COVID-19 Evidence Accelerator Collaborative

Lab Meeting #6

Thursday, May 21, 2020, 3:00-4:00 pm ET

Call Summary

Introduction to Lab Meeting 6

The theme for this week's lab meeting was "Crowdsourcing the Question." Almost seven weeks ago, the Accelerator began with a list of several initial COVID-19 questions identified by the FDA. Since then, our understanding of COVID-19, the key questions of interest in the pandemic, and the messaging around different types of data, including real-world data, have evolved. Two goals were outlined for lab meeting six: 1) spend time learning about new questions for the Accelerator and 2) begin thinking about how we can work together as a community to start solving these questions quickly.

Four presentations given at the lab meeting highlighted this evolution and posed new questions to the Accelerator:

1. Presentation on the Google Question Hub COVID-19 Health Authority Program (Robert Califf, Google/Alphabet)
2. Presentation on Alpha Blockers and the PREVENT-COVID Trial (Susan Athey, Chetan Bettegowda, Johns Hopkins)
3. Presentation on Health Catalyst (Sadiqa Mahmood & Dale Sanders, Health Catalyst)
4. Presentation on COVID-19 and Cancer—Harnessing the Power of RWE to Inform Clinical and Regulatory Considerations: RWE gets real (Harpreet Singh, FDA/OCE)

Lab Meeting Presentations

Presentation on the Google Question Hub COVID-19 Health Authority Program

- People all over the world are using Google to ask questions about COVID-19
  - Although many of these questions have already been answered by an authoritative source, many have not
- Through the Google Question Hub COVID-19 Health Authority Program
  - Google is able to identify important COVID-19 user queries unaddressed by existing web content
  - Google is able to share these insights with accredited medical authorities so they can prioritize COVID-19 web content creation on their owned and operated websites in a scalable way
- Ask of Health Authority Partners:
  - Confirm you have a Google Account
  - Identify a point of contact for the Google team to liaise with
  - Review open queries in the simple online user interface and identify which topics to answer

- o   Publish targeted answers on your own properties as often as possible each week

Presentation on Alpha Blockers and the PREVENT-COVID Trial

- Alpha blockers prevent death from cytokine storm in animal models
  - o   Overactive immune responses account for much of the tissue damage and mortality in COVID-19 (JCI 2020)
  - o   Catecholamines (e.g. adrenaline) amplify inflammation by increasing cytokine production, leading to "cytokine storm" (J of Neuroimmunol. 1996)
  - o   Alpha blockers (prazosin, doxazosin, tamsulosin) are widely used, inexpensive, and well-tolerated
  - o   Inhibiting catecholamine effects with alpha blockers prevented cytokine storm in mice (Nature 2018)
  - o   Alpha blockers lower mortality from 80% to 13% (Nature 2018)
- Retrospective studies allow for quick generation of evidence when examining drugs which are already commonly prescribed.
- Retrospective study design:
  - o   Patient may be prescribed alpha blockers following a diagnosis of, e.g. BPH
  - o   Patient experiences respiratory distress following, e.g. an infection
  - o   Patient admitted to hospital with ARDS diagnosis
  - o   Outcomes (ventilation, discharge, or death)
- This group used claims data to conduct a retrospective study comparing the outcomes of those already taking alpha blockers for another condition who were admitted to the hospital due to a non-related respiratory infection versus those not taking alpha blockers who were admitted to the hospital due to a respiratory infection **(referred to as Study 1).**
- Study 1 demonstrated that alpha blockers prevent death in patients with acute respiratory disease.
  - o   Adjusting for age and a variety of comorbidities, patients on alpha blockers do substantially better with a lower probability of progression to ventilation or death.
- This group also partnered with the VA system to conduct a retrospective study of alpha blockers in patients with COVID-19 to see if the observations from Study 1 held in suspected COVID-19 patients **(referred to as Study 2).**
- Study 2 revealed that alpha blockers prevent death in patients suspected with COVID-19.
- This group is now organizing a prospective study of alpha blockers in COVID-19 patients: The PREVENT-COVID Trial
  - o   Study design: Randomized 1:1, standard of care: prazosin
  - o   Primary objective: Evaluate the efficacy of treatment with prazosin (given for a total of 28 days) to prevent severe COVID-19 in treated versus untreated subjects
  - o   Primary endpoint: Composite disease severity scale including increased O2 requirement, mechanical ventilation, ECMO, admission to ICU and death
  - o   Key eligibility criteria: Age > 45, requiring 4L or less of supplemental O2
  - o   Key exclusion criteria: Age > 85, history of orthostatic hypotension, significant cardiac history

