Fall 2020 SWOG ADOLESCENT & YOUNG ADULT COMMITTEE Meeting – Virtual

SUMMARY

Date: Wednesday, September 23, 2020
Time: 1:00 – 2:00 pm CT

Agenda:

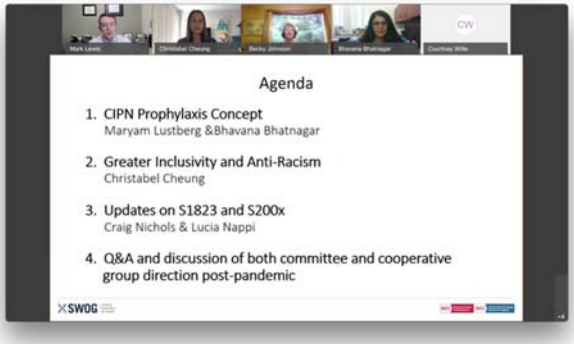
1. CIPN Prophylaxis Concept – Maryam Lustberg & Bhavana Bhatnagar
2. Greater Inclusivity and Anti-Racism – Christabel Cheung
3. Updates on S1823 and S200x – Craig Nichols & Lucia Nappi
4. Q&A and discussion of both committee and cooperative group direction post-pandemic

0:00:00
Mark Lewis welcomed attendees to the meeting.

0:00:22
Lewis noted all were on mute by default to reduce background noise.

0:00:34
Lewis reviewed the meeting agenda.

- Problem of chemo-induced peripheral neuropathy (CIPN)
    - Particularly a problem in AYA cancers
    - Concept group heard about at the fall 2019 group meeting in Chicago
    - An ounce of prevention worth a pound of cure
- Said second item would be presented by patient advocate Christabel Cheung
    - Greater inclusivity and antiracism
    - Among tumult of 2020, this issue has come to the forefront
    - AYA oncology is area of great disparity
- Also getting updates on germ cell tumor studies from executive officer Craig Nichols and Canadian collaborator Lucia Nappi
- Then co-chair Becky Johnson would review work to cross-connect with other NCTN members using digital tools
- Lewis said Q&A would follow
- Also ad hoc presentation on NCI trial that's expanding to AYA space



CIPN Prophylaxis Concept

0:02:05

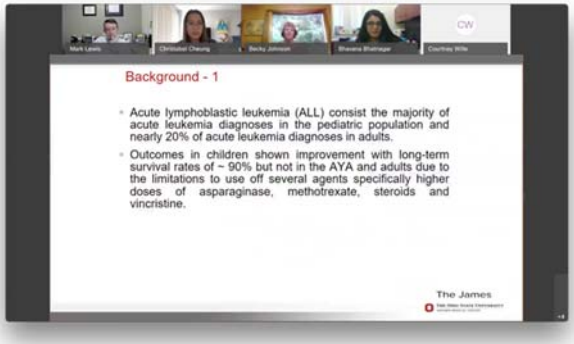
Bhavana Bhatnagar said Maryam Lustberg and she would review updates on their work to prevent vincristine-induced neuropathy in AYA ALL patients.

- Noted drug is backbone of almost all ALL regimens

0:02:37

Background:

- ALL much more common in pediatric patients
- Survival rates in these patients have improved remarkably
  - Pediatric patients' 5-year OS rate exceeds 90%
- On older end of spectrum, outcomes haven't quite matched pediatric outcomes
  - Reasons include worse disease biology and prior comorbidities that limit dosage



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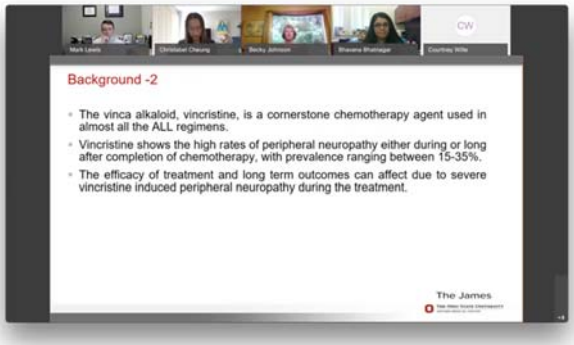
- Vincristine is part of basically every ALL regimen
    - Tons of regimens; all include it
- Particularly the AYA protocols provide many doses of it
    - In CALGB 10403 trial, patients can get up to 30 doses
- It's known to produce high rates of sensory peripheral neuropathy
- Can occur immediately or at any point during therapy
- Can linger as lifelong effect
- At its least severe, it's annoying
- At its most severe it can lead to dosage reduction or even discontinuation



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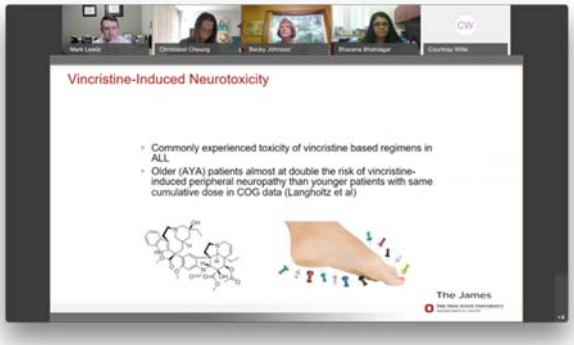
Neurotoxicity

- Older you get, more likely you are to get CIPN from vincristine
- No tested ways to prevent it
- Once present, can try neuropathic drugs
    - Not always effective



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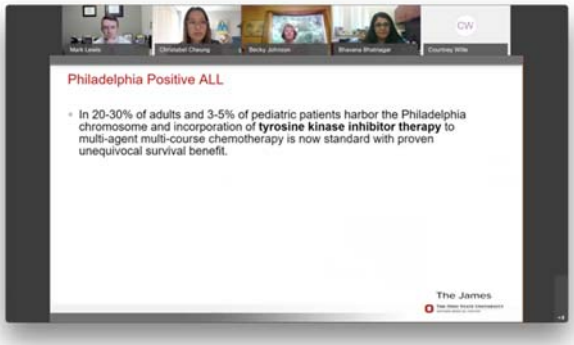
- Most patients with ALL do not have Philadelphia chromosome (translocation 922)
- About 20%–30% of adults, including AYA, harbor this chromosome
- These patients are given tyrosine kinase inhibitor (TKI) therapy as part of treatment
    - Many studies have shown dramatic benefit with TKI therapy
- Considered standard of care for Ph+ ALL
- Issue with TKI therapy will become important later in talk, as potentially one way to target CIPN from vincristine



