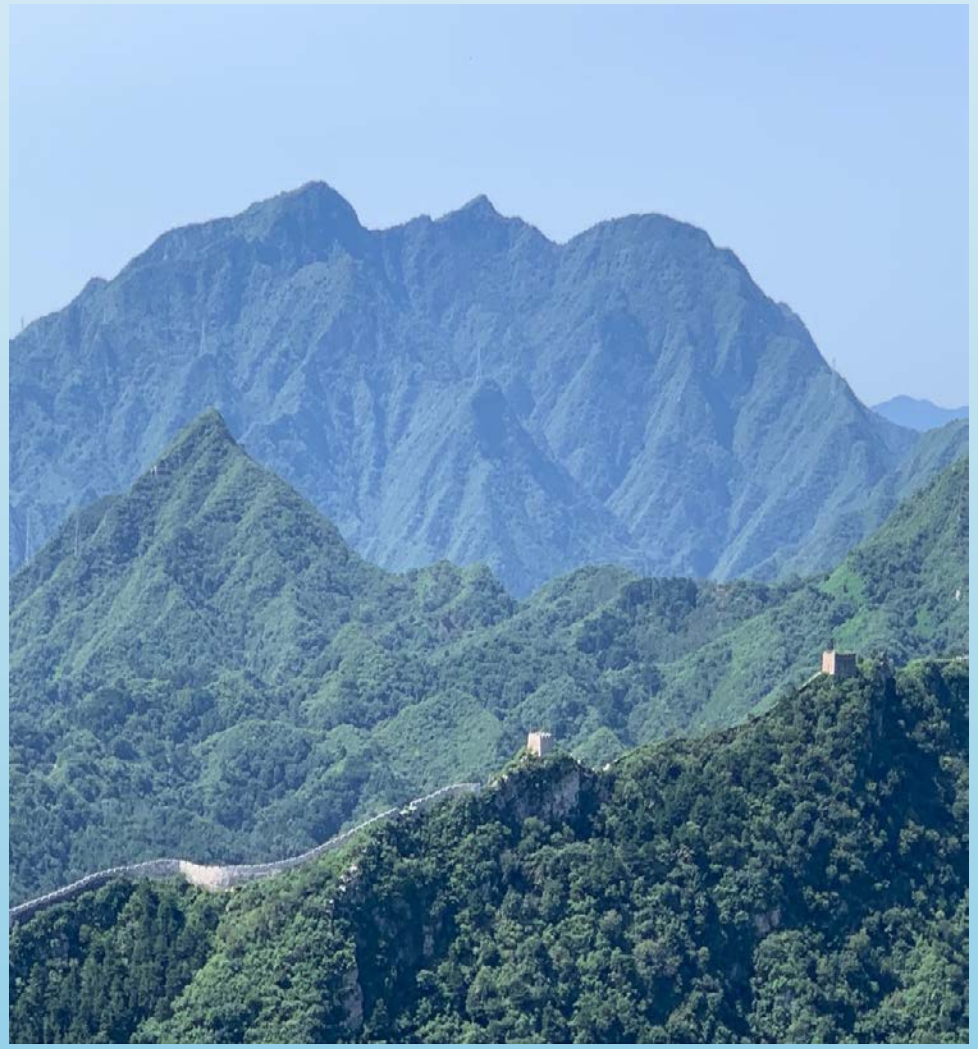
A View of Our Own: Preparing for New Policy, Technology and Opportunity

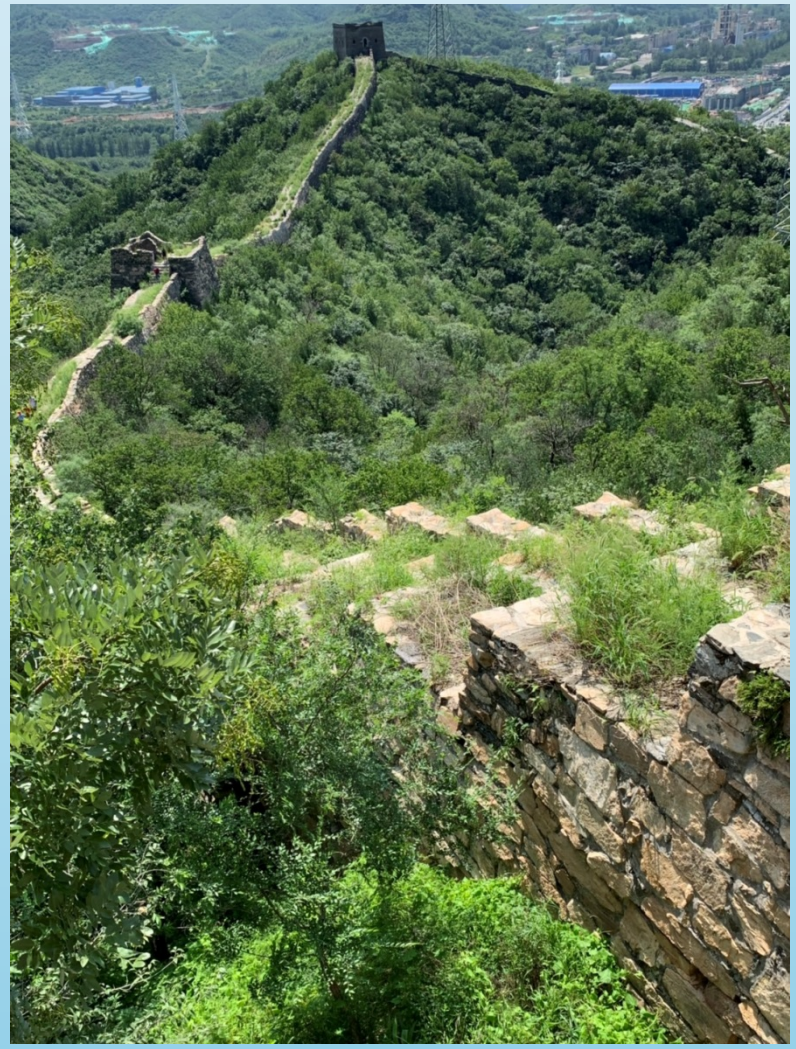
PharmaSUG China 2019

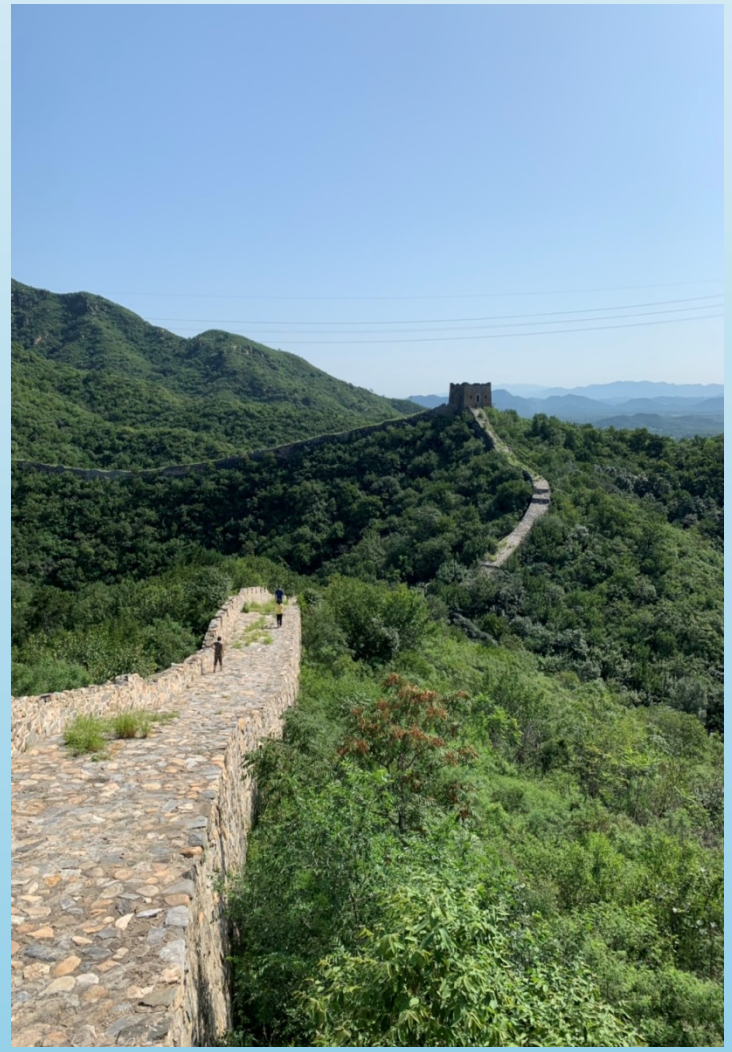
Keynote

Todd Case

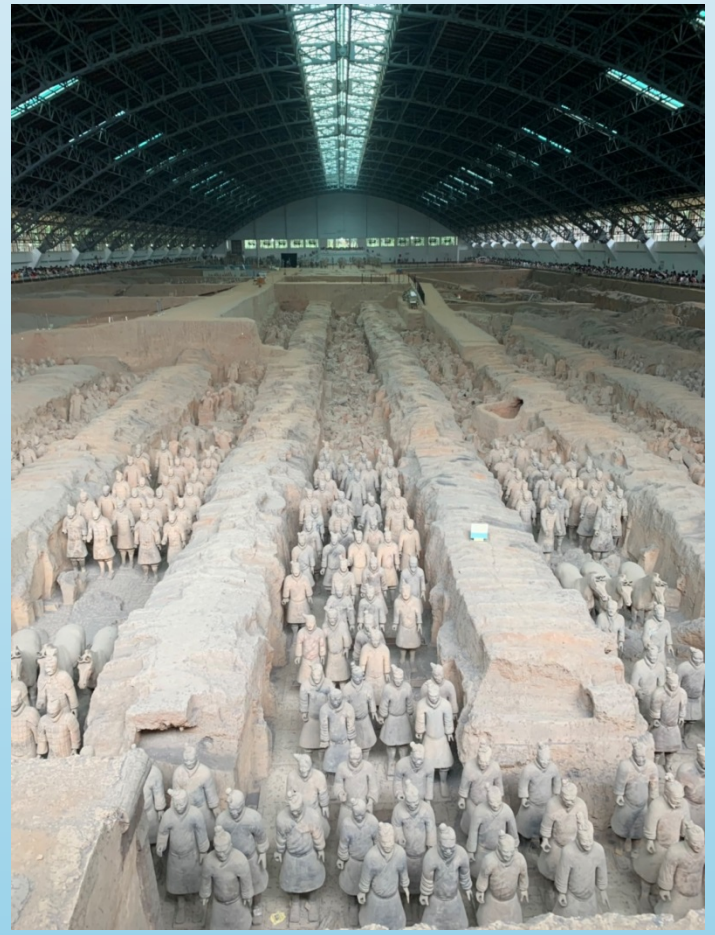
‘Wild’ Great Wall at Huairou







Xi'an



Introduction/Bio

- Currently leading the Data Standards, Strategic Outsourcing and Quality Assurance Biometrics teams at Vertex Pharmaceuticals.
- Previously at Allergan, Genentech, Bristol Myers-Squibb and Biogen
  - Participated, led and managed Statistical Programming teams to many successful regulatory filings:
- Initiated, led and hosted:
  - PhUSE Single Day Events, Cross-Company Meetings, Industry Working Groups.
- Requested presenter and panelist as well as author of papers and presentations at conferences in the US and internationally, including:
  - JSM (Joint Statistical Meetings), NESUG (Northeastern SAS Users Group), PharmaSUG, PharmaSUG China, PharmaSUG Single Day Event (SDE), PhUSE, PhUSE SDE, SAS Global Forum, and the Women's Innovation Network.
- MS degree in Epidemiology from Columbia University in the City of New York.
- Enjoy travelling, reading, spending time with my family, and volunteering

Overview

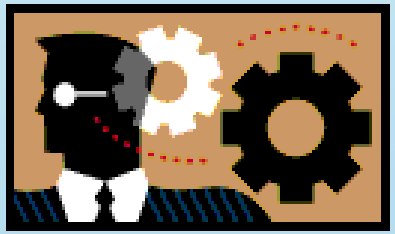
- Technology
  - AI is Here
- Policy
  - History of Regulation in the USA
  - FDA/PMDA *Emerging* Regulations
- Opportunity
  - The Potential for Machine Learning and Natural Language Processing
  - Examples
  - Challenges
  - Recommendations
- Conclusion

AI is Here…

Sent: Tue 5/21/2019 3:49 PM
To: Todd Case

Dear Todd,

90% of the data in the world today was created in the last two years alone, at 2.5 quintillion bytes of data per day.

