2.55: Hydroxychloroquine for COVID-19, ASCO, QOTW, Private Equity in Medicine with Dr. Jane Zhu

Type	Plenary Session
Category	

We Discuss:

- Hydroxychloroquine for COVID-19 [1:45]
- ASCO [7:42]
- JAVELIN [10:58]
- ECOG-ACRIN [17:56]
- ENDURANCE [21:50]
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- Question from a Medical Student with Audrey Tran [53:47]
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Plenary Session 2.55 Show Notes

Overview

Hydroxychloroquine for COVID-19 [1:45]

- **A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19**

> *"After high-risk or moderate-risk exposure to Covid-19, hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection when used as postexposure prophylaxis within 4 days after exposure." - Boulware et al.*

- **Endpoint**
  - The primary outcome for this study was confirmed or probable COVID-19
    - Confirmed COVID-19 was emblematic of a laboratory-confirmed diagnosis
    - Probable COVID-19 was defined as "symptoms compatible with COVID-19"
  - This is a bias susceptible endpoint because hydroxychloroquine has more side effects than a sugar pill
    - Of the 344 participants in the hydroxychloroquine group 47% correctly identified that they received hydroxychloroquine and 10% believed that they received placebo.
    - Of the 353 participants in the control group 35.7% correctly identified that they received placebo and 16.7% believed that they received hydroxychloroquine
  - The "will to believe" may affect the self reporting of the symptoms
  - Solutions
    - Upon symptomatic progression → test for COVID
    - Blindly ascertain the endpoint in some subset of the people in each arm
    - Active placebo

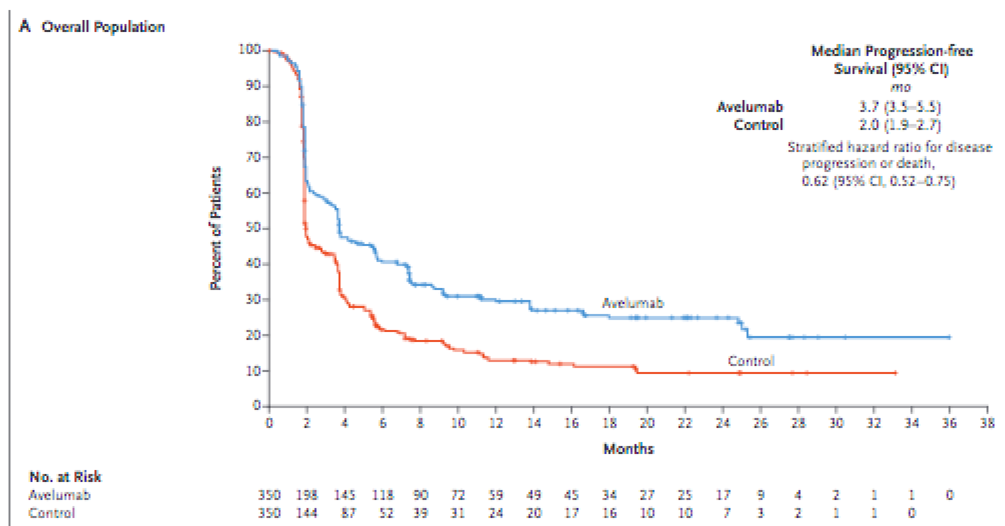
ASCO [7:42]