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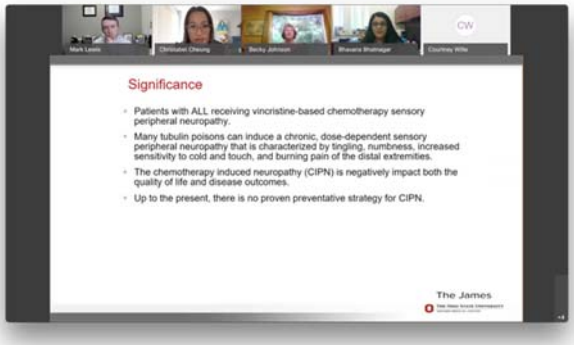
Significance

- For CIPN from vincristine, there is no – (Bhatnagar lost contact in the virtual meeting)



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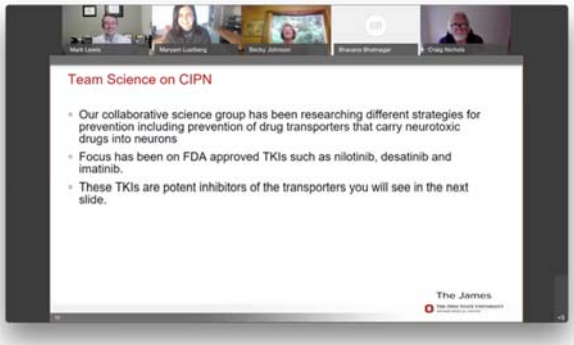
Maryam Lustberg took over for Bhatnagar.

Team science on CIPN

- Premise is work of collaborative science group in College of Pharmacy at the Ohio State University
    - All preclinical work
- Looking at FDA-approved TKIs such as nilotinib, dasatinib, and imatinib that are used in Ph+ ALL
    - They also are potent inhibitors of drug transporters, as in next slide



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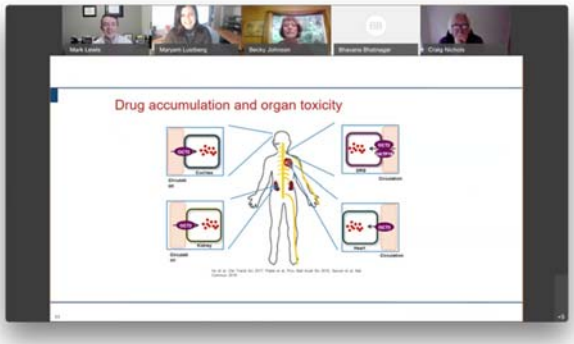
Drug accumulation and organ toxicity

- These drug transporters and pathways are how neurotoxic chemo agents get into various tissues



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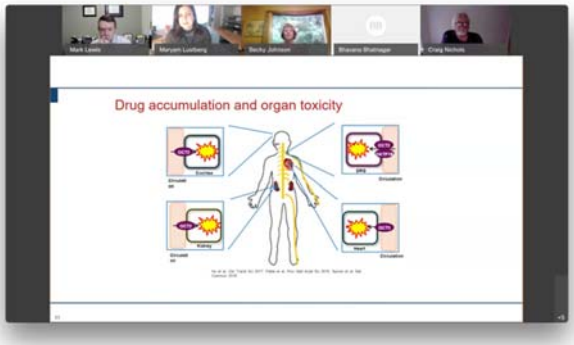
- That's part of damage that occurs, leading to …
    - E.g., in dorsal root ganglion
- … neuropathy
- In cochlear or inner ear, patients can experience ototoxicity



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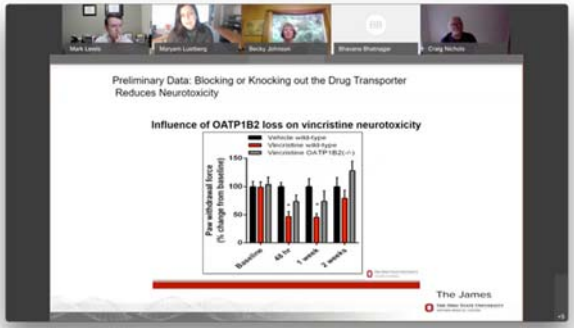
- Part of collaborative team has shown that by blocking these transporters and inhibiting uptake of these drugs in nervous tissue, they can prevent neurotoxicity in mice



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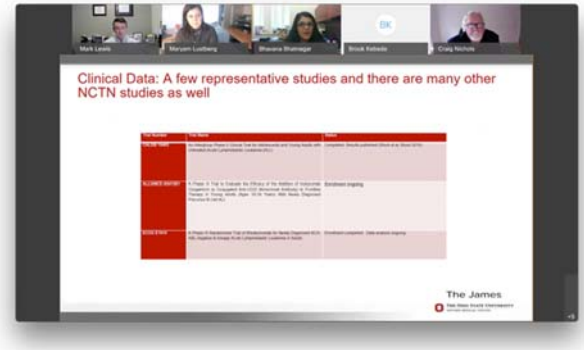
Bhatnagar returned to continue presentation.

