COVID-19 Evidence Accelerator: Public Meeting

October 20, 2022
1-4 p.m. Eastern Time
Thank you for joining

This webinar is being recorded. The slides, transcript, and video recording will be available on the Evidence Accelerator website after the meeting.

Due to the meeting size, your microphone and video will remain off during the meeting.

While we won’t have time to directly address audience questions during today’s meeting, you may use the Zoom chat function for comments.
1 p.m. Welcome & Introduction – Susan C. Winckler, RPh, Esq.
1:03 p.m. Opening Remarks – Namandjé N. Bumpus, PhD
1:08 p.m. Remarks – Robert M. Califf, MD, MACC
1:10 p.m. Keynote Speech – Amy Abernethy, MD, PhD
1:25 p.m. Session One: FDA Perspectives on the COVID-19 Evidence Accelerator
2:10 p.m. Session Two: Research Findings and Methodologies
3:10 p.m. Session Three: How COVID-19 and the Evidence Accelerator Have Shaped the Use of Real-World Data
3:50 p.m. Closing Thoughts
Opening Remarks

Namandjé N. Bumpus, PhD
Chief Scientist
FDA
Keynote Speech

Amy Abernethy, MD, PhD
President of Clinical Studies Platforms
Verily
FDA Perspectives on the COVID-19 Evidence Accelerator

Moderator

Jeff Allen, PhD, President and CEO, Friends of Cancer Research

Panelists

Sara Brenner, MD, MPH, Center for Devices and Radiological Health, FDA

Jacqueline Corrigan-Curay, JD, MD, Center for Drug Evaluation and Research, FDA

Peter Marks, MD, PhD, Center for Biologics Evaluation and Research, FDA
Research Findings and Methodologies

Moderator

Dr. Carla Rodriguez-Watson, Director of Research, Reagan-Udall Foundation for the FDA

Panelists

Dr. Nicolle Gatto, Chief Science Officer, Aetion, Inc

Sandy Leonard, SVP of Partnerships and RWD Solutions at HealthVerity

Dr. Vincent Lo Re III, tenured Associate Professor of Medicine at the University of Pennsylvania Division of Infectious Diseases

Dr. Anand Chokkalingam, Executive Director and Head of Real-World Evidence for Gilead’s Virology Therapeutic Area

Dr. Nancy Lin, Director of Epidemiology, Real World Solutions at IQVIA

Dr. Aloka Chakravarty, Director of Data Analytics and Senior Statistical Advisor in the Office of the Commissioner, FDA
Reagan-Udall Foundation for the FDA/Friends of Cancer Research
Evidence Accelerator
Work Streams

**THERAPEUTICS EA**
- Twice-Monthly Lab Meeting (1st and 3rd Thursdays)
- Weekly Parallel Analysis Accelerators
- Monthly PA Broad Discussion (2nd Wednesdays)

**DIAGNOSTICS EA**
- Twice-Monthly Lab Meeting (1st and 3rd Thursdays)
- Weekly Parallel Analysis

**TBD [VACCINES EA]**
- Weekly Lab Meeting
- Weekly Parallel Analysis

Oncology work group
Other work groups
Purpose: to assemble a community where questions about COVID-19 could be *urgently* explored through the lens of RWD and RWE generation.
Community Took a Step by Step Approach to Parallel Analysis

- Started with FDA prioritized research questions.
- Identified common data elements and developed translation tables between common data models.
- Created common protocol for repeated analysis of priority research questions across multiple data partners—the “parallel analysis.”
- Held meetings and forum for rapid cycle feedback and learning.
- Focused individual accelerator communities on specific topics (e.g., therapeutics, diagnostics).
Together, we will **create** and **lead**.

**CREATE**
- **CONTEXT** — tie data to the question, address bias, explain validation strategies.
- **RESPECT** — for patient privacy and the patient voice is paramount.
- **EARN TRUST** — show processes, analytic approaches, and comparisons. Be open to input. Challenge with productive intent.
- **ACT FAST AND DO GOOD WORK** — act with a sense of urgency, but not at the expense of quality or credibility.
- **TRANSPARENCY** — ruthless transparency.
- **EMBRACE AND EXPLORE** — convergence and discordance to facilitate understanding and generate knowledge.

