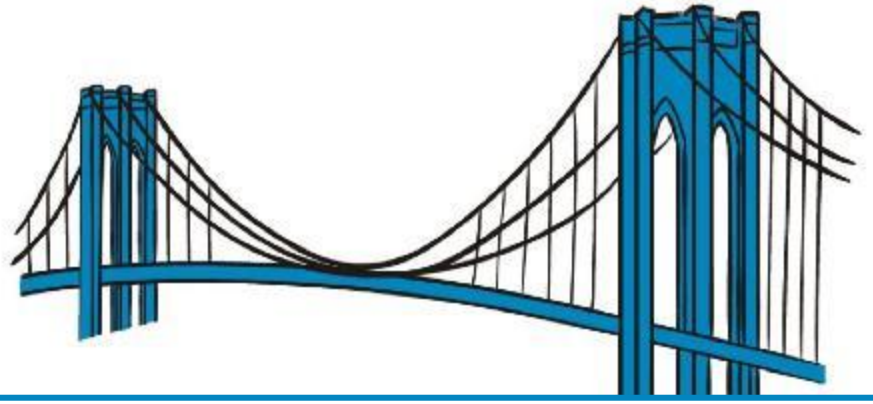


SLE: Building Bridges from Clinical Trials to Clinics

Association of Women in Rheumatology
2022 Annual Conference

Saira Z Sheikh, MD

Linda Coley Sewell Distinguished Professor of Medicine
Director, Clinical Trials Program
UNC Thurston Arthritis Research Center
Director, UNC Rheumatology Lupus Clinic
University of North Carolina at Chapel Hill

DISCLOSURES

Grant funding from Pfizer

Advisory boards:
Aurinia Pharmaceuticals Inc.,
AstraZeneca, Lilly USA, LLC, GSK

LEARNING OBJECTIVES

"Why should I listen to this talk?"

- Recognize the importance of inclusion of diverse patients in clinical trials
- Identify common patient and provider specific barriers to clinical trial participation
- Understand the role of physicians in introducing clinical trial opportunities to patients
- Create a culture of integrating clinical trials into clinical care

OUTLINE

- Why a clinical trial?
- Underrepresentation of diverse groups in clinical trials
- Bridging the gap

THE MIRACLE CURE

"The woman, crippled and wheelchair-bound for over five years, regained full function within four days of treatment. She could now walk, suffering no muscular soreness or stiffness".

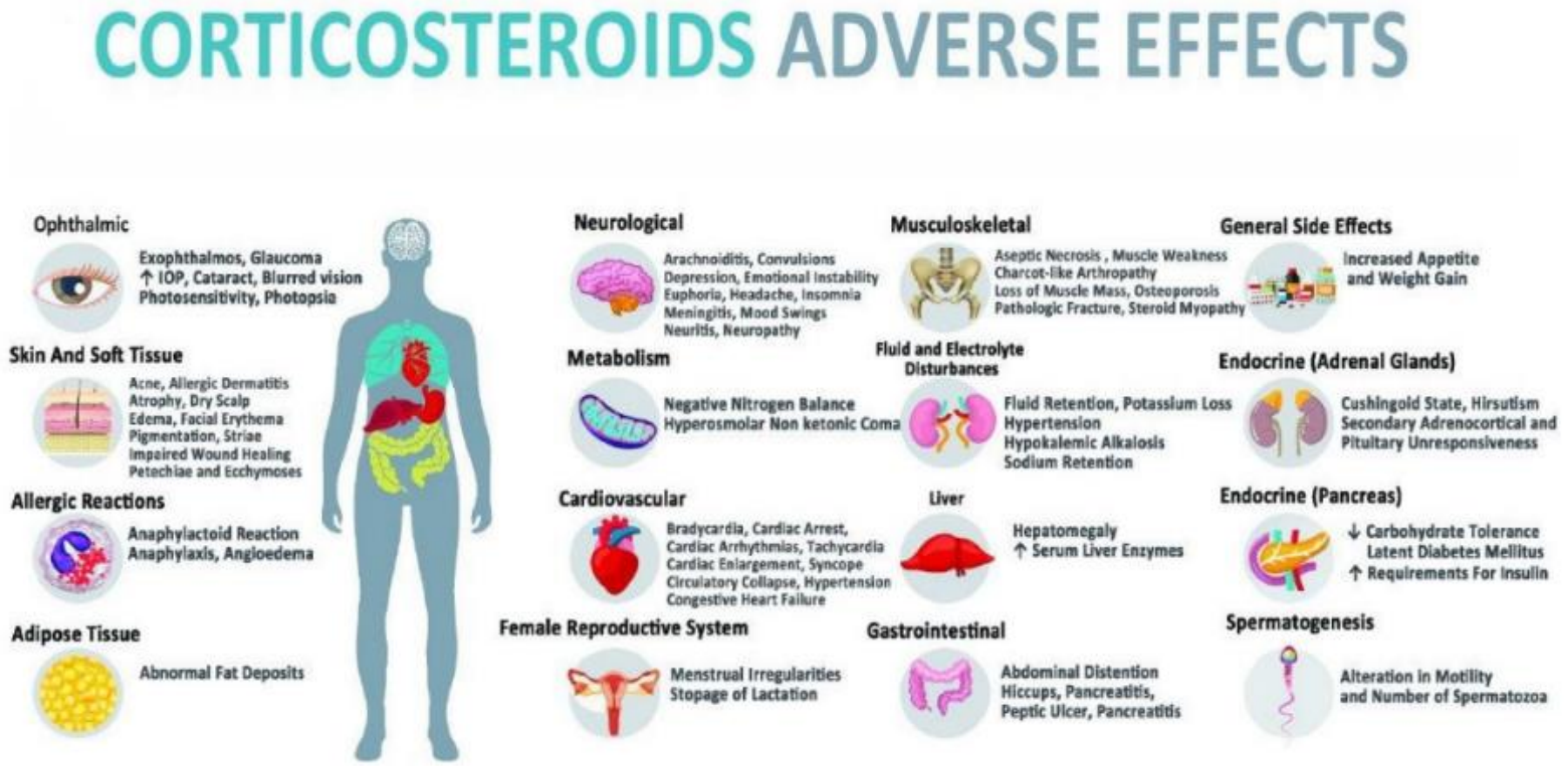
The Nobel Prize in Physiology/Medicine 1950