- Said at last SWOG meeting they had discussed possibility of designing prospective studies using TKIs to prevent CIPN
- Felt they first needed strong retrospective data to support those
- Been in discussion with John Perentesis at U Cincinnati
    - They will collaborate on these retrospective studies

0:09:04
Clinical data

- Bhatnagar showed data from cooperative group studies for AYA ALL population
- All have vincristine-containing chemo regimens
- Potentially are studies for data mining to determine number of patients who developed CIPN from vincristine



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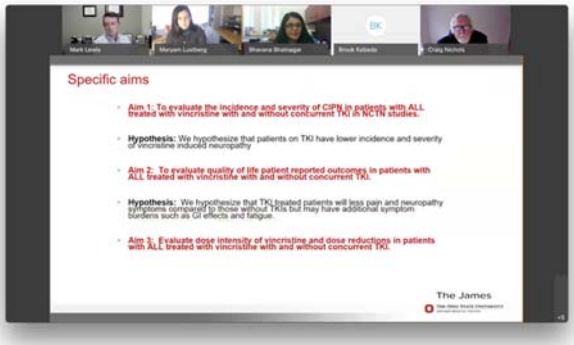
Proposal aims

- Evaluate incidence and severity of CIPN in ALL patients treated with vincristine +/- TKI
    - Both Ph+ and Ph- disease
    - They hypothesize that patients on TKI have lower incidence and severity
- Evaluate QoL with PROs to evaluate dose intensity of vincristine and whether CIPN severity warranted dose reduction or discontinuation of treatment in patients who did or did not get TKI



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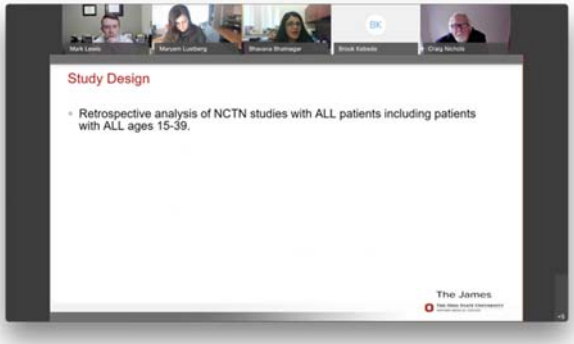
Design

- Proposing retrospective analysis of NCTN studies with ALL, including all AYA patients to age 39



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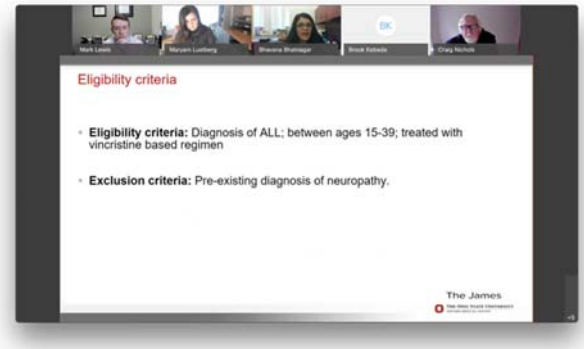
Eligibility

- Broad criteria
- Only exclusions are patients with pre-existing diagnosis of neuropathy
    - Because it could confound severity of neuropathy



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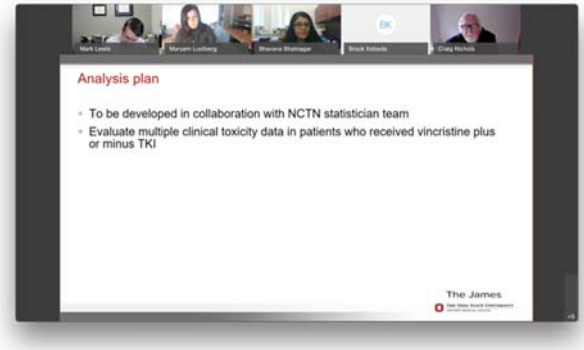
Analysis

- Working with NCTN statistician to develop robust statistical plan
- Will evaluate clinical toxicity data in patients who get vincristine with or without a TKI



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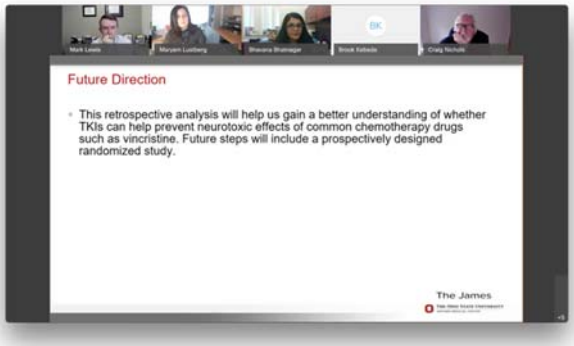
Future direction

- Once they collect information, may lay foundation for proposing prospective study that uses TKI in patients without the Philadelphia chromosome as part of treatment to prevent CIPN
- Would design prospective randomized study to address this issue with patients randomized to receive TKI or not



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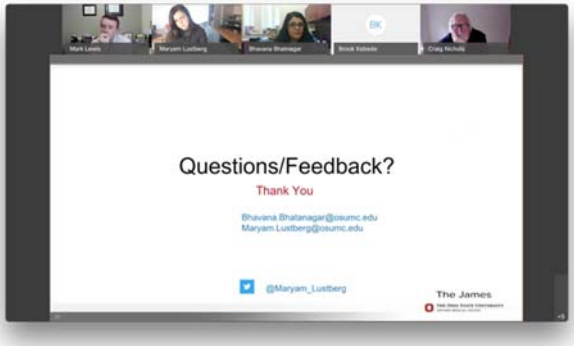
Questions?

Lewis relayed question asking whether there are lower rates of neuropathy with hyperCVAD plus TKI vs hyperCVAD alone.

- Bhatnagar said in literature there has not been a statistically significant difference between two
    - She also wonders whether it's an older age group of patients that receive hyperCVAD
    - Wondered whether rates would differ for younger population

Craig Nichols asked what effect size they would be looking for.

- Seemed to him that to justify use of TKI the effect would have to have pretty marked reduction in CIPN
- Lustberg replied that in animals—and humans may be entirely different ecosystem—pretty profound mitigator
    - With very low intermittent dosing
    - Thought is that even for Ph- patients, dose or two before chemo and after may be sufficient
- Said retrospective analyses should give them info on effect sizes
- Will look at time to neuropathy development



    - And amount of dose reduction
- Lustberg thought that if animal models are true, and mechanism is primary driver of development of neuropathy, they expect pretty sizable effect

Nichols also asked how many people get clinically disabling vincristine neuropathy with ALL regimens.