- Ask for the Accelerator:
  - Do any groups have data that could be useful in answering the following questions?
    - Do individuals with COVID-19 who are on alpha blockers for pre-existing conditions have diminished disease severity?
    - Do individuals taking alpha blockers for pre-existing conditions have decreased risk of requiring hospitalization for COVID-19?

Presentation on Health Catalyst

- Health Catalyst is an Analytics and Data Technology + Professional Services organization
- They have a Data Operating System (DOS) at each client site, which should be thought of as a next generation Enterprise Data Warehouse.
- DOS instances feeds Touchstone, a national data repository.
- Health catalyst used Touchstone to create a patient registry for COVID-19. They began with three patient types of interest:
  - High-risk community members with influenza-like illness (~ 700,000 patients)
  - Suspected COVID-19, not tested (~ 67,000 patients)
  - COVID-19 confirmed (~ 32,000 patients)
- Health Catalyst use case generation
  - Hypothesis generation
    - Involvement of critical care, infectious disease, epidemiologists, and emergency physicians who have seen critical mass of COVID-19 patient volume is key
    - Other than age and underlying conditions, symptom expression is highly variable, why?
    - AI pattern recognition and clustering
- Creating the patient's digital twin
  - Developing three fundamental AI pattern recognitions in healthcare
    - Patients like this (pattern)
    - Who were treated like this (pattern)
    - Had these outcomes and costs (pattern)
  - This is less about predictions and more about patterns
- Currently Health Catalyst is working on six areas of investigation:
  - Clustering of COVID-19 patient types and subtypes
    - Phenotypic and genotypic presentation of disease
  - Preventative effect of BCG Intravascular Immunotherapy among early stage bladder cancer patients
  - Preventative effect of ACEi, anticoagulants, and Famotidine
  - Hospital capacity planning based on prevalence, incidence, and severity predictive models
  - Hospitalized patients receiving HCQ/AZ, IL-6 inhibitors, Remdesivir
  - Understanding Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19
- Ask of the Accelerator:

- - We have the data rights and data content—lets leverage the Touchstone repository as a national asset
  - Collaborate on existing and new hypotheses
  - Define the workgroups and processes for collaboration
  - Assess strengths and weaknesses of existing RWD in Touchstone
    - Address the gaps

Presentation on COVID-19 and Cancer—Harnessing the Power of RWE to Inform Clinical and Regulatory Considerations: RWE gets real

- The Oncology Center of Excellence (OCE) has several COVID-19 and cancer efforts:
  - Conducting OCE Listening Sessions with advocacy groups and investigators
  - Providing regulatory support for review of COVID-19 related submissions
  - Engaging multiple stakeholders to discuss clinical trial conduct
  - Participating in meetingsto discuss current guidance for clinical trial conduct during the COVID-19 pandemic (6/22-24: AACR COVID-19 and Cancer: Guidance for Clinical Trial Conduct and Considerations for RWE)
- Crowdsourcing for COVID-19:
  - Initially asked OCE staff which COVID-19 questions they would ask if they had infinite access to RWD sources.
  - This effort produced a significant number of questions in buckets such as efficacy and safety of immunotherapy in COVID-19 and natural history of cancer patients and pediatric cancer patients with COVID-19
- Implications for Oncology clinical trials:
  - Harmonizing eCRF's across industry-sponsored trials
    - What COVID-19 related info should be added to common data elements?
  - Documenting COVID-related protocol deviations
    - Dataset for COVID-related deviations- explore impact on trial outcomes
  - Eligibility criteria
    - Enrolling patients with COVID-19 history, or testing upon enrollment
  - Statistical considerations
    - Stratification factors, separate cohorts, increased censoring, resizing
  - Safety monitoring
    - Additional monitoring based on COVID-19 history and therapy
    -