**LEAD**
- **LEARN** — continually integrate best practices from sharing process, limitations, pitfalls, and successes.
- **EXERCISE PATIENCE** — state when a question can’t be answered right away and institute action to answer it.
- **ACCESSIBILITY AND TRACEABILITY** — document data generation, processing, curation, and analytics.
- **DISSEMINATE WORK** — to show what good looks like. *Teach, Don’t Preach.*
HYDROXYCHLOROQUINE

Nicolle Gatto, PhD
Chief Science Officer, Aetion, Inc
The Process

- First COVID-19 Evidence Accelerator research project (+ publication)
- 7 research groups; 9 total partners
- Piloted the common protocol and collaborative, but independent parallel analysis approaches
- 6 EMR data sources + 1 hospital chargemaster with linked claims
- Parallel analysis by each partner, allowed for flexibility due to differences and unique limitations of each data source
Using a parallel analysis format, describe outcomes associated with the use of hydroxychloroquine (HCQ) with/without azithromycin (AZ) for hospitalized COVID-19 patients across seven real-world datasets in the United States.

1. Characterize the baseline demographics, comorbidities and medical history of hospitalized patients with COVID-19
2. Characterize treatment patterns of HCQ (with or without AZ) therapy administered in the inpatient setting
3. Describe safety and effectiveness outcomes of interest among hospitalized patients receiving HCQ (with or without AZ)
Inclusion Criteria: Patients hospitalized with COVID-19 between Jan 2020 - Jun 2020

Treatment groups: HCQ alone, HCQ+AZ, and neither HCQ nor AZ.

Outcomes: Time-to-event for outcomes of mechanical ventilation, discharge, and mortality.

Analytic approaches: Cox proportional hazards models were used for outcome associations among HCQ+AZ-treated vs. neither treatment populations; various propensity score methods undertaken to adjust for confounding.

*Approach for index date assignment (and start of follow-up) varied across data partners.
7 parallel analysis partners -- 20,371 total COVID-19 patient hospitalizations

Aetion/HealthVerity
COTA/Hackensack Meridian Health
Dascena
Health Catalyst
Syapse
TriNetX
Veteran’s Health Administration

Analytic Partner Coverage

Example: Differences in data characteristics, definitions, & design aspects across data partners
Results: Baseline data and unadjusted risks

- Demographic and comorbidity distributions varied across datasets, but trends were generally similar for HCQ+AZ versus no treatment groups within each dataset.
- Patients receiving HCQ+AZ were typically older than 45 with a larger proportion of males.
- Prior to adjustment, risks of mortality and mechanical ventilation were generally higher among HCQ+AZ patients as compared to those with neither treatment.

### Race
- Demographic and comorbidity distributions varied across datasets, but trends were generally similar for HCQ+AZ versus no treatment groups within each dataset.
- Patients receiving HCQ+AZ were typically older than 45 with a larger proportion of males.
- Prior to adjustment, risks of mortality and mechanical ventilation were generally higher among HCQ+AZ patients as compared to those with neither treatment.

### Comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Aetion</th>
<th>COTA</th>
<th>Dascena</th>
<th>Health Cat</th>
<th>Syapse</th>
<th>TriNetX</th>
<th>VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CVD</td>
<td>1302</td>
<td>688</td>
<td>1284</td>
<td>1101</td>
<td>256</td>
<td>1243</td>
<td>737</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-</td>
<td>18%</td>
<td>4%</td>
<td>18%</td>
<td>13%</td>
<td>15%</td>
<td>19%</td>
</tr>
<tr>
<td>Obesity</td>
<td>7%</td>
<td>6%</td>
<td>3%</td>
<td>-</td>
<td>6%</td>
<td>-</td>
<td>9%</td>
</tr>
</tbody>
</table>

### Risk of outcome (%; unadjusted)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aetion</th>
<th>COTA</th>
<th>Dascena</th>
<th>Health Cat</th>
<th>Syapse</th>
<th>TriNetX</th>
<th>VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality %</td>
<td>25%</td>
<td>29%</td>
<td>18%</td>
<td>30%</td>
<td>11%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Mech. vent %</td>
<td>16%</td>
<td>29%</td>
<td>35%</td>
<td>-</td>
<td>35%</td>
<td>-</td>
<td>15%</td>
</tr>
</tbody>
</table>

Aetion, Inc. Confidential. Preliminary results, not for distribution.
Results: Primary outcome comparative analysis

• Confounders generally well-balanced across treatment groups, after adjustment

• Overall, across the 5 groups who ran adjusted comparative analyses, we observed no clear association between HCQ treatment (w/out AZ) and mortality or mechanical ventilation