Let's think about this: 

```
  913.125 quintillion bytes of data between the beginning of time and 5/21/2019
+  91.3125 quintillion bytes before 5/21/2019 (to equal 100%)
=1004.4375 Total quintillion bytes as of 5/21/2019
+ 100      days since 5/21/2019
*   2.5 quintillion bytes / day -conservative, not static @ 2.5 quintillion/day
=1254.4375 quintillion bytes of data as of today, August 29th, 2019
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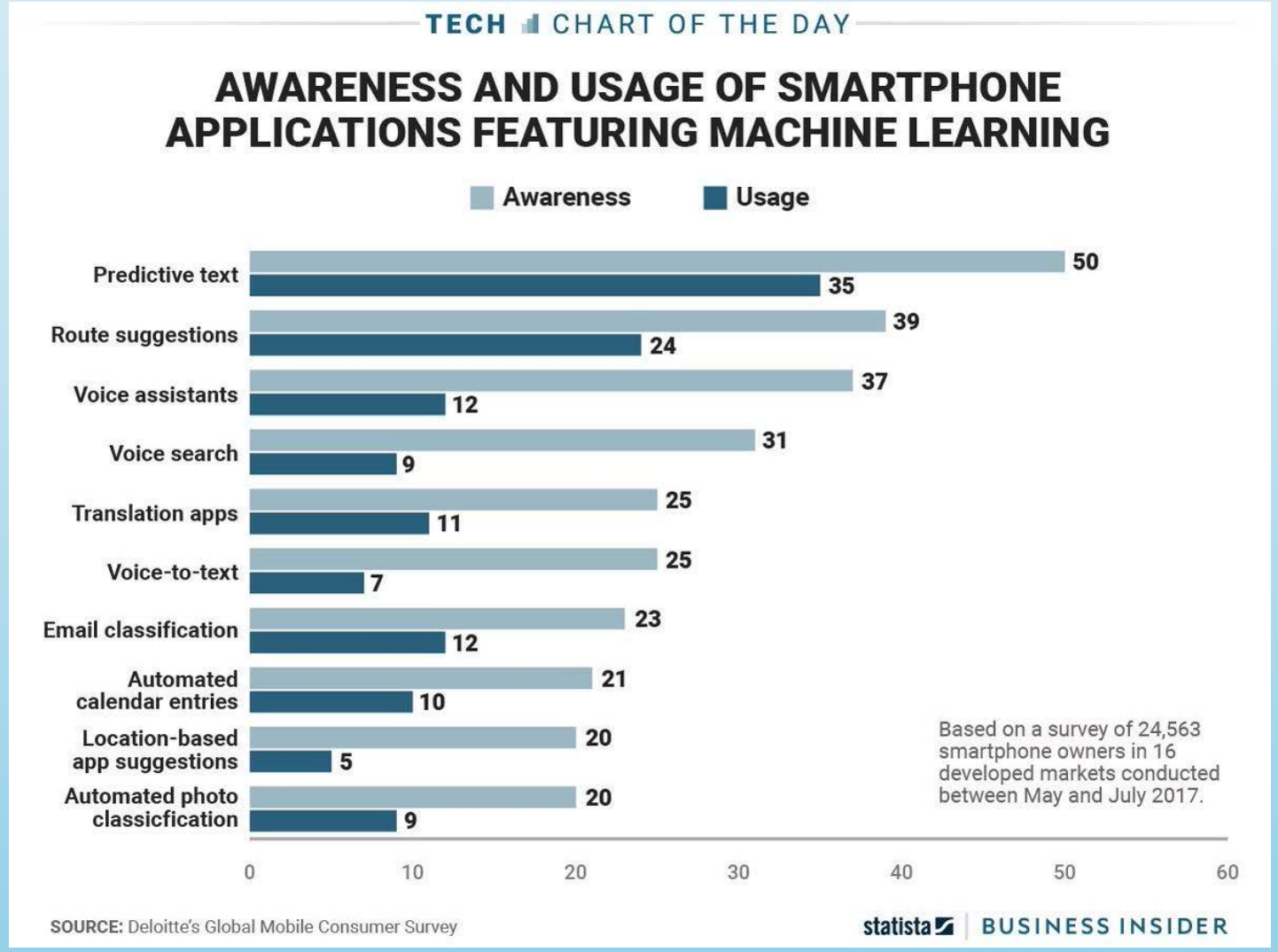
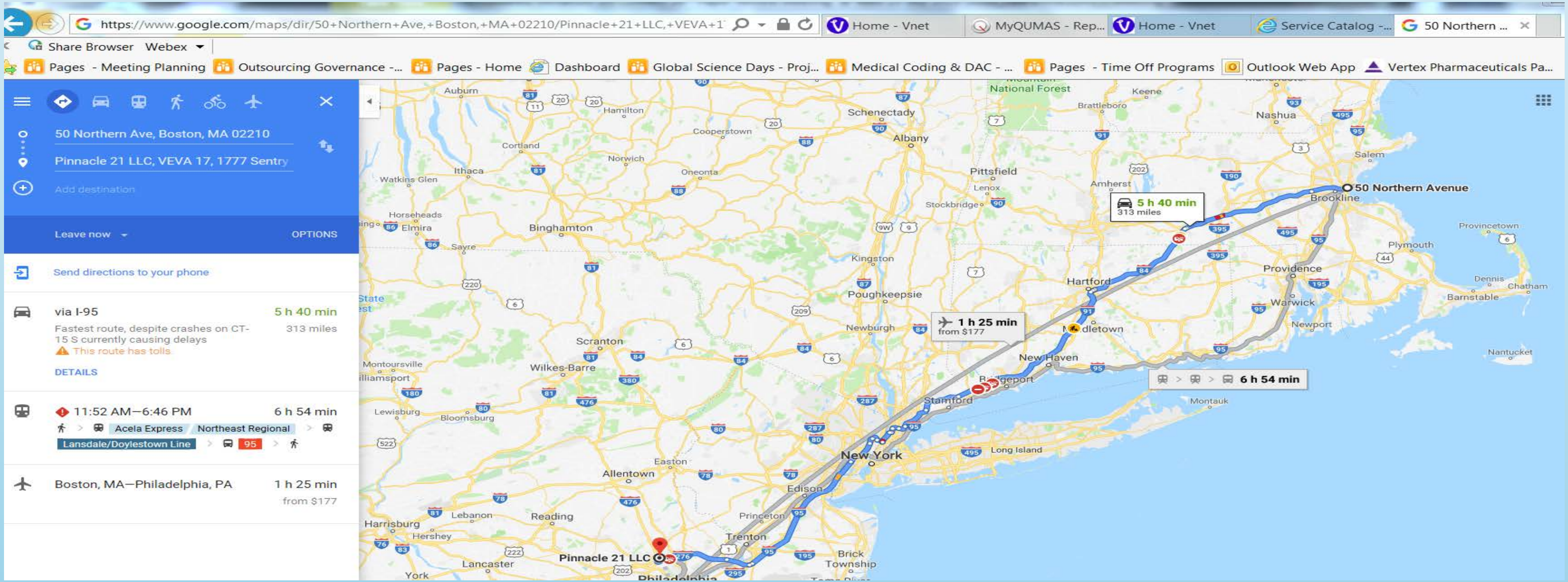
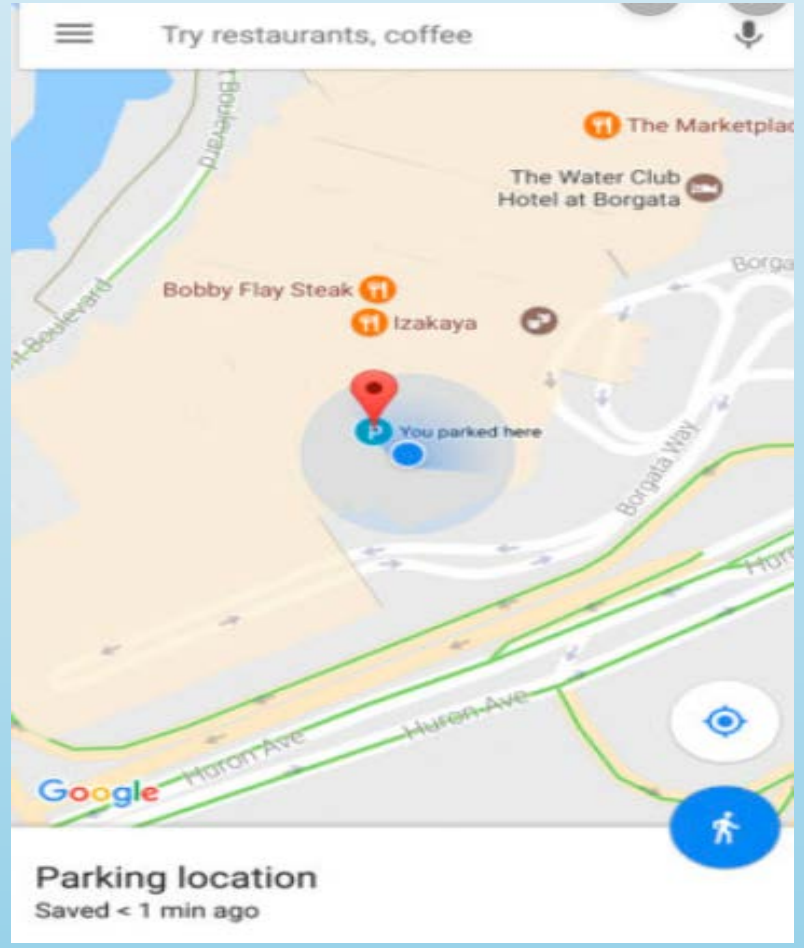
Artificial Intelligence: Huawei/Apple



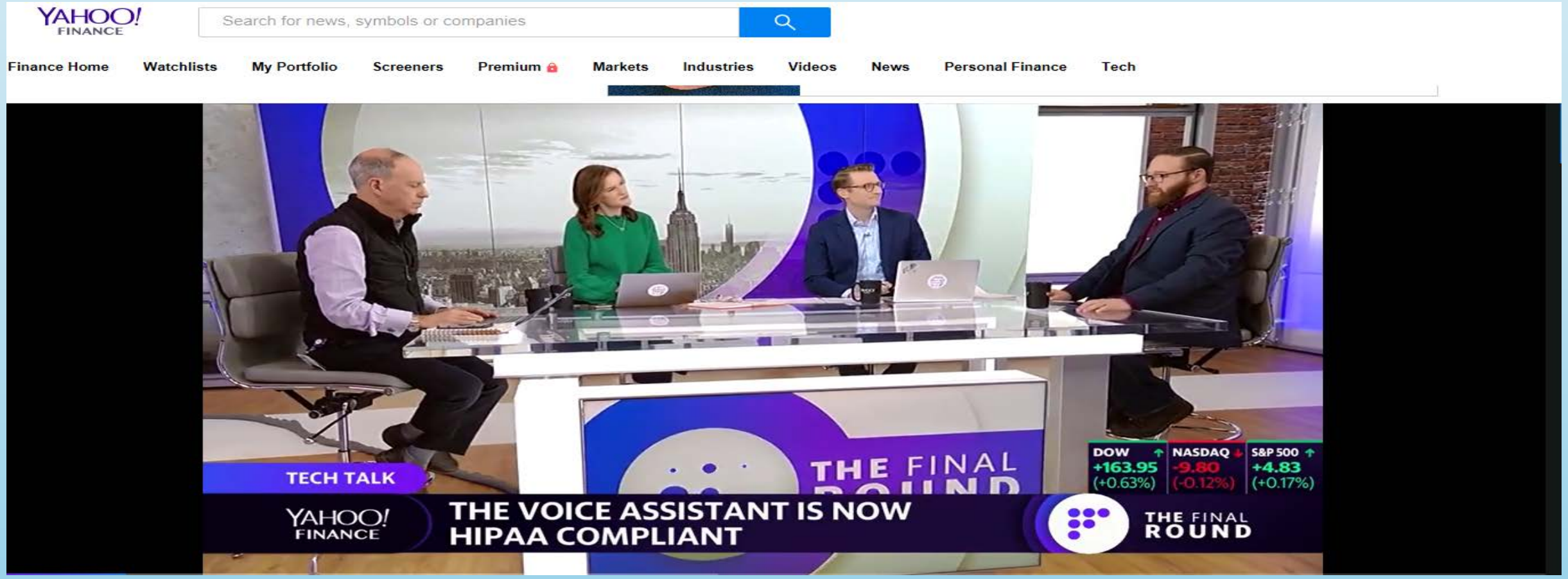
AI is Here…


https://www.google.com/maps/dir/50+Northern+Ave,+Boston,+MA+02210/Pinnacle+21+LLC,+VEVA+1
Home - Vnet
MyQUMAS - Rep...
Home - Vnet
Service Catalog -...
50 Northern ...
Share Browser
Webex
Pages - Meeting Planning
Outsourcing Governance -...
Pages - Home
Dashboard
Global Science Days - Proj...
Medical Coding & DAC - ...
Pages - Time Off Programs
Outlook Web App
Vertex Pharmaceuticals Pa...
50 Northern Ave, Boston, MA 02210
Pinnacle 21 LLC, VEVA 17, 1777 Sentry
Add destination
Leave now
OPTIONS
Send directions to your phone
via I-95
5 h 40 min
Fastest route, despite crashes on CT-15 S currently causing delays
313 miles
This route has tolls
DETAILS
11:52 AM—6:46 PM
6 h 54 min
Acela Express
Northeast Regional
Lansdale/Doylestown Line
95
Boston, MA—Philadelphia, PA
1 h 25 min
from $177
5 h 40 min
313 miles
1 h 25 min
from $177
6 h 54 min
50 Northern Avenue
Brookline
Pinnacle 21 LLC
Philadelphia