Edward Calvin Kendall

Tadeus Reichstein

Philip Showalter Hench

TURNS OUT…NOT THE MIRACLE CURE



Langarizadeh et al. (2021). https://doi.org/10.17179/excli2020-3196

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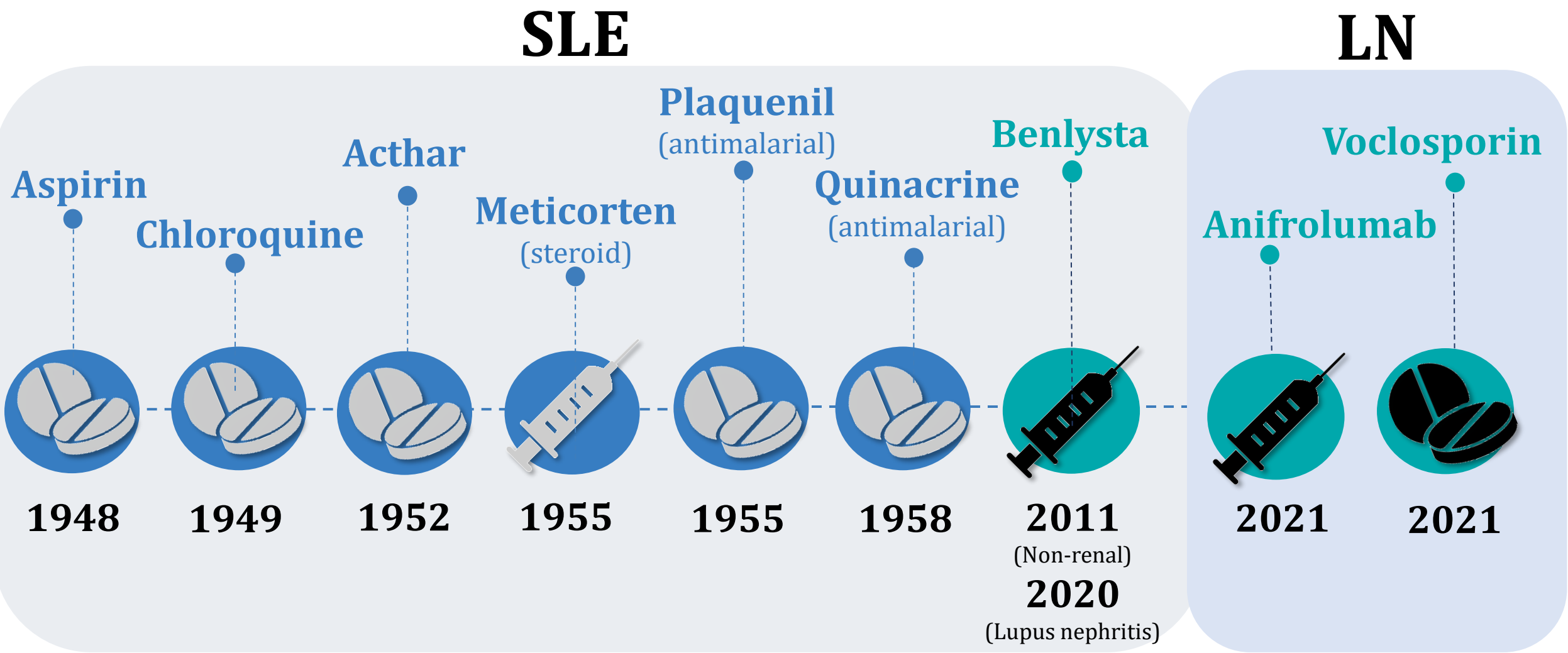
FDA APPROVED TREATMENTS FOR LUPUS



UNMET NEEDS IN LUPUS THERAPIES

50%
Response rates

10-15%
Premature death

10-40%
Renal Response

>30%
Progress to ESRD


Fatigue,
Quality of life


Biomarker
Development


Efficacious
therapies


Safer
Therapies

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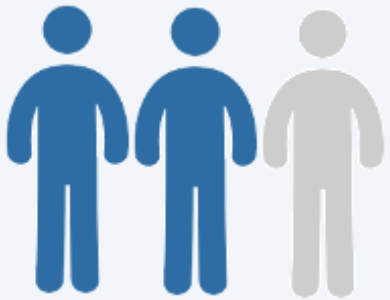
THE PATIENT PERSPECTIVE