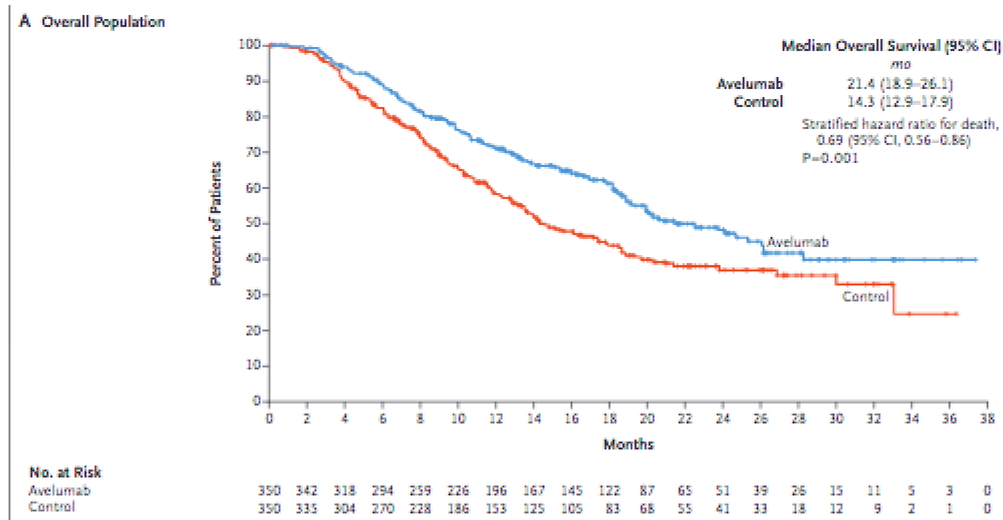
> [In Reference to Influencer Ranking at the ASCO Meeting] "To influence something, you have to have an original thought, you have to take your original thought and apply it to people who don't share that thought. And then you have to cajole and move and sway the opinion of many people.

> And measuring this, it turns out just can't be done in an automated fashion" - Dr. Prasad

JAVELIN [10:58]

- **Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line (1L) chemotherapy in advanced urothelial carcinoma (UC)**
  - 700 patients were randomly assigned to maintenance avelumab + best supportive care (BSC) vs. BSC alone
    - If assigned to the control arm–the only relevant question that should be asked is:
      - Do you have a better overall survival and better health related quality of life over the duration of your cancer journey?
- **Undertreatment**
  - Eligible patients were patients with progression after 4-6 cycles of gemcitabine with either cisplatin or carboplatin
    - Potential bias is that enrolling on JAVELIN may lead to undertreatment for people who were on 4 cycles of GemCis
- **PFS and Post Protocol Care**





Powles et al.

- The precipitous fall in the control arm for PFS (median PFS = 2 months) and the median OS of 14.3 months suggests these patients must receive a PD-1 antibody (SoC)
    - However, the rate of subsequent progression PD-1 therapy is lower than anticipated
        - Only 43% of people who progress on best supportive care get a subsequent PD-1 antibody
        - 34% get a different drug (not acceptable SoC)
        - 30% discontinue with no subsequent therapy
            - This is a poor rate of appropriate post protocol care

> "And that [lack of SoC] speaks volumes–that basically poison your entire OS, you're not giving your controller an appropriate standard of care when they progress. Therefore your overall survival is utterly unreliable, and it can't be used to draw conclusions. You're not actually answering the question that you ought to answer for the US audience" - Dr. Prasad

- **Second-line therapy**
    - After first line chemotherapy, only 25 to 55% of patients received second line treatment

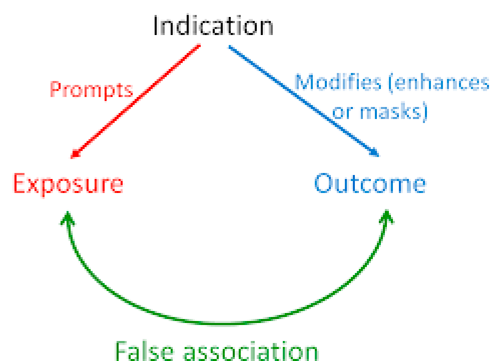
- It is unfair for the researchers to compare rates of receipt of second line therapy in average community practices
    - The researchers are documenting that at least 50% of people are progressing by two months and 50% of people are living 14.3 months
        - There's a huge space to be giving appropriate second line therapy

ECOG-ACRIN [17:56]

- A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer

> *"Stage IV patients with IPT were registered, treated with optimal systemic therapy (OST) based on patient and tumor characteristics; those who did not progress during 4-8 months of OST were randomized to locoregional treatment (LRT) for the IPT, or no LRT." - Khan et al.*

- **Results**
    - There was no significant difference in OS (p = 0.63, HR = 1.09, 90% CI: 0.80, 1.49)
    - Health related quality of life was significantly worse if patients received LRT
- **Confounding by Indication**