New York
Hartford
Providence
New Haven
Stamford
Bridgeport
Long Island
Trenton
Allentown
Scranton
Binghamton
Albany
Schenectady
Pittsfield
Poughkeepsie
Newburgh
Kingston
Edison
Princeton
Reading
Lancaster
Harrisburg
Wilkes-Barre
Easton
Worcester
Nashua
Salem
Plymouth
Warwick
Newport
Montauk
Amherst
Brattleboro
Keene

AI is…. Where my car is!



April, 2019


YAHOO! FINANCE
Search for news, symbols or companies
Finance Home
Watchlists
My Portfolio
Screeners
Premium
Markets
Industries
Videos
News
Personal Finance
Tech
TECH TALK
THE FINAL ROUND
DOW +163.95 (+0.63%)
NASDAQ -9.80 (-0.12%)
S&P 500 +4.83 (+0.17%)
YAHOO! FINANCE
THE VOICE ASSISTANT IS NOW HIPAA COMPLIANT
THE FINAL ROUND

HIPAA* Features of Alexa

- Cigna Health Today
  - Check wellness program goals, receive health tips, and more…
- My Children's Enhanced Recovery After Surgery (ERAS)
  - Boston Children's Hospital's ERAS program can send updates to their care teams on recovery progress
- Livongo Blood Sugar Lookup
  - Query latest blood sugar reading, check blood sugar monitoring trends (e.g., weekly average reading) and receive *personalized* health tips
- Atrium Health
  - Patients can find urgent care locations near them and schedule same-day appointments and current waiting times

* The Health Insurance Portability and Accountability Act (**HIPAA**) sets the standard for sensitive patient data protection. Companies that deal with protected health information (PHI) must have physical, network, and process security measures in place and follow them to ensure **HIPAA Compliance**.