Loss of income

8

Prescription Meds Daily

44%

Satisfied with therapy

Lupus Foundation of America Survey (2012)

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LUPUS: A LEADING CAUSE OF DEATH

SLE ranks among the **top 20 leading causes of death** among US females 5 – 64 years

Among young **Black and Hispanic females, SLE is ranked 5th & 6th leading causes of death**

5th

15 – 24 years

6th

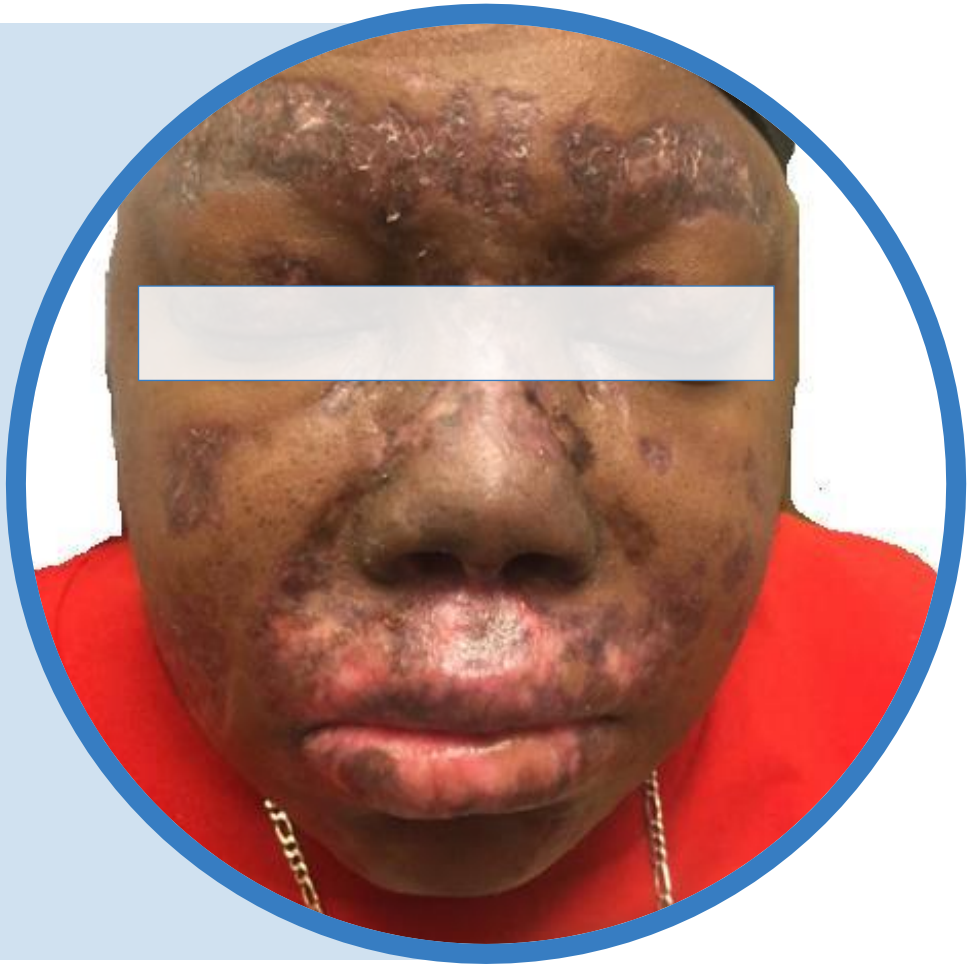
25 – 34 years

Yen & Singh 2018. Arthritis & Rheumatology, DOI: (10.1002/art.40512), https://www.lupus.org/resources/lupus-facts-and-statistics