- Bhatnagar said majority of patients do
- 85% – 90% have some type of neuropathic pain during treatment
- Rare to see patient with no complaints
- About 50% of patients she sees have lingering neuropathy once they get into their maintenance and beyond
- Nichols asked whether this impaired function
    - Noted most of his patients who finished MOP therapy in past had durable pins and needles, particularly in feet, but it didn't stop them from working, buttoning buttons, etc.
- Lustberg said collectively patients with CIPN can have impaired function with balance
    - Body of literature suggesting increased falls
    - Range of effects
    - Lot of work suggesting who is at risk
- Can impact function and QoL
- Can also interfere with dose intensity these patients are getting for potentially curative treatment

0:17:52
Lustberg responded to Chat question asking why not do phase 2 study and look at this prospectively.

- She said they're also considering that
- They have NCI R01 looking at prospective phase 2 in breast cancer patients getting paclitaxel using this mechanism
- The retrospective look described here wasn't to be in place of prospective study but complement to it to mine large body of work
- Acknowledged some PROs will be limited

- Prospective study absolutely needed

Becky Johnson asked whether their long-term goal if this proves to be effective was to treat all ALL patients with small doses of TKI to prevent CIPN altogether vs. treating people with CIPN to prevent from progressing.

- Lustberg said that if their hypothesis is proved correct, that would be one approach
- Said because mechanism is related to transporter mechanism of these neurotoxic drugs actually entering the tissue, this would not work for treatment of established neuropathy
    - Other exciting work in that area
- One way to look at this for future of personalized survivorship care would be to target high-risk population, genetically or clinically, and direct them to this type of preventative approach

Lewis noted that Dr. Blanke has described SWOG as an information platform.

- Said it strikes him that as this committee is histology-agnostic, would be good to connect with Leukemia Committee on Friday

Lewis noted time was up, but he would keep track of questions, session was being recorded, and attendees have contact information for two presenters.

Greater Inclusivity and Anti-Racism
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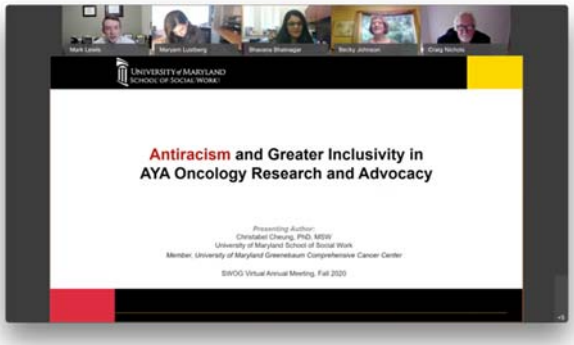
Christabel Cheung presented.

- Wanted to present line of research prompted by current socio-political context
- In particular, she sought out Mark Lewis for input in the process



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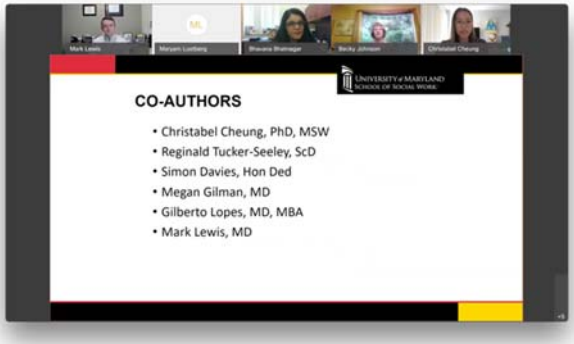
Co-authors listed on slide.

- Christabel Cheung
- Reginald Tucker-Seeley
    - USC and one of Cheung's mentors
    - Research funded by NCI
- Simon Davies
    - Executive director Teen Cancer America
- Megan Gilman
    - AYA psychiatrist at MSKCC
- Gilberto Lopes
    - U Miami and ASCO
- Mark Lewis



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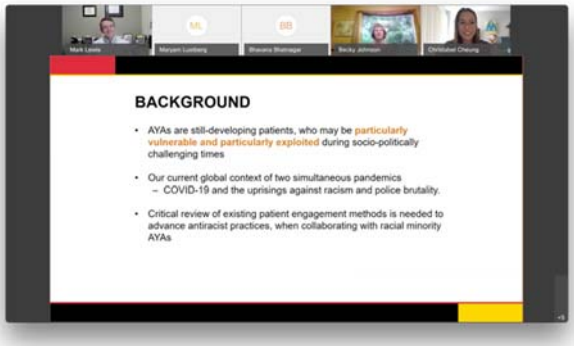
Background

- Developing review paper for special issue of journal on patient engagement
- Background to project is COVID-19 context
- In AYA oncology, we work with young adults still developing psychosocially
- For racial minorities, racial identity is developing concurrently with cancer treatment and with organizations wanting them to participate in research
- Said she is talking about patient engagement in research
    - But not in terms of communications with providers or advocating for care
- Current global context with uprisings following murder of George Floyd
- Awakening within non-Black communities around racism
- Call to action will emerge from critical review
- All co-authors excited because work brings attention to young racial minorities they work with



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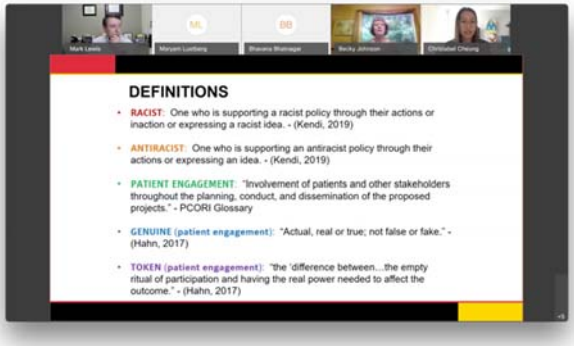
Definitions

- Ibram Kendi is theorist she draws upon for her definition of racism
- Racist: One who supports racist policy through actions or inaction or expressing racist idea
    - Not important whether you are racist of antiracist but whether you support a racist policy
    - Focusing on behavior
    - For Cheung, in middle of racial spectrum, she has engaged in both racist and antiracist actions
    - Personalizing it too much makes people defensive and stops conversation
    - About acknowledging that systems we work in have racist policies
- Patient engagement: Per PCORI glossary, it is involvement of patients and stakeholders through planning, conduct, and dissemination of projects



- In Cheung's review, she and coauthors dichotomize aspects of engagement with patients into genuine and token
- Gotten into bad habit of relying on certain ways of including patients that may just be token and may not give them the voice they need