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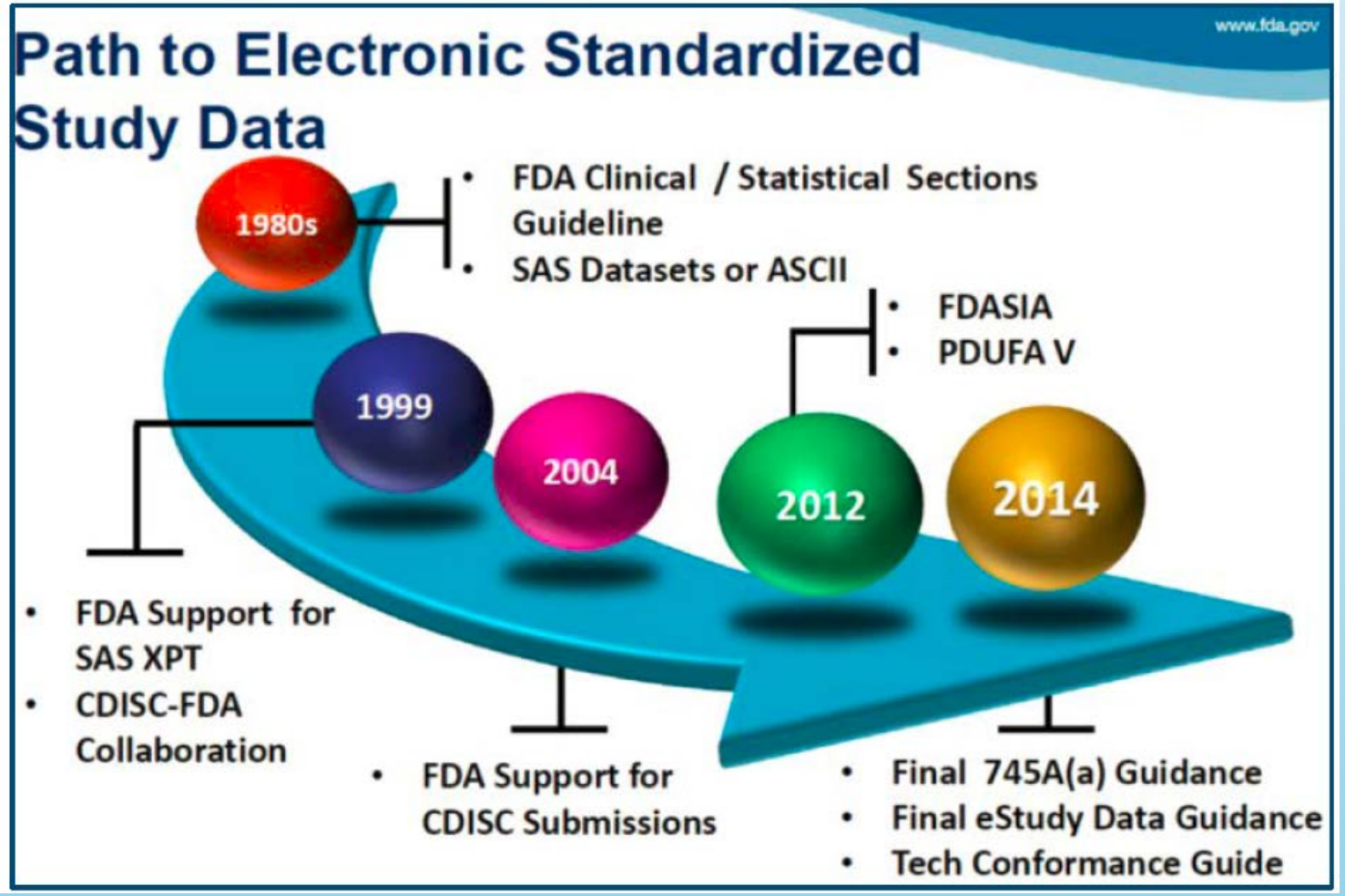
FDA "e-Regulatory Policy", 1980s-present



FDA/PhUSE Computational Science Symposium
Mary Ann Slack, FDA/CDER
March 18, 2013

https://www.phusewiki.org/docs/2013/CSSPresentations_/Mary%20Ann%20Slack%20.pdf

Policy

- Prescription Drug User Fee Acts (PADUFA's)
  - The Prescription Drug User Fee Act (**PDUFA**) **was** a law passed by the United States Congress in 1992 which allowed the Food and Drug Administration (FDA) to collect fees from drug manufacturers to fund the new drug approval process.
  - Helps the Food and Drug Administration (**FDA**) to fulfill its mission of protecting the public health and accelerating innovation in the industry

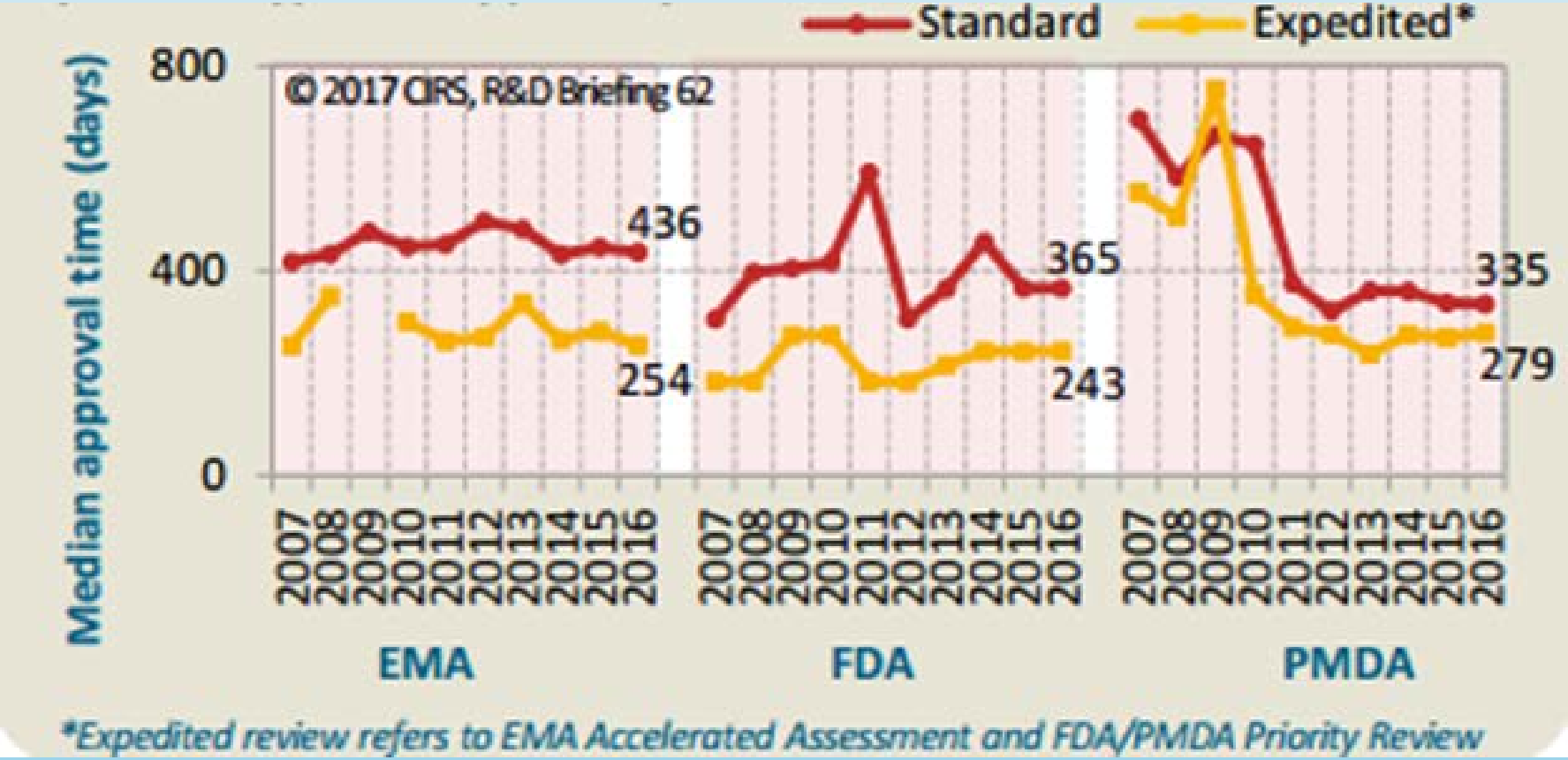
Policy

- PADUFA V was a reauthorization (covering 2013-2017)
- This particular reauthorization included a 5-year plan for achieving specific Information Technology (IT) goals:
  1. **Supporting Regulatory Operations**—describing the approach to strengthening the Electronic Submissions Gateway to support the long-term exchange and review of drug and biologics applications.