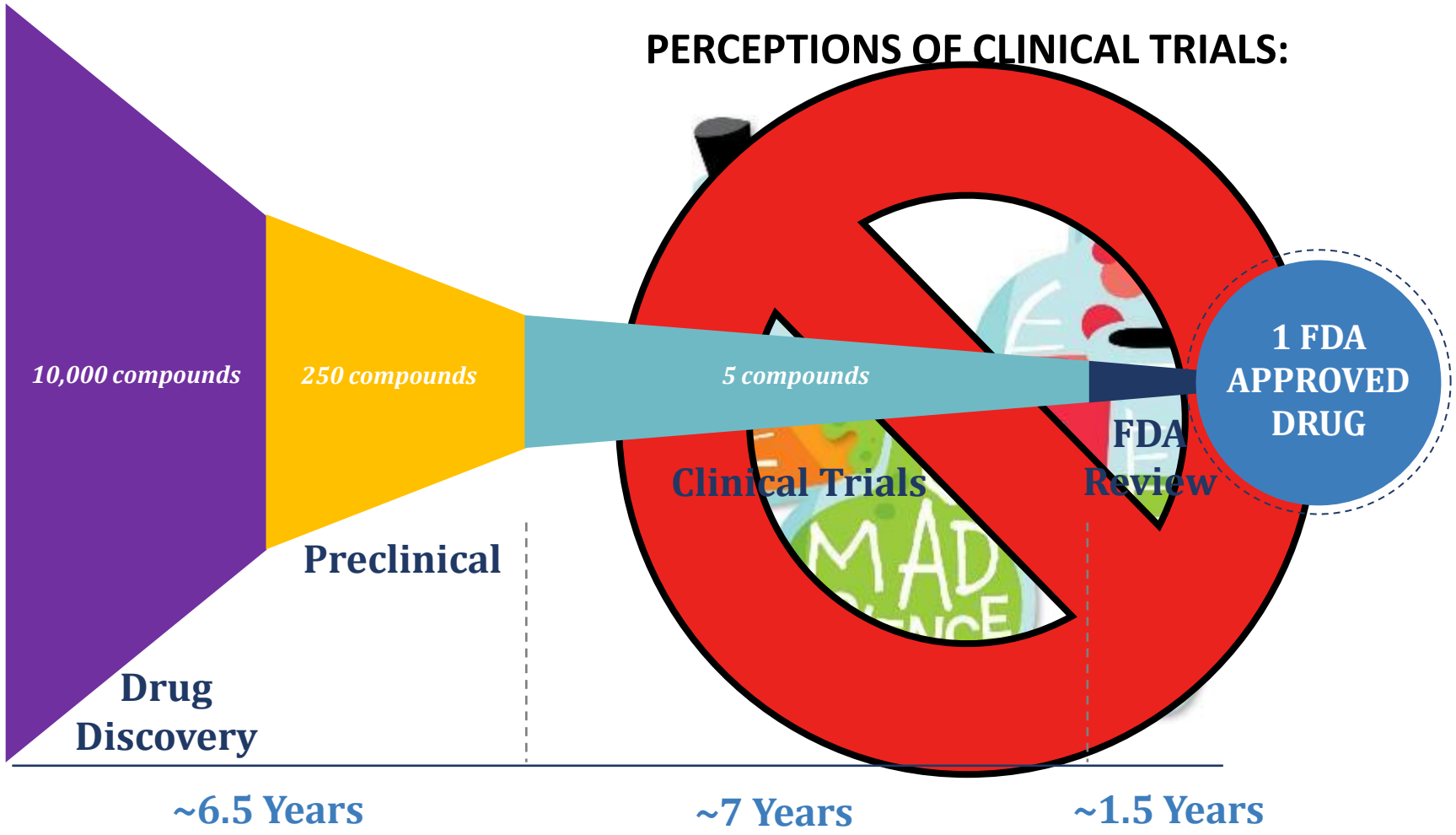
WHY A CLINICAL TRIAL?

Has she failed multiple therapies – or have the therapies failed her?

* informed verbal and written consent obtained for use of photograph



DRUG DISCOVERY & DEVELOPMENT TIMELINE



$1–2.4 billion

Cost of developing a prescription drug that gains market approval

Tufts Center for the Study of Drug Development

BETTER HEALTH OUTCOMES FOR CLINICAL TRIAL PARTICIPANTS

*"Several groups of investigators have suggested that **older children and adults who participate in a randomized controlled trial have better health outcomes** than eligible nonparticipants…"*

Schmidt et al. https://doi.org/10.1016/S0022-3476(99)70428-2.

*"…we suspect that **strict adherence to a carefully designed protocol** and possibly also the **additional scrutiny from study personnel may have benefited infants** in the placebo arm of the trial..."*

*"[Lung cancer] patients enrolled in a clinical trial have an **improved survival**, independent to other prognostic factors."*