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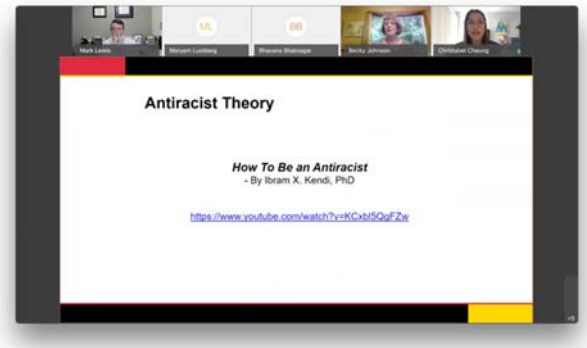
Antiracist theory

- Cheung wanted group to hear about this theory directly from Kendi
- Book published September 2019
- Not many paid attention then
- This year it blew up



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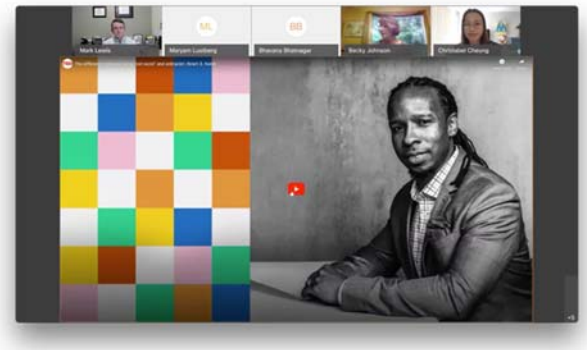
Video of approximately 4 minutes was played.

- https://www.youtube.com/watch?v=KCxbl5QgFZw



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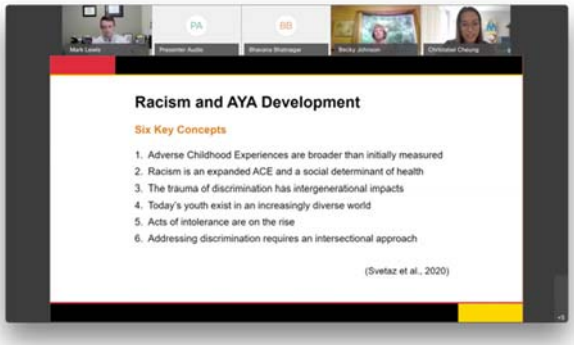
Cheung said another compelling reason she chose this book was a chapter near the end of the book called “Survival.”

- Dr. Kendi in 2018 was diagnosed with stage 4 metastatic colon cancer
- Cheung said he writes eloquently about experiencing racism in the health care system
- His wife was diagnosed with breast cancer 5 years before his diagnosis
- His mother was also diagnosed with breast cancer
- He is involved in health disparities issues
- Cheung noted he helps reader go beyond saying we’re concerned about disparities by asking why they exist
- Accrual rates of racial minorities are consistently low
- Accrual rates in areas of economic deprivation are low
- Cheung spoke of paper by Joe Unger looking at patients in socioeconomically deprived areas who received guideline-concordant care in a clinical trial
    - They still experienced disparities in cancer outcomes compared to counterparts in other areas



Cheung referred to one particular issue Kendi raises re the denial of racism.

- She thought this may be particularly difficult for medicine
- Spoke of TED talk by Dr. Brian Goldman called “Doctors Make Mistakes Too”
- Talks of how Goldman throughout his career has struggled with expectation of perfection and pressure to not make mistakes
- Culture in medicine—she assumed oncology is same—of not talking about mistakes
- Noted that as a social worker in health settings, she hears about complaints and problems
- Sees a need to join across disciplines and professions to discuss health disparities in practical ways
- Need to mobilize disciplines we’re in to antiracist positions

Cheung sees need to discuss racism and AYA development together.

- Child psychology has notion of adverse childhood experiences (ACES)

- Typically ACES are thought of as occurring within child's household
- Now thinking more broadly of ACES as environmental
- Racism identified as another ACE that is social determinant of health for racial minorities
- Racism is pervasive trauma all racial minority youths experience
- Increasing diversity of youth experiences
- Acts of intolerance on the rise, particularly on social media

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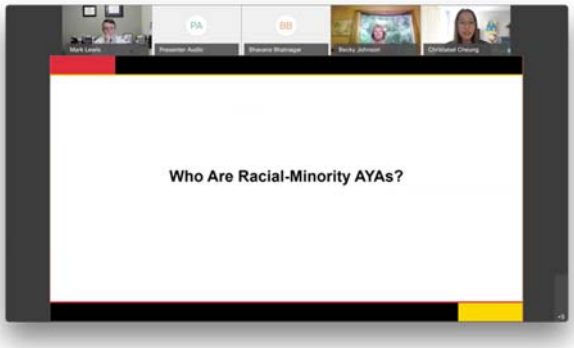
Who are racial minority AYAs?



- On personal level, at start of recent uprisings Cheung was contacted by several mainstream cancer advocacy organizations for help assembling quick knee-jerk reactions to respond to the awakening among non-Black communities
- Said no to all
- For one group, she had organized a panel on survivorship in communities of color
    - Group wanted to change format to live discussion about current context
    - Cheung canceled it to protect her young advocates
    - Didn't want to expose them to violence that might occur in live discussion with expected all-white female audience
- Cheung said those declines were teaching moments for those organizations
    - Told them to imagine giving a women's health talk while being only woman in conference of men
- Forced them to think about how these young racial minority patients were called on to represent their racial group or intersectionality
- Thinks most of harm caused in this way results from organizational self-interest

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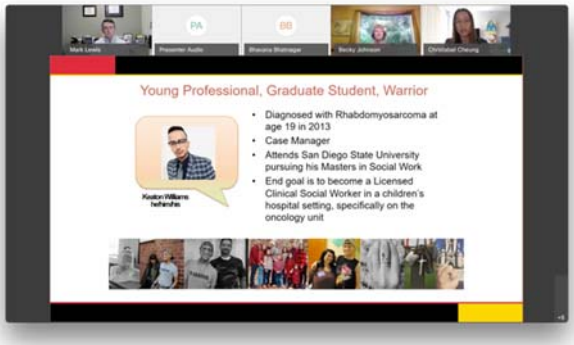
0:39:04
Cheung introduced some of the young racial minority advocates she has worked with who have inspired her.