  2. **Electronic Regulatory Submissions**—providing a consistent approach to the creation and review of regulatory submissions.
  3. **Data Standards**—defining and implementing standards supporting drug efficacy, drug safety, manufacturing, product identification, and other areas.
  4. **Metrics and Measures**—tracking progress and assessing implementation of goals.
  5. **Communications and Technical Interactions**—disseminating information to stakeholders to help improve the program.

Policy

- PADUFA VI was a continuation in many ways of the IT goals outlined in PADUFA V, with the following new overarching aim of Enhancing Capacity to Support Analysis Data Standards for Product Development and Review, as follows:
  - …
  - By end of FY 2019, FDA will convene a public workshop to advance the development and application of analysis data standards.
  - FDA will collaborate with external stakeholders and participate in public workshops held by third parties such as standards development organizations, on development of data standards, processes, documentation and continuous improvement of clinical trials and regulatory science.
  - By end of FY 2020, FDA will develop or revise, as appropriate, relevant guidance, MAPPs, SOPPs and training associated with submission and utilization of standardized analysis datasets and programs used in review, and on the processes, procedures, and responsibilities related to the receipt, handling, and documentation of submitted analysis data and programs.

Accelerated Speed of Approval



*European Federation of Pharmaceutical Industries and Associations: White paper on reliance and expedited registration pathways in emerging markets, 23Nov2019

Exponential Speed of Approval

Dennis, Sweitzer, LinkedIn: https://www.linkedin.com/feed/update/urn:li:activity:6571522525426176000/
https://www.medpagetoday.com/publichealthpolicy/generalprofessionalissues/81725

"n-of-1" Clinical Trials

- Market Exists:
  - "There are more than 10,000 human disorders caused by mutations in single genes, which together affect about 1% of the population…"
- A new therapy, Antisense Oligonucleotides (ASO) allows targeting of diseases caused by genetic variations unique to single patients, so the only clinical trial option is N-of-1 study.
- "by doing many of these, they are going to get faster and cheaper so ultimately a personalized drug for each person who has a different mutation"
- …"manufacturing capacity will increase and competition, as well as economies of scale, will drive costs down."

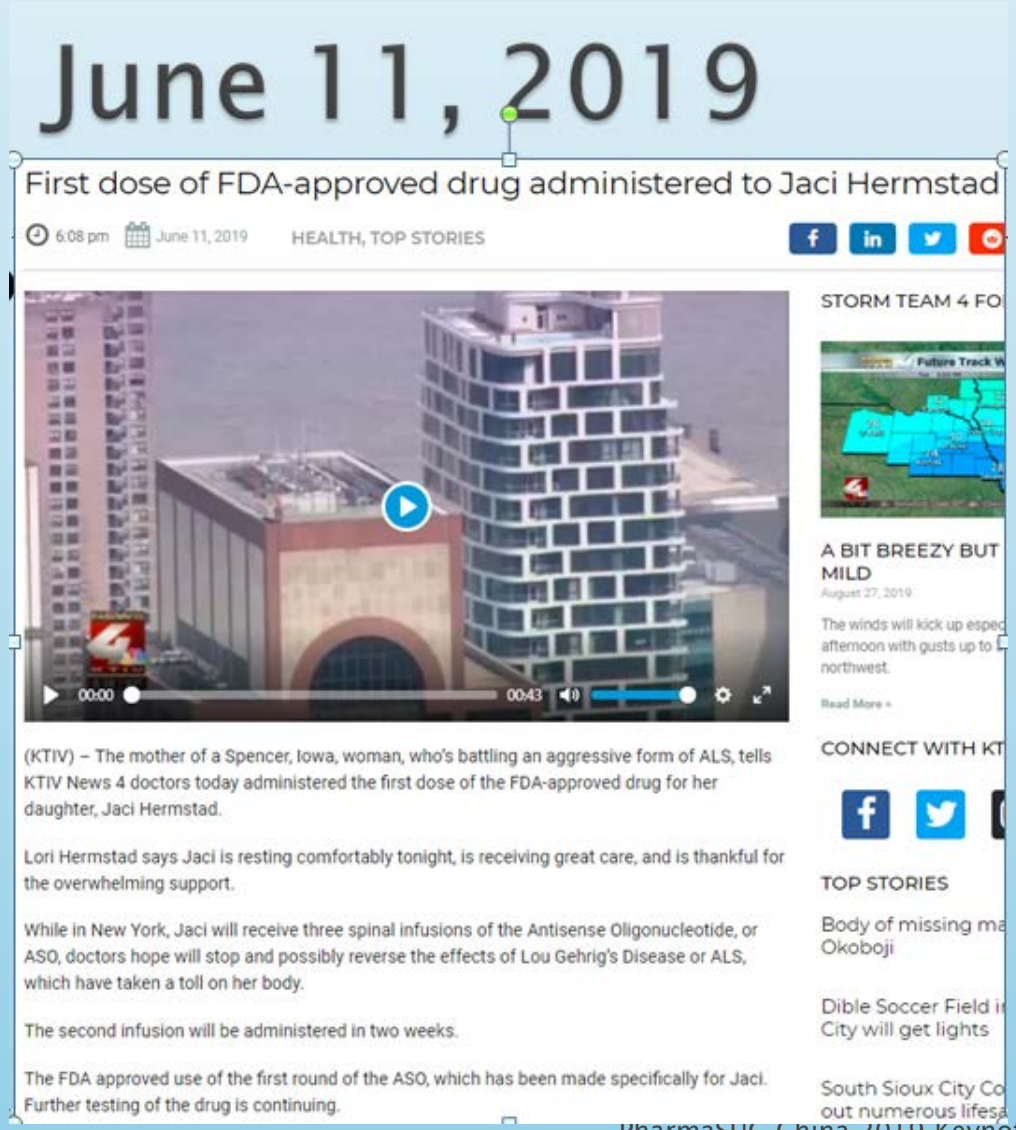
Dennis, Sweitzer, LinkedIn: https://www.linkedin.com/feed/update/urn:li:activity:6571522525426176000/
https://www.medpagetoday.com/publichealthpolicy/generalprofessionalissues/81725

Jaci Hermstad

- Jaci Hermstad is a 25-year-old who loves horseback riding, and has a rare genetic form of amyotrophic lateral sclerosis (ALS).