Arrieta O, et al. doi: 10.1159/000447404

UNDERREPRESENTATION OF DIVERSE GROUPS IN CLINICAL TRIALS

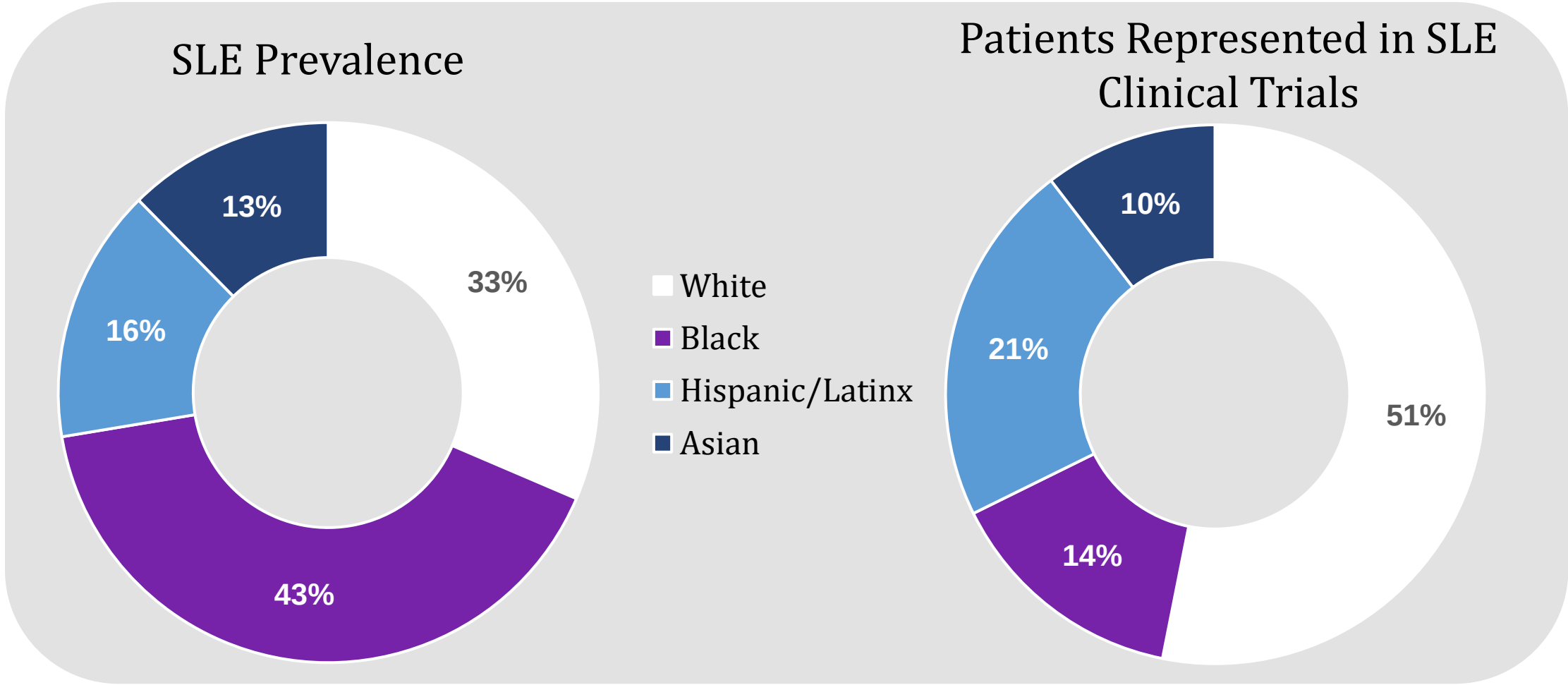
LACK OF DIVERSITY IN CLINICAL TRIALS ACROSS THE BOARD

An analysis of data from the main US COVID-19 vaccine clinical trials reported on clinicaltrial.gov or PubMed by the end of September 2021 found that:

> *'White participants were overrepresented, and Black or African American, American Indian or Alaska Native adults, and Hispanic or LatinX participants were underrepresented, especially in early-phase pandemic vaccine adult clinical trials including those regarding the current COVID-19 vaccine.'*

Khalil et al. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8875029/

SLE CLINICAL TRIAL PARTICIPANTS DO NOT REFLECT LUPUS PATIENT POPULATION



Falasinnu et al. DOI: 10.1007/s11926-018-0728-2 https://link.springer.com/article/10.1007/s11926-018-0728-2

LET ME TELL YOU A STORY…

THE STORY OF EMBRACE

ACR Open Rheumatology
Vol. 0, No. 0, Month 2022, pp 1–6
DOI 10.1002/acr2.11477

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

EDITORIAL

EMBRACE: One Small Story in Lupus—One Giant Challenge in Clinical Trials

Saira Z. Sheikh,[1] Tessa R. Englund,[1] Susan W. Burriss,[2] Jonca Bull,[3] Anya Harry,[2] James G. Groark,[2] Ashley M. Hall,[2] Michelle Miller,[2] and David A. Roth[2]

F.D.A Approves Drug for Lupus

An Innovation After 50 Years

The New York Times

March 9, 2011

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NEW LUPUS DRUG GETS ONLY MIXED REACTIONS FROM PATIENTS, EXPERTS

The Washington Post

By Arthur Allen June 13, 2011

Drug is not recommended for patients whose disease is severely damaging their kidneys or central nervous systems because it was not tested on those patients.

African-Americans, who have a far higher incidence of lupus than white people, did not appear to respond to the drug.

BELIMUMAB LABEL- MARCH 2012

HIGHLIGHTS OF PRESCRIBING INFORMATION

8.6 Race

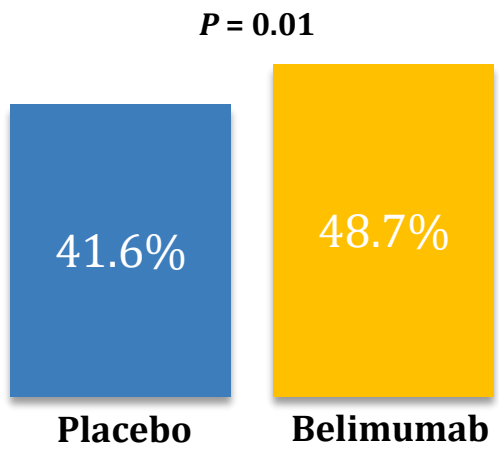
In Trial 2 and Trial 3, response rates for the primary endpoint were lower for black subjects receiving BENLYSTA relative to black subjects receiving placebo *[see Clinical Studies (14)]*.

Use with caution in black/African-American patients.