Source

- When you look in a retrospective data set, there is going to be a fundamental confounding variable that you are going to have a difficult time of adjusting for

            - This is that surgeons and radiation therapists are not deploying this intervention in two women equally
                - They are likely preferentially doing LRT in people who are more healthy, fit, and have good performance status

ENDURANCE [21:50]

- Carfilzomib, lenalidomide, and dexamethasone (KRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) for initial therapy of newly diagnosed multiple myeloma (NDMM)
    - This trial randomized patients with NDMM to receive VRd or KRd in a 1:1 manner
- **Results**
    - The KRd regimen did not improve progression-free survival compared with the VRd regimen
        - KRd also added toxicitiy

> "I think what this trial shows rather conclusively is that there is no PFS benefit ergo it is unlikely that care the upfront a more costly regimen is able to translate into the things we really care about" - Dr. Prasad

- **High Risk Cytogenetics**
    - There are still some proponents who say that carfilzomib has a role for high risk myeloma
        - These claims need to be proven before starting to treat people with costly novel drugs

KEYNOTE-177 [28:40]

- Pembrolizumab versus chemotherapy for microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer
    - Patients were randomly assigned to receive pembrolizumab vs. chemotherapy
- **Current SoC for MSI-H CRC**

- FOLFOX → FOLFIRI +/- Pembrolizumab → Pembrolizumab

- **What this study should have done**
  - Mandate crossover in the control arm
    - Compare to pembrolizumab and then chemotherapy while following HRQoL and OS for the entire time horizon
      - Look to see if the upfront use of pembrolizumab conferred a survival benefit
- **PFS endpoint**

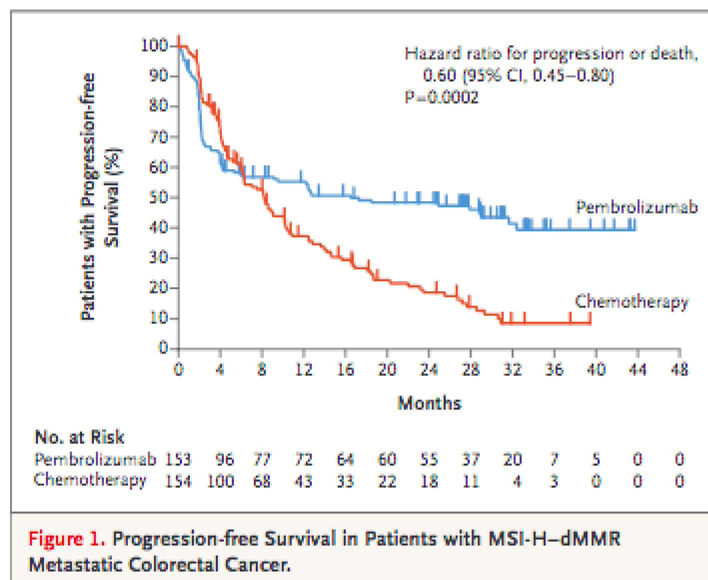


Figure 1. Progression-free Survival in Patients with MSI-H–dMMR Metastatic Colorectal Cancer.

André et al.

  - The initial crossing of the PFS curves suggests there are some people who would have faired better with FOLFOX
    - Cox proportional hazard modeling may be technically inappropriate in this setting where there are two periods of risk here:
      1. Initial period
      2. Later period
- **Takeaway**
  - Since pembrolizumab is already improved in latter lines of therapy, the focus should be on HRQoL over an extensive period of time

- **Commonalities**
  - Many of these studies are not debuting a novel agent–they are asking if routine upfront administration of drugs already approved for latter lines of therapy confer benefit in earlier lines
    - This is a question that matters a great deal to drug companies
      - Market share is a funnel and it dwindles the further along a drug is positioned in lines of therapy