- She has survived longer than her identical twin sister, Alex, who developed her first ALS symptoms at age 11 and died in 2011 when she was 17.
- FDA approved her experimental treatment, which went beyond recent "right-to-try" laws since it hadn't been tested in humans.
- But what about FDA Review/Regulations?

Dennis, Sweitzer, LinkedIn: https://www.linkedin.com/feed/update/urn:li:activity:6571522525426176000/
https://www.medpagetoday.com/publichealthpolicy/generalprofessionalissues/81725


June 11, 2019
First dose of FDA-approved drug administered to Jaci Hermstad
6:08 pm
June 11, 2019
HEALTH, TOP STORIES
00:00
00:43
(KTIV) – The mother of a Spencer, Iowa, woman, who's battling an aggressive form of ALS, tells KTIV News 4 doctors today administered the first dose of the FDA-approved drug for her daughter, Jaci Hermstad.
Lori Hermstad says Jaci is resting comfortably tonight, is receiving great care, and is thankful for the overwhelming support.
While in New York, Jaci will receive three spinal infusions of the Antisense Oligonucleotide, or ASO, doctors hope will stop and possibly reverse the effects of Lou Gehrig's Disease or ALS, which have taken a toll on her body.
The second infusion will be administered in two weeks.
The FDA approved use of the first round of the ASO, which has been made specifically for Jaci. Further testing of the drug is continuing.
STORM TEAM 4 FO
A BIT BREEZY BUT MILD
August 27, 2019
The winds will kick up espec
afternoon with gusts up to
northwest.
Read More »
CONNECT WITH KT
TOP STORIES
Body of missing ma
Okoboji
Dible Soccer Field i
City will get lights
South Sioux City Co
out numerous lifesa

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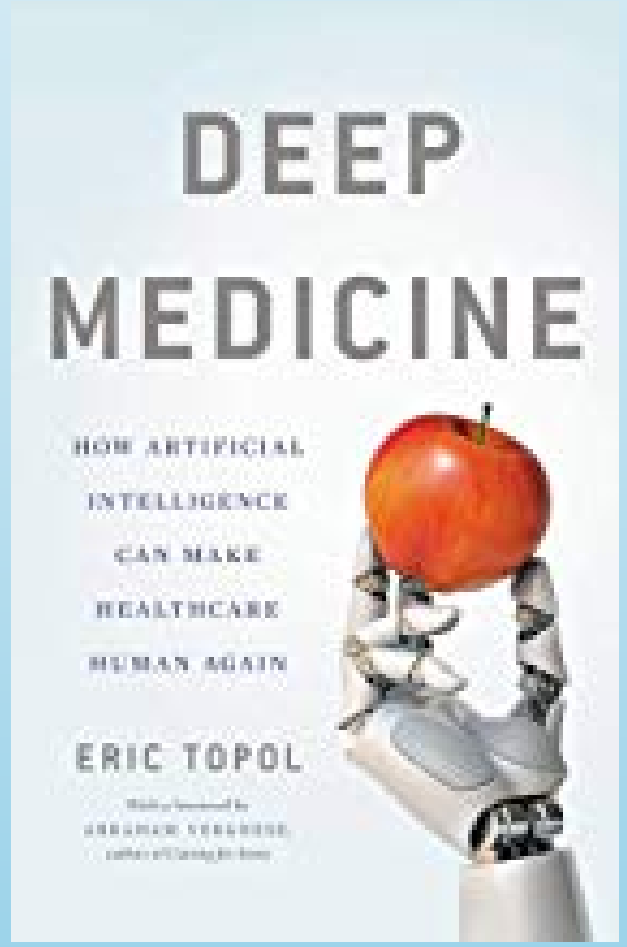
Deep Medicine: AI's Potential



- Allowing Physicians to spend more time with patients, using information from AI/NLP Tools
  - AI: Understand Medical History, prescriptions, recommend diagnosis and treatments
  - Physicians: Use AI in conjunction with their interactions with patients to make a final diagnosis and treatment plan
- What's going on with the patient's life right now, TODAY (e.g., job loss, loss of a family member, other stresses that are not known by machines)

Something Like This:

Zebra

- "Profound," a fully automated software that provides a second opinion on mammograms, CT scans and other medical imaging reports.
- The database used by Profound comes from thousands of anonymous patients' reports collected from hospitals and clinics all across the world.

http://www.medsnews.com/health/zebra-profound-provides-second-opinion-ct-scans/

Zebra, cont'd

- "Profound" does not seek to substitute the expertise of a healthcare provider and does not replace a doctor's proper medical examination
  - "2nd Opinion"
  - Provide a full algorithm-based analysis of a medical imaging report to find even the smallest detail that a physician could miss
  - Patients can upload their scan online at any time, and the software will perform a real-time analysis that will search for hidden health insights and then provide a second opinion within a couple of minutes.
  - Reduce Patient Anxiety
  - Reduce the chance of a "false negative" as patients can follow up with their physician whenever something suspicious is found

Virtual Clinical Trials

OCTOBER 24

Science 37 and AOBiome Complete Industry-First Virtual Clinical Trial Through Metasite™ (Decentralized) Operating Model

Virtual Clinical Trials

PLAYA VISTA, Calif. (October 24, 2017) – Science 37, a trailblazing company focused on "site-less" clinical trials, announced today the completion of a Phase 2b study for AOBiome, a clinical-stage life sciences company, in which it screened over 8,000 people with mild-to-moderate acne and enrolled 372 participants to take part in this research study all from the comfort of their own homes. This is the first time that a Phase2b interventional randomized placebo controlled trial of this kind has been successfully run one hundred percent virtually. In a separate announcement, AOBiome reported positive efficacy and safety findings from the study, available at this link.

AI in Pharma/Biotech

1. Aggregate and Synthesize Information
   - Pfizer: has accumulated data from 25 million Medline article abstracts and 1 million medical journal articles compared to the 200-300 articles a human researcher can read in a single year.
   - Do the Math:
   - 83,333.1/3 years

     At the fastest pace of 300 articles in a year!

148 Startups Using Artificial Intelligence in Drug Discovery*

* Simon Smith: https://blog.benchsci.com/startups-using-artificial-intelligence-in-drug-discovery

In vitro Clinical Trials

- Blood glucose controller for neonatal intensive care
  - Knowledge of the metabolic state of the *neonate* is vital for optimal, safe Blood Glucose control using insulin administration
  - This study presents an adaptive, model-based predictive controller designed to incorporate the unique metabolic state of the neonate
    - https://europepmc.org/articles/pmc2769904

Use in Stat Programming: Intern Presentation from 2018

- Used Python and NLP packages to look at ~10,000 rows of comments from aggregated QC Trackers
  - Text Analysis of QC/Issue Tracker by Natural Language Processing (NLP)
- What datasets and Tables/Figures/Listings are the most problematic?
- Within those, what about them are the most problematic?
- How can we fix those problems?