The following are 4 critical research topics and associated questions, which OCE proposes as demonstration projects for use of RWE via the FDA Evidence Accelerator.

- Multiple myeloma: IMiDs, Thrombosis, and COVID-19
  - Lenalidomide/Dexamethasone: common therapy for MM, given with low dose aspirin due to thrombosis risk, however if additional risk factors, more aggressive treatment is given (low weight molecular heparin)
    - Evaluate rates of thrombosis in patients treated with IMiD regimens
    - Evaluate rates of thrombosis in patients with Smoldering MM (+/- COVID-19)

- o Should we change our current treatment for patients with MM who are treated with these regimens (i.e. more aggressive risk prevention)?
- Immunotherapy in Lung Cancer
  - o Immunotherapy is a cornerstone of lung cancer treatment.
  - o Symptoms of COVID-19 and toxicities of immunotherapy are overlapping, including pneumonitis and interstitial lung diseae.
    - ▪ Characterize outcomes of patients with lung cancer and COVID-19
    - ▪ Evaluate effectiveness of immunotherapy in patients with lung cancer and COVID-19
  - o Do patients with mild or asymptomatic COVID-19 infections, treated with immunotherapy, require additional safety monitoring to evaluate lung function?
- Impact of Reduced Cancer Screening
  - o Rates of preventative cancer screenings have massively dropped in the US, and presumably worldwide.
  - o Prolonged disruption in cancer screening may lead to later stage disease at the time of diagnosis
    - ▪ Characterize impact of delayed screening (mammography, colonoscopy)
    - ▪ Evaluate if increase in time from onset of symptoms to seeking medical attention based on patient reported histories
- Impact of Reduced or Altered Cancer Treatment
  - o Are patients and physicians changing approach to treatment?
  - o Are patients foregoing adjuvant treatments that require high level of sustained healthcare engagement (adjuvant systemic chemotherapy, adjuvant radiation therapy)?
    - ▪ Characterize whether rates of radical prostatectomy have increased compared with definitive radiation therapy in prostate cancer
    - ▪ Evaluate rates of adjuvant chemotherapy administration
    - ▪ Evaluate the time from diagnosis to resection/radiation in Melanoma, Breast Cancer, Prostate Cancer
- Future directions
  - o Prioritizing OCE questions
  - o Developing milestones for data capture and analysis
  - o Mechanism for additional questions/topics as COVID-19 evolves

Opportunities and Next Steps for the Evidence Accelerator

- Today's lab meeting presentations underscore the enormous opportunity and complexity we face as we move forward
- Thus far, we have taken a phased approach to addressing COVID-19 using RWD:
    1. initiation of the Accelerator and development of approaches to answer a common set of questions.
    2. Develop working groups and expand partnerships across government organizations as well as the broader RWE community.
    3. Expand approach into new areas such as diagnostics and vaccines and work to continue expanding our partnerships.

- Next steps stemming from each presentation today include:
    - Google Question Hub:
        - FDA internal prioritization process developed to identify those questions which need to be answered by the FDA, those questions which need to be answered by the Accelerator, and those questions which need to be passed to other groups or back to Google
    - Vogelstein Lab and Health Catalyst
        - Identify teams
        - Partners self-identify
        - Develop process in the future
    - OCE
        - Develop a new Cancer & COVID-19 workstream
        - Prioritize questions for the Accelerator to answer