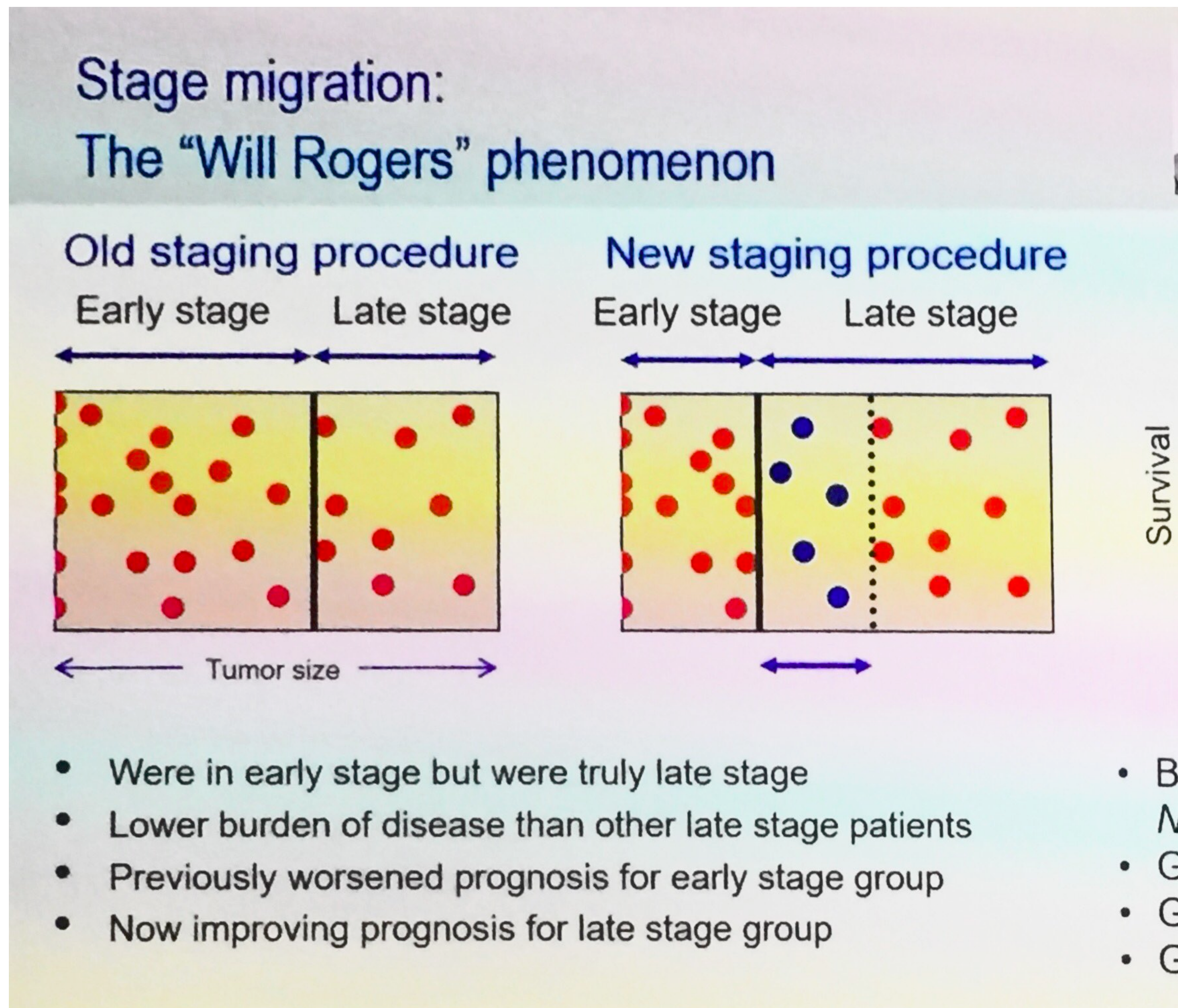
> "When you have a drug that has already proven to benefit in the latter line of therapy, and you want to move it forward, crossover is mandatory to ask the right question" - Dr. Prasad

ADAURA [38:01]

- Osimertinib as adjuvant therapy in patients (pts) with stage IB–IIIA EGFR mutation positive (EGFRm) NSCLC after complete tumor resection
  - This trial randomized patients with completely resected EGFR mutation–positive NSCLC to receive osimertinib vs. placebo for 3 years
- **Patient Enrollment**
  - This study allows people to enroll without receiving adjuvant chemotherapy
    - This stacks the deck in favor of the novel adjuvant drug and is a disservice to the adjuvant treatment delivered in the real world
- **CT Scans for the Brain**
  - "Brain imaging was performed" is too vague
    - CTs can not be used to stage–an MRI of the brain is needed to stage
- **Adjuvant**
  - By giving a adjuvant upfront, are you improving the curative fraction?
    - What do you have to do to perform this trial correctly?
      1. Adjuvant therapy must be given according to real clinical care
      2. Proper US staging