- Said Keaton Williams and she yearly do minority training in the cancer control research panel for NCI
- Getting master's in social work
- Diagnosed at 19 with rhabdomyosarcoma
- Has sister and mother diagnosed with cancer
- Works as child life specialist part-time while he is in school
- Major part of his journey was coming out as gay male during his cancer care
- A struggle he discusses as an advocate is being typecast to bring the brown perspective on cancer
- Said people haven't been ready for intersectionality of his being gay man



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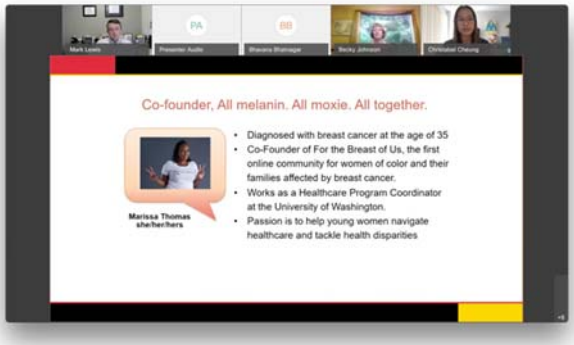
Marissa Thomas was diagnosed at 35

- Started For the Breast of Us
- Can follow on Twitter
- Brings sassy approach to sharing stories of women of color on her site
- Works at U Washington as program coordinator
- A mom too
- Passionate about Black women and addressing health disparities following breast cancer



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Court Simmons started working at Team Cancer America as Courtney.

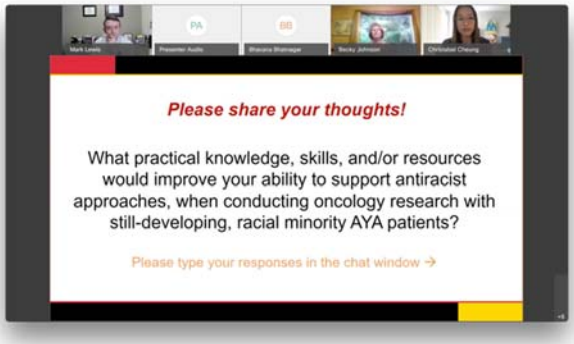
- Was diagnosed at 16 with osteosarcoma
- She and her family carry Li Fraumeni trait
- Lost her mom when she was 17
- Entered foster care system
- Diagnosed at 24 with triple-positive breast cancer
- Is now 25
- In Philadelphia
- Interested in psychosocial aspects of cancer
- Brings so much with her
- Foster system concurrent with cancer concurrent with loss of parent
- Also lost her sister to cancer
- Complexity of issues these patients bring
- Barely fresh out of what they've experienced
- Think of what you're asking of them in terms of research
    - Reach back into all of that and bring it up
    - What do we do with them afterward?
- Cheung tries to build community among them
- Hoping to involve them and long-time advocates in AYA oncology to continue this line of research
- In first phase working with AYA oncology leaders
- Will bring those recommendations to these patients to cocreate recommendations with impact

0:43:20
Purpose of study

- To advance best practice recommendations in antiracist patient engagement in research that will guide ongoing development of effective strategies for collaborating with still-developing racial minority AYAs in oncology research and advocacy initiatives.
- Will look at framework for patient engagement
    - Critique framework
    - Make recommendations to enhance with antiracist lens
    - Share with AYA patients
    - Bring back to this committee to provide practical strategies and language
        - Problem in oncology is lack of language to talk about issues of race
        - Record stops there because people don't want to say wrong thing
        - Need to stop being afraid to talk

0:44:20
Please share thoughts.

- Asked committee to share in chat this:
    - What practical knowledge, skills, and/or resources would improve your ability to support antiracist approaches when conducting research?
    - Focus is on research
    - What would help you in working with still-developing racial minority AYA patients?



0:44:57
Cheung invited collaboration.

- Hoped they could produce recommendations that are
    - Helpful to committee
    - Bring richness to the work
    - Are not patronizing and silly

Lewis said likewise group wants to make sure their engagement with Cheung is authentic and not coming across as tokenist.

- Said Cheung was helping group attack events of this year head on
- Encouraged group to engage Cheung in dialogue

Updates on S1823 and S200x
0:45:46
Craig Nichols and Lucia Nappi presented.

- Nichols provided update on S1823
- Study is opening across the country
- Have encountered some COVID barriers in terms of IRB backlogs
- Study had been put on hold by NCI because of pandemic
- 93 sites now have it open
- 5 accruals to date
- Many large centers just coming online
- Have number of grants for microRNA 371 and 375 to drive survivorship endpoints and chemo-sparing options for certain stages and classes of tumor
- Nichols said they met with NCI communications group to get tips on amplifying message that trial is open and easy to enroll to
- Was a long pathway to launch

Lewis said it was an important trial and hoped it would be platform for biology-based research

- Nichols described it as one of few liquid biomarker translational trials without a therapeutic endpoint but a survivorship patient burden endpoint

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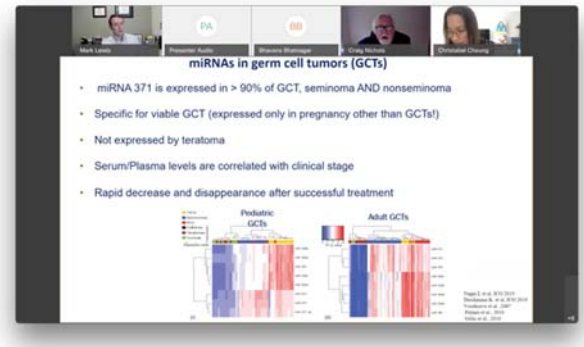
- Hoped it would be example for similar concepts in other diseases in, e.g., Hodgkin lymphoma and others

Lewis noted prospect of reducing cost of care financially and iatrogenically over longitudinal timespan for AYA is crucial.

- Asked Nappi if she had further slides to present from

0:50:22
Nappi presented.