<table>
<thead>
<tr>
<th></th>
<th>Mortality HR (95% CI)</th>
<th>Mechanical Ventilation HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aetion/HV*</td>
<td>Not assessed</td>
<td>1.29 (0.96, 1.74)</td>
</tr>
<tr>
<td>COTA/HMH</td>
<td>1.16 (0.90, 1.51)</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Dascena</td>
<td>1.90 (0.91, 4.1)</td>
<td>2.50 (1.20, 5.20)</td>
</tr>
<tr>
<td>Health Catalyst</td>
<td>1.09 (0.76, 1.56)</td>
<td>Not assessed</td>
</tr>
<tr>
<td>TriNetX</td>
<td>0.99 (0.73, 1.35)</td>
<td>Not assessed</td>
</tr>
<tr>
<td>VA</td>
<td>1.18 (0.88, 1.58)</td>
<td>1.54 (1.07, 2.23)</td>
</tr>
</tbody>
</table>

*Includes all HCQ users, regardless of AZ exposure
Process learnings for future parallel analyses

- Consider a stepwise approach to first evaluate sample sizes, geographic coverage and patient characteristics, with feasibility assessment for the research question of interest
- Use information from initial descriptive assessment to optimally design the subsequent comparative study and identify appropriate analyses
- Apply uniform definitions and methods where possible, tailor analysis as needed to accommodate dataset variation (where dataset otherwise deemed fit for purpose)
- Clearly describe any variations and limitations for each dataset / analysis
Anand Chokkalingam, PhD
Executive Director and Head of Real-World Evidence for Gilead’s Virology Therapeutic Area
REMDESIVIR AIMS

**Aim 1:** Characterize use of remdesivir among hospitalized patients with COVID-19 after implementation of the EUA

**Aim 2:** Develop and construct a propensity score model to achieve balance on observed characteristics to apply in aim 4

**Aim 3:** Assess weighting technique assumptions and diagnostics, and confirm that baseline balancing is achievable

**Aim 4:** Assess risk for AKI, ventilation, discharged alive, in-hospital mortality, and length of stay among hospitalized COVID-19 patients treated with remdesivir vs. untreated.
• Importance of accounting for COVID-19 severity
• Methodological considerations such as immortal time bias, channelling bias that were especially acute at the start of the pandemic
• Importance of common operational definitions of medications, both for exposure and covariates
• Challenge of examining narrow window of exposure and of subsequent outcomes
COAGULOPATHY

Vincent Lo Re III, M.D., M.S.C.E
Associate Professor of Medicine, University of Pennsylvania, Division of Infectious Diseases
Aim: 90-day absolute risk of ATE and VTE in:

Patients initially diagnosed with COVID-19 in hospital (Apr 2020 – May 2021)

vs.

Patients initially diagnosed with influenza in hospital (October 2018 - April 2019)
Data varied by Partner:

- EHR + claims (Sentinel, HealthPals)
- Claims, retail pharmacy, remittance (Datavant)
- Cancer EHR + linked mortality, SEER data (Syapse)
COMMON ANALYTIC APPROACH

Calculated 90-day:
- Absolute risk
- Incidence rate
- PS-adjusted hazard ratios
COVID-19 (n=417,985) // Influenza (n=345,934)

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0261786
**RESULTS**

HRs for 90-Day ATE Among Patients Hospitalized With COVID-19 vs. Influenza

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Patients</td>
<td>No. Events</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID-19</td>
<td>41,443</td>
<td>6,559</td>
</tr>
<tr>
<td>Influenza</td>
<td>8,269</td>
<td>1,190</td>
</tr>
<tr>
<td>All-cause 30-day mortality after inpatient ATE event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID-19</td>
<td>6,559</td>
<td>1,482</td>
</tr>
<tr>
<td>Influenza</td>
<td>1,190</td>
<td>94</td>
</tr>
</tbody>
</table>

* HRs calculated after adjustment for Data Partner and propensity score fine stratification with stratum-specific weighting.
## RESULTS

**HRs for 90-Day VTE Among Patients Hospitalized With COVID-19 vs. Influenza**

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
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<td></td>
<td></td>
</tr>
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<td>3,917</td>
</tr>
<tr>
<td>Influenza</td>
<td>8,269</td>
<td>440</td>
</tr>
<tr>
<td>All-cause 30-day mortality after inpatient VTE event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID-19</td>
<td>3,917</td>
<td>714</td>
</tr>
<tr>
<td>Influenza</td>
<td>440</td>
<td>24</td>
</tr>
</tbody>
</table>

* HRs calculated after adjustment for Data Partner and propensity score fine stratification with stratum-specific weighting.
RESULTS

Unweighted (total sample and by place of service) and propensity score matched hazard ratios and 95% CI of arterial events or venous thrombotic events among patients diagnose with COVID-19 compared to influenza