3. When people in the control arm did relapse–did they receive osimertinib?
4. Did they improve OS

- **QALY**



Source

Literatute Cited:

- CARMINA
- Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma
- CALGB
- FIRE-3

- FLAURA

Question from a Medical Student with Audrey Tran [53:47]

The USMLE Step 1 has recently adopted a pass/fail grading system. What is the significance of this shift?

- **Why do people hate USMLE Step 1?**
    - A more recent critique is that people hate the idea that anyone should ever get any evaluation
        - Dr. Prasad is not super sympathetic to this viewpoint
    - Another critique is that the content that makes up Step 1 is heavily irrelevant for clinical practice
        - Dr. Prasad does not agree with triviality and minutia the test focuses on
- **Pass/Fail**
    - Making Step 1 P/F is a step in the right direction because students can focus on passing and clawback the time to learn how to actually be a doctor
        - There is currently dueling goals in the medical curriculum

Vinay Prasad MD MPH
@VPrasadMDMPH

Replying to @VPrasadMDMPH

We face 2 tasks in medical education
1. make trainees better
2. ranking trainees

Folks lamenting loss of step 1 score are overly focused on 2.

I think that the need for #2 has been largely driven by the fact competitive specialties have few spots

11:53 AM · Jun 14, 2020 · Twitter Web App

3 Retweets **30** Likes

Vinay Prasad MD MPH @VPrasadMDMPH · Jun 14, 2020
Replying to @VPrasadMDMPH
I believe however if pay scales shifted, competitiveness would shift overnight.

If general medicine, peds and family were $$ more comparable to other fields, interest in these specialties (with + spots btw) would grow

And the need to #2 rank trainees would mostly evaporate

3 6 44

Vinay Prasad MD MPH @VPrasadMDMPH · Jun 14, 2020
Then we could focus more on #1, which I think we do a suboptimal job at.

Students are terrific largely in-spite of a tangential education system, not because of it.

cough though often limited education in critical appraisal

1 1 30

Vinay Prasad MD MPH @VPrasadMDMPH · Jun 14, 2020
Of course, some will argue that we still need to rank to decide who gets to go to Brigham IM vs. UVA IM...

On that topic, you may also not like my opinion: the educational diff. btw those residencies is trivial. And we do a disservice to students when we...