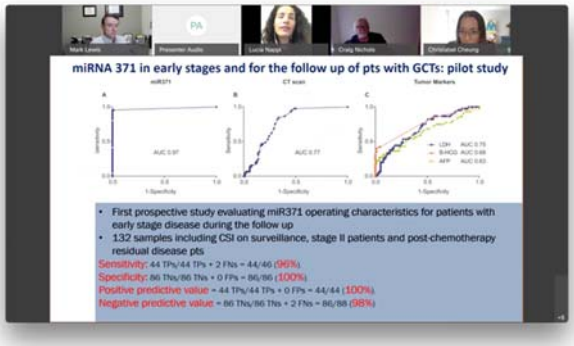
- As background, Nappi said some microRNAs are highly expressed in germ cell tumors, both pediatric and adult



0:50:42
Nappi described results of pilot study published November 2019 in *JCO.*

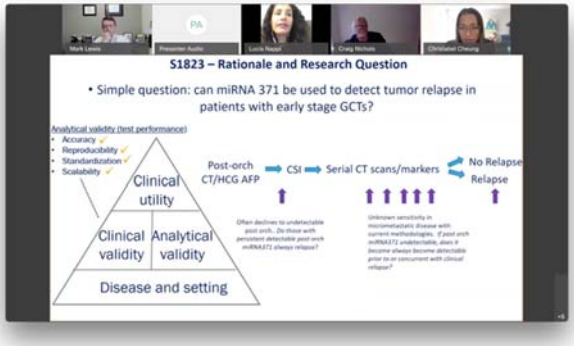
0:50:49

- Said slide shows at left ROC curve of microRNA compared to CT scan and tumor markers
- Occurrences of microRNA 371 exceed those for CT scan and tumor markers
- Specificity and positive predictive value were 100%
- Sensitivity was 96%
- Percentages were better than anything else they have used



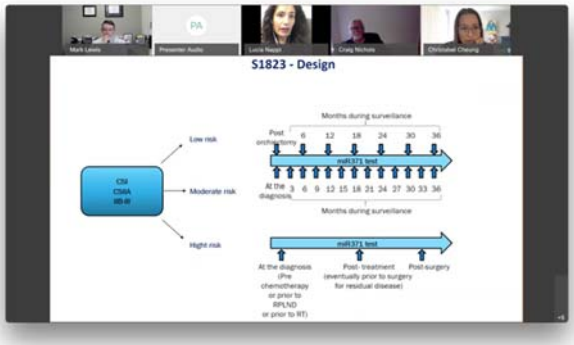
0:51:02
Development status

- In terms of clinical validity and utility
- They have validated clinical validity of microRNA, but they need to validate clinical utility in larger sample
- This is goal of S1823



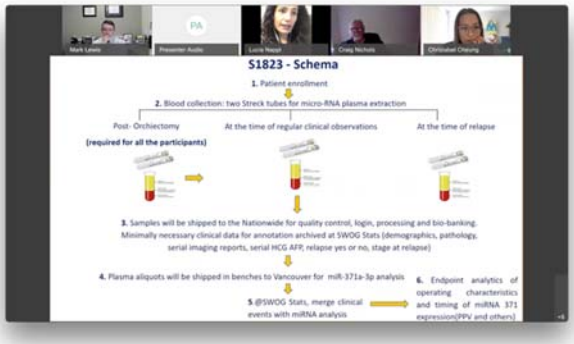
0:51:58
Design

- Patients have stage 1 and 2a disease
- Will also enroll patients with stage 2b and 3, both seminoma and nonseminoma
- Stratified into 3 groups based on estimated risk of harboring the germ cell malignancy
- Follow-up blood collection schedule illustrated in slide
    - Low-risk patients at baseline and every 6 months for 3 years
    - Moderate-risk patients, including 1b nonseminoma and 2a seminoma and nonseminoma, every 3 months
    - High-risk patients with metastatic disease give blood pre- and post-treatment
- These are recommendations for microRNA 371 blood collection but do not dictate surveillance schedule
    - Every investigator can use their own schedule



0:53:50
Schema

- Minimal workload on providers and patients
- Collect blood in Streck tubes when patients go to lab for standard-of-care tumor assessment
- Tubes sent to Nationwide for banking
- Nappi said the aliquots for microRNA won't be done in real time
    - Treatment decisions not based on microRNA analysis



0:54:32
Endpoints

- Primary: establish positive predictive value of miRNA 371 in tumor relapse
- Also establish sensitivity power to detect subclinical tumor relapse
    - Will have serial samples to look for gain in tumor diagnosis
- Collecting information about schedule, radiology, pathology
- Will biobank germline DNA from patients
    - Will create biggest clinically annotated biobank in germ-cell tumors
    - Will help future studies
    - Correlative studies with chemo

0:55:51
Eligibility

- Broad
- Patients with early or advanced stage 2a or even more advanced testicular cancer or germ cell tumor

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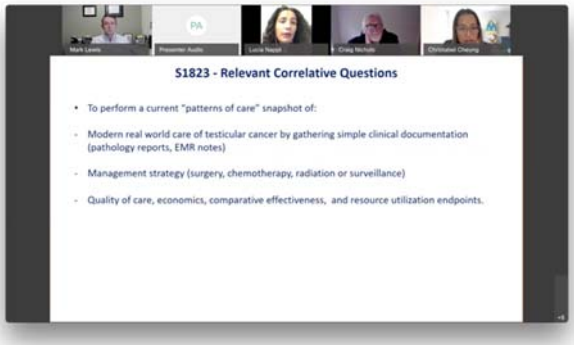
0:56:11
Correlative questions



0:56:22
Statistics

- Nappi said they want to enroll 806 patients with low or moderate risk
    - Stage 1 or 2a
- 150 high risk patients
- Interim analysis after 40 relapses in seminoma and 40 in nonseminoma
- Estimated this would occur within 2 years
- Accrual eased by broad eligibility criteria
    - Little extra work required
- Have commitment of largest germ cell tumor care centers in North America
    - Includes Canadian centers
- Thought this is reasonable because pilot study in BCCA recruited 1,100 patients in <24 months
- COG study AGCT 1531 also accrued well

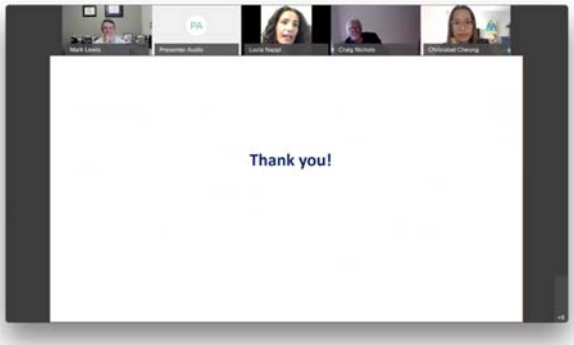
0:57:56
Timeline

- Study activated June 1
- Has 5 patients
- Canadian activation CTG activated August 27
- Working with their IRB to open study in British Columbia
    - Expect to open in October
- Other centers in Canada have started IRB applications

0:58:52

0:58:57
Lewis echoed it was an easy trial for sites.