BENLYSTA (belimumab) for injection.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125370s016lbl.pdf

EFFICACY AND SAFETY OF BELIMUMAB IN BLACK RACE PATIENTS WITH SLE (EMBRACE): POST-MARKETING COMMITMENT TO THE FDA

Even though primary endpoint was not achieved, improvement with belimumab versus placebo was observed suggesting that belimumab remains a suitable treatment option for SLE management in Black patients



EMBRACE NCT01632241

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EMBRACE IMPLICATIONS: CAUTION REMOVED FROM BELIMUMAB LABEL 2020

HIGHLIGHTS OF PRESCRIBING INFORMATION

8.8 Racial Groups

In Trial 2 and Trial 3 (intravenous dosing), SLE Responder Index-4 (SRI-4) response rates were lower for black patients receiving BENLYSTA plus standard therapy relative to black patients receiving placebo plus standard therapy *[see Clinical Studies (14.1)]*.

In Trial 4 (intravenous dosing), a 2:1 randomized, placebo-controlled trial in black patients, SLE Responder Index (SRI-S2K) response rates were higher for black patients receiving BENLYSTA plus standard therapy (49%) relative to black patients receiving placebo plus standard therapy (42%). However, the treatment difference was not statistically significant *[see Clinical Studies (14.1)]*.

In Trial 6 (subcutaneous dosing), SRI-4 response was 45% (26/58) in black patients receiving BENLYSTA plus standard therapy compared with 39% (13/33) in black patients receiving placebo plus standard therapy *[see Clinical Studies (14.2)]*.

The safety profile of BENLYSTA in black patients was consistent with the known safety profile of BENLYSTA administered in the overall population *[see Adverse Reactions (6.1)]*.

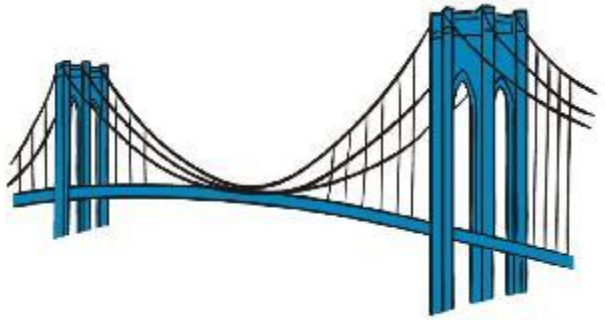
BENLYSTA (belimumab) for injection, for intravenous use; for subcutaneous use.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125370s068,761043s008lbl.pdf

REAL CONSEQUENCES

- Potentially **delayed Black patients' access** to belimumab → compounding existing **SLE disparities**
- **Inadequate representation** of clinically relevant populations can lead to **insufficient safety and effectiveness data** for product labeling

FDA (2020). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial

BRIDGING THE GAP:
Creating a Culture of Integrating Clinical Trials into Clinical Care



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PATIENTS LEARN ABOUT CLINICAL TRIALS FROM THEIR PROVIDERS

77%

of patients who participate in a clinical trial learn about it from their provider

National Institute of Health. (2016) The Need for Awareness of Clinical Research http://bit.ly/2ogudw6
(Comis, 2009)

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POLLING QUESTION #1

Do you feel comfortable discussing the option of a clinical trial with your patient?

A. Very comfortable
B. Somewhat comfortable
C. Not comfortable

POLLING QUESTION #2

Have you ever discussed a clinical trial with a patient?

A. Always
B. Frequently
C. Sometimes
D. Rarely
E. Never

THE CONVERSATIONS THAT NEVER OCCUR

The Patient Perspective

I had no idea about clinical trials. It was foreign to me. It's like a foreign word. I had never heard of it before.

Brown et al J Oncol Pract. 2013 Nov; 9(6): 287–293

WHY THESE CONVERSATIONS DO NOT OCCUR: COMPETING DEMANDS

- Overload of information-difficult to understand and process
- New diagnosis, prognosis
- Medications, doses, side effects, cost
- Impact of family, beliefs, culture, limited English proficiency

85%

of patients were **unaware** that participation in **a clinical trial was an option** at the time of diagnosis

Approximately **90%** of clinical trials **fail to meet recruitment goals**

75%

of these patients **said they would have been willing to enroll** had they known it was possible

Harris Interactive Survey (2001)