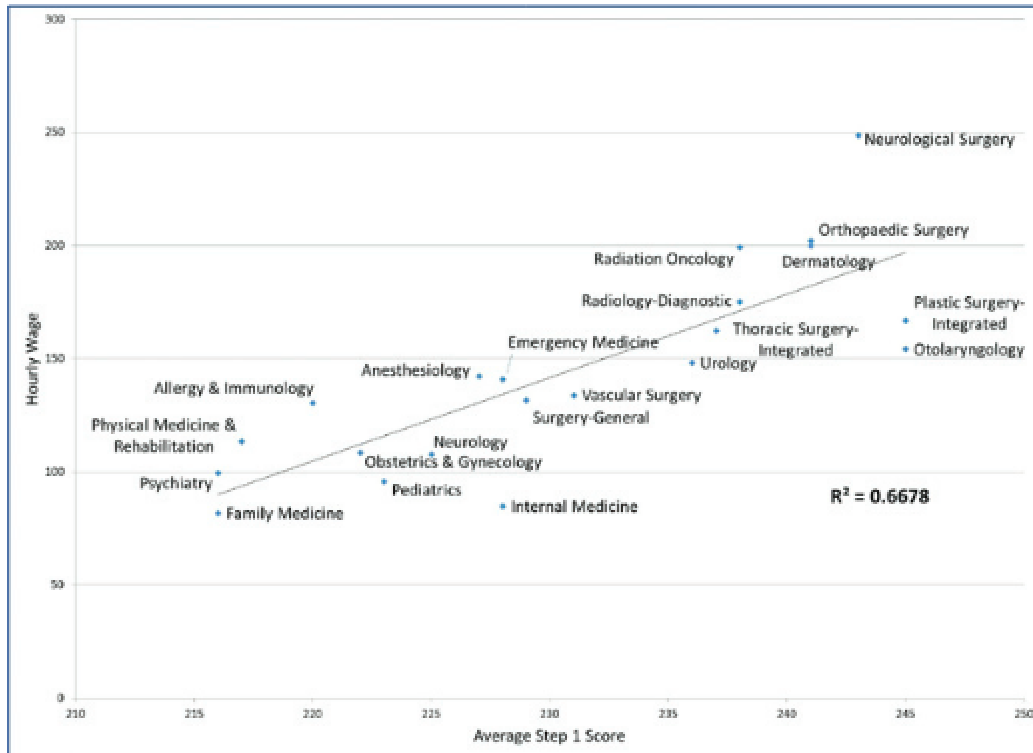
1 2 34

Vinay Prasad MD MPH @VPrasadMDMPH · Jun 14, 2020
perpetuate the great lie that there is some magically hierarchy to clinical residency programs.

Truth is, if you read every day, and care about your patients, and push yourself, you can be a great doctor from *nearly all* programs

- **Specialty Pay**

Figure 2. Relationship between USMLE Step 1 scores of matched residents and attending hourly wage



Source

  - Why did this association occur?
    1. Ranking students
    2. RVU scoring system
       - Once specialties saw that their RVUs scored highly, there was a tremendous lobbying incentive into preserving that hierarchy

- **Reform**
  1. Reform pay scale based on societal need and value
     - The fields we need a lot more of are the ones we have a lot more spots in

> "We don't need to spend all this energy creating tests to figure out who's the best medical student, because we need a ton of

> family practice doctors that we cannot even educate in this country." - Dr. Prasad

2. Evaluating students
    - Shadowing students based on clinical performance

Conversation with Dr. Jane Zhu [1:32:12]

- **Introduction**
    - Dr. Zhu is a primary care physician and Assistant Professor of Medicine in the Division of General Internal Medicine at OHSU
        - She earned her undergraduate degree at Duke
            - She earned her M.D. and MPP at Harvard
    - She has been on the Plenary Session before (Episode 1.31)
- **Private Equity**
    - Private Equity Acquisitions of Physician Medical Groups Across Specialties, 2013-2016
        - There's clearly a financial benefit to buying physician medical group practices
            - They offer medium sized returns (~20%/yr) for 3-7 years
        - Concerns:
            1. Selling to the highest bidder (may have poor intentions or incentives)
            2. End-of-career physicians that are partners may be selling the group to consolidate profits and undermining the future partners (i.e., associates) that have no say
- **Data Availability**
    - Data that's available right now is through financial databases → which are privately owned
        - Even the data that is produced is limited because it does not include *private* transactions
    - The purchasing of these physician-owned groups is relatively new

        - In this study, 355 physician practice acquisitions were recorded between 2013-2016, but this number has skyrocketed since then
    - Irving Levin Associates website
        - Aquisitions were then linked to the SK&A data set
- **Results**

> *"The most commonly represented medical groups included anesthesiology (19.4%), multispecialty (19.4%), emergency medicine (12.1%), family practice (11.0%), and dermatology (9.9%)" - Zhu et al.*

    - Why are anesthesiology and emergency medicine practices being acquired the most?
        - Out-of-network billing
            - These bills are more likely to occur with anesthesiologists, pathologists, radiologists, and emergency medicine doctors whose model is to contract with hospitals
                - The Price Ain't Right? Hospital Prices and Health Spending on the Privately Insured
- **When private equity has reaped the short term profit–to whom do they sell these position groups?**
    - Often they sell to other private-equity groups
- **What will the impact be on patient care?**
    - The largest concern is what the impact will be on patients and the care they receive
        - Will these groups still be held to necessary care standards?
            - Or will there be an underlying theme of profitability driving a lot of health care decisions?

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Host: Vinay Prasad, MD MPH from University of California, San Francisco.

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