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>All patients - Hazard Ratio (95% CI)</th>
<th>Inpatient - Hazard Ratio (95% CI)</th>
<th>Outpatient - Hazard Ratio (95% CI)</th>
<th>Site and PS matched Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary arterial endpoint</td>
<td>0.87 (0.68-1.10)</td>
<td>0.69 (0.28-1.65)</td>
<td>0.85 (0.47-1.55)</td>
<td>1.10 (0.72-1.67)</td>
</tr>
<tr>
<td>Primary venous endpoint</td>
<td>0.82 (0.61-1.10)</td>
<td>0.54 (0.20-1.45)</td>
<td>0.74 (0.39-1.38)</td>
<td>0.74 (0.21-2.67)</td>
</tr>
</tbody>
</table>

*Models adjusted for age, gender, ethnicity, oral anticoagulant use, hypertension, diabetes mellitus, chronic kidney disease, cerebrovascular disease, cancer, asthma, heart failure, venous thromboembolism (arterial endpoints), peripheral arterial disease (venous endpoints), atrial fibrillation, neurological disease*
Among persons with cancer, rate of **venous thromboembolism** higher in COVID-19 vs. influenza. Absolute risk, rate of **arterial thrombosis** not higher in COVID-19 vs. influenza.

### RESULTS

<table>
<thead>
<tr>
<th>Primary Endpoints (primary or secondary Hospital Discharge ICD-10-CM Diagnosis)</th>
<th>COVID-19 cohort (N = 7,591)</th>
<th>Influenza cohort (N = 319)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absolute risk (N, %)</td>
<td>Incidence rates (per person-year)</td>
</tr>
<tr>
<td>Arterial thrombosis, first event (combined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute MI</td>
<td>81</td>
<td>0.0470</td>
</tr>
<tr>
<td>Acute ischemic or embolic stroke</td>
<td>80</td>
<td>0.0464</td>
</tr>
<tr>
<td>Venous thromboembolism, first event (combined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute upper/lower deep venous thrombosis (DVT)</td>
<td>99</td>
<td>0.0575</td>
</tr>
<tr>
<td>Acute pulmonary embolism (PE)</td>
<td>158</td>
<td>0.0924</td>
</tr>
</tbody>
</table>
RESULTS Summary

• Different data sources, including one specific to cancer patients, to address study aim

• 3 of 4 partners observed similar findings:
  • ↑ 90-day risk of VTE in COVID-19 vs. influenza
  • No ↑ 90-day risk of ATE in COVID-19 vs. influenza
COVID-19 is associated with higher risk of venous thrombosis, but not arterial thrombosis, compared with influenza: Insights from a large US cohort

Andrew Ward, Ashish Saraju, Donghyun Lee, Kanchan Bhasin, Sanchit Gad, Rob Beetel, Stella Chang, Mac Bonafede, Fatima Rodriguez, Rajesh Dash

Published: January 12, 2022 • https://doi.org/10.1371/journal.pone.0261786
Nancy Lin, ScD
Director of Epidemiology, Real World Solutions, IQVIA
Aim 1: Describe serological testing by demographic, geographic, location, baseline clinical presentation, & key comorbidities
  • Understand current state of data interoperability across instrument, laboratory & clinical data

Aim 2: Estimate the positive percent agreement (PPA) of serological samples from people with positive SARS-CoV-2 by molecular assay
  • Identify factors associated with seropositivity.
<table>
<thead>
<tr>
<th>PARTNERS</th>
<th>Data Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>AETION</td>
<td>Mar 1, 2020-Dec 31, 2020</td>
</tr>
<tr>
<td>Optum Labs</td>
<td>Mar 1, 2020-Dec 31, 2020</td>
</tr>
<tr>
<td>University of California</td>
<td>Mar 1, 2020-Dec 31, 2020</td>
</tr>
<tr>
<td>HealthCatalyst</td>
<td>Mar 1, 2020-Dec 31, 2020</td>
</tr>
<tr>
<td>CERSI</td>
<td>Mar 1, 2020-Dec 31, 2020</td>
</tr>
<tr>
<td>Regenstrief Institute</td>
<td>Mar 1, Apr 30, 2021</td>
</tr>
</tbody>
</table>
- **Descriptive Statistics** to describe utilization of serology by baseline characteristics
- **Positive Percent Agreement** = \( \frac{\text{No. of +antibody results}}{\text{No. of +RNA results}} \times 100 \).
- Binomial Distribution to estimate **odds ratio** for seropositivity by baseline characteristics
RESULTS 1

FIGURE 1: Distribution of Serological Tests by Days After Positive PCR

FIGURE 5: Median (IQR) Days Between RNA and Serology Tests Among Those Serotested
RESULTS 1