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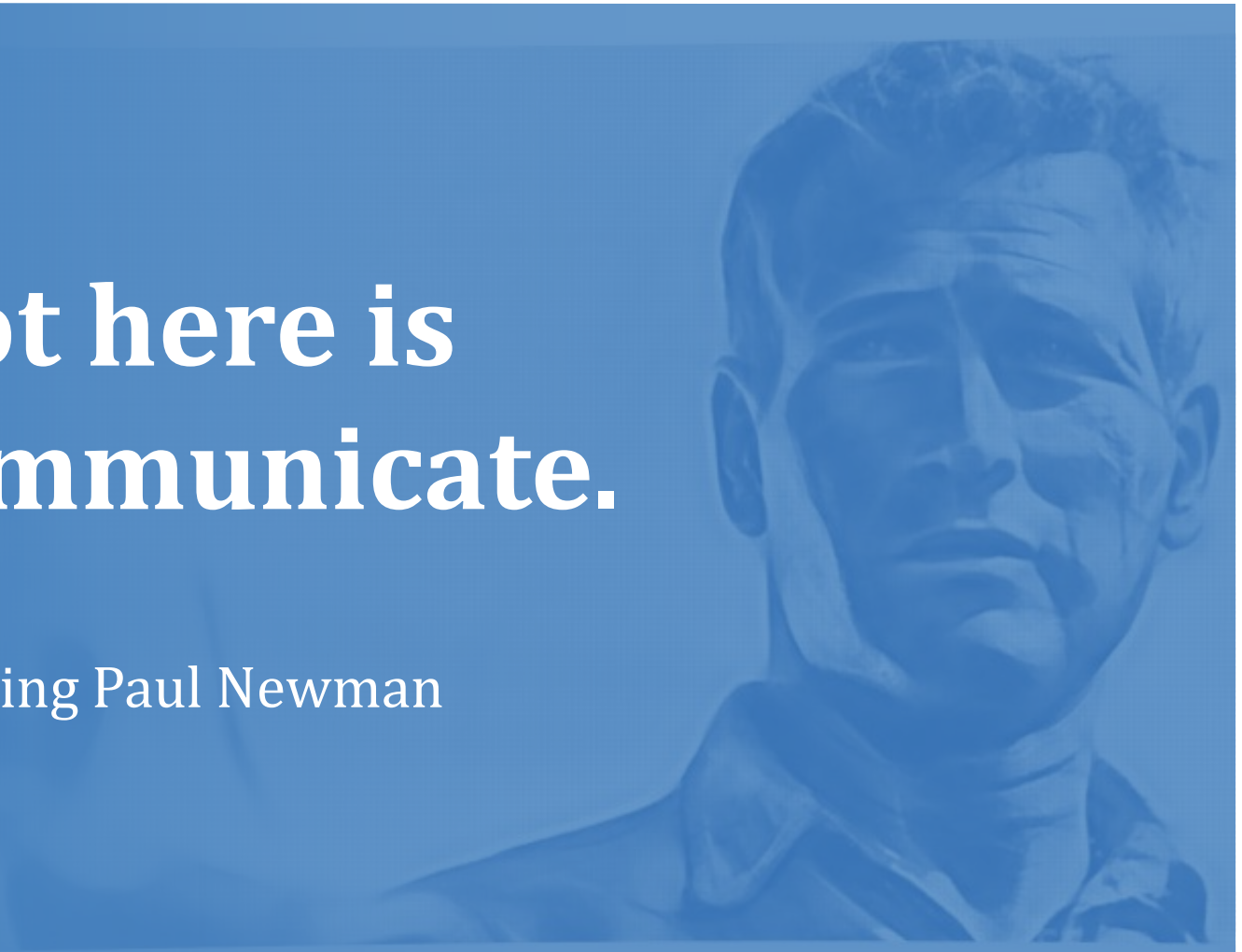
What we've got here is a failure to communicate.

1967's "Cool Hand Luke" starring Paul Newman



“UNIVERSAL PRECAUTIONS” FOR CLINICAL TRIALS

Educate all patients about clinical trials

- Check **implicit biases** at the door
- Advocate for **consideration** of participation
- **Patient-centered** communication
- **Resources** to make informed decisions
- Think about the option of a clinical trial when its time to **change** or **escalate** therapy