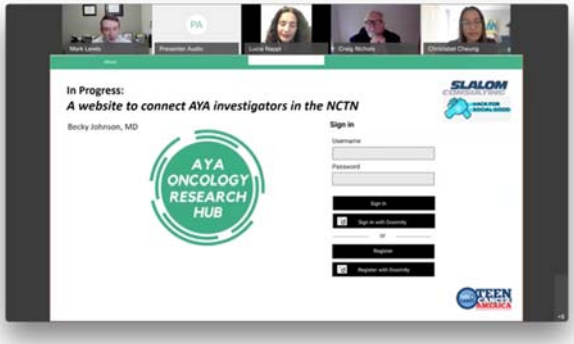
- Suggested emphasizing low institutional burden
- Particularly important during COVID



0:59:25
Lewis apologized to Becky Johnson for the brief time left but said he wanted group to hear about her work connecting cooperative groups.

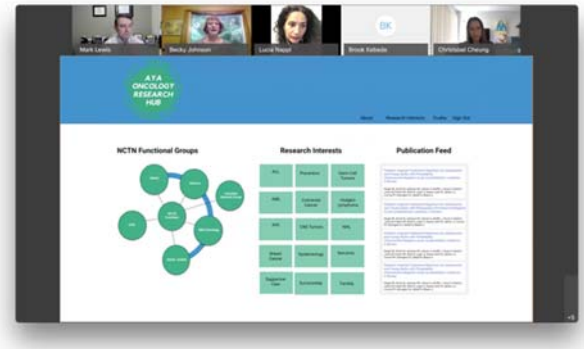
Johnson presented on AYA Oncology Research Hub

- Website to connect AYA investigators within NCTN
- Working group for AYAs has been meeting twice a year
- Site is tackling lack of overlap between committees within disease groups of NCTN organizations
- Can be difficult, as rosters are not public, for investigators to identify who to talk to when designing cross-group trials
- Collaborated with Slalom Consulting, Teen Cancer America, and Mike Roth (head of COG AYA group) and other key stakeholders
- Slalom Consulting has hackathon to help nonprofits with designing tech concepts
    - Had approached Johnson in summer about AYA problem needing solution
    - Johnson identified this
- Will create website initially for NCTN investigators
- Will be able to login with email or Doximity login



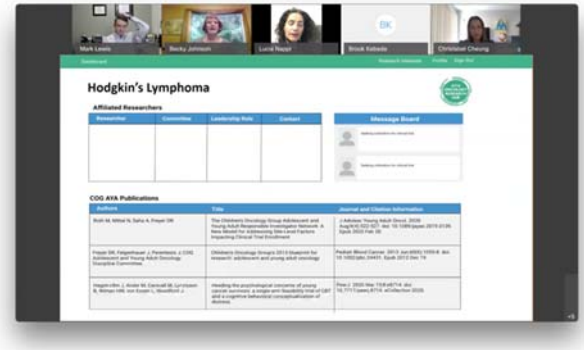
1:01:42

- Site allows search by research interest or NCI group
    - Includes disease-agnostic research groups, such as those devoted to germ cell tumors, QoL, fertility, and survivorship



1:02:40

- Mockup of research interest section
- Lists affiliated researchers
    - Filled in by those who are asked to join site
- Within next 6 months, all on call will be asked to join, enter their interests, and send invites to others who are interested in AYA
- Will include message board
- Slalom suggested automatically pulling in relevant publications
    - Serve as updated curated reading lists

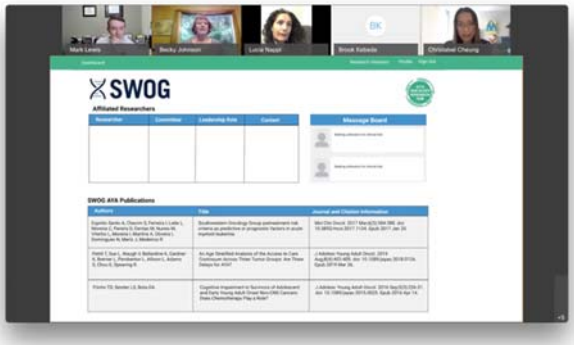


1:04:01

- Example of research group page

Johnson hoped this would be helpful.

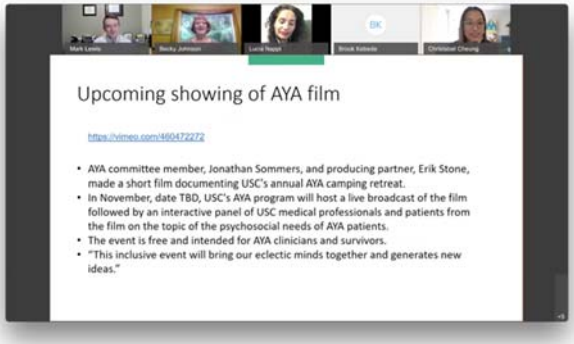
- Said Slalom team has been highly engaged
- Project is in running to win their hackathon



1:04:31

Johnson said to close out session they wanted to plug event showcasing film documenting USC's annual AYA retreat.

- Screening will be followed by discussion of psychosocial needs of AYA patients
- Open to clinicians and survivors
- Committee member Jonathan Sommers produced with his partner Erik Stone
- Johnson showed trailer
- Information will go out with details of November event



1:05:22
One-minute video trailer was played

- https://vimeo.com/460472272

1:06:20
Johnson thanked group for attending.

1:06:42
Meeting was adjourned.