FIGURE 4: Race/Ethnicity Data Among Those Serotested

FIGURE 6: Manufacturer—Serological Test Name Among Those Serotested
The #1 thing we learned: lack of data interoperability limits our ability to completely describe the use of products and its safety & effectiveness in the real-world.
### Adjusted Odds Ratio for Seropositivity

<table>
<thead>
<tr>
<th>PARTNER A</th>
<th>PARTNER B</th>
<th>PARTNER C</th>
<th>PARTNER D</th>
<th>PARTNER E</th>
<th>PARTNER F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-existing conditions: Obesity</td>
<td>Pre-existing conditions: Obesity</td>
<td>Pre-existing conditions: Obesity</td>
<td>Pre-existing conditions: Obesity</td>
<td>Pre-existing conditions: Obesity</td>
<td>Pre-existing conditions: Obesity</td>
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<tr>
<td>Chronic lung conditions</td>
<td>Chronic lung conditions</td>
<td>Chronic lung conditions</td>
<td>Chronic lung conditions</td>
<td>Chronic lung conditions</td>
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<tr>
<td>Cancer</td>
<td>Cancer</td>
<td>Cancer</td>
<td>Cancer</td>
<td>Cancer</td>
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<td>HIV</td>
<td>HIV</td>
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<td>HIV</td>
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<tr>
<td>Autoimmune conditions</td>
<td>Autoimmune conditions</td>
<td>Autoimmune conditions</td>
<td>Autoimmune conditions</td>
<td>Autoimmune conditions</td>
<td>Autoimmune conditions</td>
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<tr>
<td>Hypertension</td>
<td>Hypertension</td>
<td>Hypertension</td>
<td>Hypertension</td>
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<tr>
<td>Cardiovascular disease</td>
<td>Cardiovascular disease</td>
<td>Cardiovascular disease</td>
<td>Cardiovascular disease</td>
<td>Cardiovascular disease</td>
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<tr>
<td>Diabetes</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td>Diabetes</td>
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<tr>
<td>Sex: Female</td>
<td>Sex: Female</td>
<td>Sex: Female</td>
<td>Sex: Female</td>
<td>Sex: Female</td>
<td>Sex: Female</td>
</tr>
<tr>
<td>Age: &lt;45</td>
<td>Age: 45-54</td>
<td>Age: 65-74</td>
<td>Age: 75-84</td>
<td>Age: 65-74</td>
<td>Age: &lt;45</td>
</tr>
<tr>
<td>75-84</td>
<td>65-74</td>
<td>55-64</td>
<td>75-84</td>
<td>65-74</td>
<td>75-84</td>
</tr>
<tr>
<td>55-64</td>
<td>20-44</td>
<td>30-44</td>
<td>20-44</td>
<td>20-44</td>
<td>20-44</td>
</tr>
<tr>
<td>20-44</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
</tbody>
</table>
Positive Percent Agreement (95% CI) of +Serology for +Molecular Tests of SARS-CoV-2

Among Hispanics vs. Non-Hispanics

Data Not Available

Among 1+ Pre-Existing Conditions vs. No Pre-Existing Conditions

Among Those Presenting 1+ vs. No Symptoms

Data Not Available

Data Not Available
What were some of the most salient methodological or data issues you saw arise and what was an important lesson about how your group drove towards a common protocol?
evidenceaccelerator.org\covid-19-real-world-evidence-primer
RACE for communities of color

reaganudall.org/real-world-accelerator-evolve-standard-care-and-engagement-clinical-studies-race-communities-color

Join the Conversation starting January 1, 2023

This project is supported by the U.S. FDA of the U.S. HHS as part of a financial assistance award (FAIN) totaling $499,514 (100% of the project)
How COVID-19 and the Evidence Accelerator Have Shaped the Use of Real-World Data

Moderator

Susan C. Winckler, RPh, Esq, CEO, Reagan-Udall Foundation for the FDA

Panelists

Nancy Dreyer, PhD, MPH, IQVIA
Adrian Hernandez, MD, MHS, Duke University of School of Medicine
Harvey Kaufman, MD, Quest Diagnostics
Nilay Shah, PhD, Delta Airlines
Closing Thoughts

Speakers

Susan C. Winckler, RPh, Esq, CEO, Reagan-Udall Foundation for the FDA

Ellen V. Sigal, PhD, Chairperson and Founder, Friends of Cancer Research, and Chair of Board of Directors, Reagan-Udall Foundation for the FDA
Thank you!

www.evidenceaccelerator.org