https://www.pharmasug.org/proceedings/2019/AD/PharmaSUG-2019-AD-052.pdf

Use in Stat Programming: Extern Presentation from 2019

- Unigrams (single words) and Bigrams (2 word combinations)

Table 2: The 5 most correlated unigrams and bigrams for each category

AdaM and Specs	Unigram	ablfl, avisit, aperiod, adsl, paramcd
	Bigram	add variables, adam spec, analysis dataset, baseline records, core variables
Raw Data	Unigram	coded, dsdrug, dsdat, randno, subject
	Bigram	subjects dm, aedecode missing, subject updated, randno subject, subject day
SAP	Unigram	Indicates, adhoc, xxxx, figure, decision
	Bigram	d figure, need d, add footnote, footnote need, annotated sap
SDTM and Specs	Unigram	raw, y, decision, updated, closed
	Bigram	column j, epoch missing, column g, usubjid vx17, raw data
TFL	Unigram	shell, footnote, y, decision, closed
	Bigram	dose group, min max, sap shell, shell missing, footnote shell

We can see that the most corrected unigrams and bigrams are reasonable and are consistent with our expectations. Specifically, we can see that for most of them, unigrams tell us *where* the problems are and bigrams tell us *what* the problems are.

https://www.pharmasug.org/proceedings/2019/AD/PharmaSUG-2019-AD-077.pdf

Most Commonly Used Word in Statistical Programming

Theranos – The Bad

Theranos

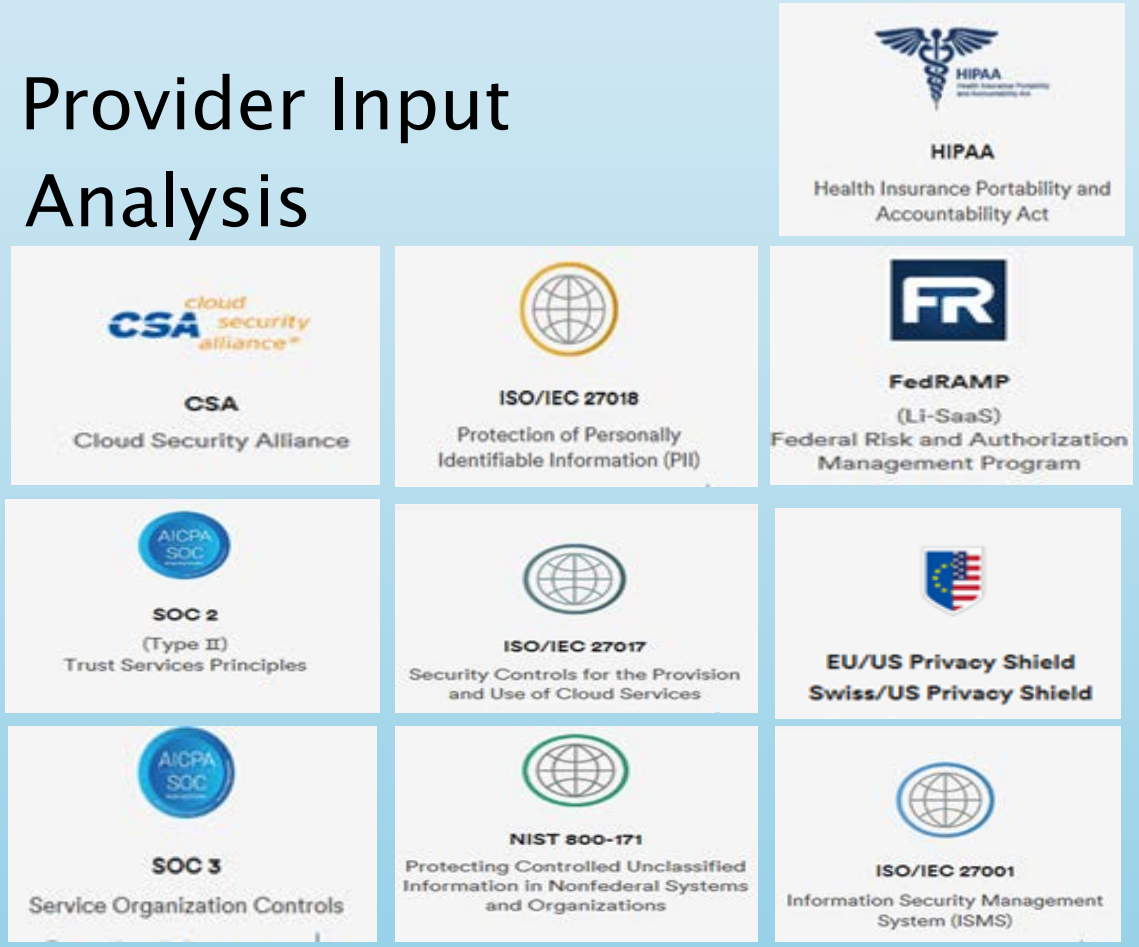
- Elizabeth Holmes Started Theranos at 19
- World's 1st, youngest, female "Billionaire"
- Grew Theranos to a valuation of $9 billion USD
  - Holmes took investors' money on the condition that she wouldn't have to reveal how Theranos' technology worked.
  - Bottom Line: Lab Test using a draw the size of a "pin prick" could not perform tests accurately on the 100s of assays that a "conventional lab" does
  - Many tests were actually performed on "conventional lab" equipment, saying they were generated by Theranos
    - In June 2018, Theranos announced that Holmes was stepping down as CEO. On the same day, the Department of Justice announced that a federal grand jury had charged Holmes, along with Balwani, with nine counts of wire fraud and two counts of conspiracy to commit wire fraud.

Google Flu Predictions

- Relied on monitoring millions of users' health tracking behaviors online, the large number of Google search queries gathered can be analyzed to reveal if there is the presence of flu-like illness in a population
- Then compare Google Flu Trends to a historic baseline level of influenza activity for its corresponding region
- Then report the activity level as either minimal, low, moderate, high, or intense. These estimates have NOT been generally consistent with conventional surveillance data collected by health agencies, both nationally and regionally.

Concerns

- Privacy
- Lack of Health Care Provider Input
- Data Collection and Analysis
  - Accurate Results
  - "Predictability"
  - Reliability
  - Consistency



Overview

- Technology
  - AI is Here
  - Why are we so obsessed with AI?
    - Natural Language Processing, Machine Learning
- Policy
  - History of Regulation in the USA
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Suggestions for the Future

- Look at how **New Technology** has Improved our Lives
  - Can we use AI/Natural Language Processing to be more efficient?
  - Example: Using Python/NLP packages to understand where our most challenging data/table/listing/figure programs are
  - Find problem datasets
  - Look at unigram/bigrams to find the exact problem (e.g., LFT Analysis)
    - Fix the problems
  - Using Python to compare Production and QC Code
  - Building Define.xml?
- Understand Emerging/ **New Policy** and Regulations
  - Read the news, network with peers
  - Policy is changing faster than ever, e.g., the "N of 1" trials/approval(s)
- Ask Ourselves Where this Technology meets **Opportunity**
  - Define what the problem statement is
  - Build solutions around the Problem
  - Balance Risk and Reward
  - Look for opportunities to impact process
  - Don't rule out incremental change

Thanks PharmaSUG China Committee!

- Margaret Hung
- Kriss Harris
- Eason Yang

Contact Information

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LinkedIn: https://www.linkedin.com/in/todd-case-08a1576/