DISEASE ACTIVITY IN CLINICAL TRIALS: ENTRY CRITERIA & END POINTS

BILAG

BILAG A
Severe disease activity

BILAG B
Moderate disease activity

BILAG C
Mild disease

BILAG D
Inactive disease

BILAG E
System never involved

0 = no activity

1 – 3 = mild activity

4 – 8 = moderate activity

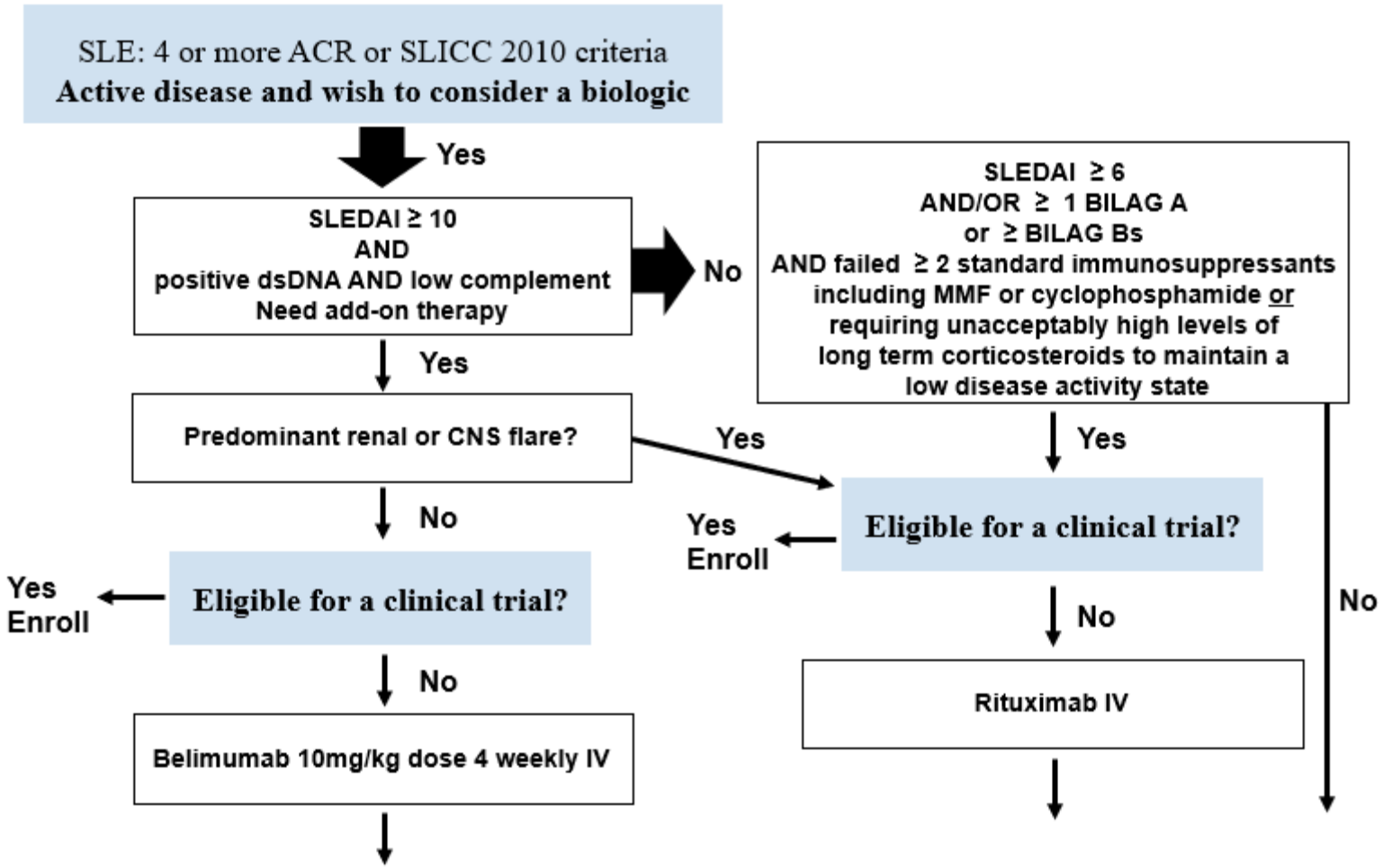
8 – 12 = high activity

>12 = very high activity

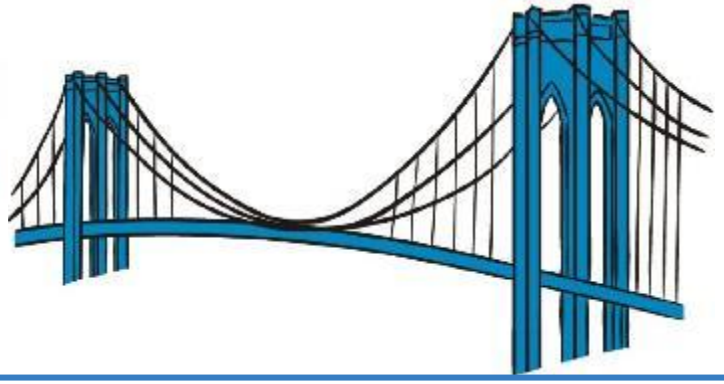
SLEDAI – 2K

Weight	Descriptor
8	Seizure
8	Psychosis
8	Organic brain syndrome
8	Visual disturbance
8	Cranial nerve disorder
8	Lupus headache
8	CVA
8	Vasculitis
4	Arthritis
4	Myositis
4	Urinary casts
4	Hematuria
4	Proteinuria
4	Pyuria
2	Rash
2	Alopecia
2	Mucosal ulcers
2	Pleurisy
2	Pericarditis
2	Low complement
2	Increased DNA binding
1	Fever
1	Thrombocytopenia
1	Leukopenia

NICE, NHS, AND BRITISH SOCIETY GUIDANCE FOR THE USE OF BIOLOGICS IN SLE



HOW TO BRIDGE THE GAP



PATIENT BARRIERS TO CLINICAL TRIAL PARTICIPATION

Access	Opportunity	Health Literacy	Cultural	Mistrust
• Limited access to rheumatologists • Logistics e.g., transportation, time/resource constraints	• Lack of awareness of clinical trials • Lack of referral by PCP & specialty providers	• Limited understanding of clinical trial process • Literacy/numeracy challenges	• Exclusion of family in the consent process and study appointments • Language barriers	• Institutional mistrust • Uncertainty and anxiety about clinical trials

Past and present context of
Structural Racism & Discrimination

PROVIDER BARRIERS

Awareness

- Access to clinical trial information
- Familiarity with clinical trial sites and PIs
- Knowledge about clinical trials

Beliefs and Implicit Bias

- Patients will not understand and adhere to protocols
- Clinical trial could have a negative impact on the provider-patient relationship
- Clinical trials are unsafe or coercive

Logistical Barriers

- Lack of time to learn of and discuss trial opportunities
- Unsure how to refer patients to clinical trial
- Limited proximity to clinical trials

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CRITICAL QUESTIONS

Can we:

- improve health care provider literacy about clinical trials?
- improve physician communication skills related to discussing trials using patient-centered communication?

PROGRAMS

National & Institutional

Provider + Patient Education

- **M**aterials to **I**ncrease **M**inority **I**nvolvement in **C**linical **T**rials (MIMICT)
- **T**raining to **I**ncrease **M**inority **E**nrollment in **L**upus Clinical Trials with Communit**y** Engagement (TIMELY)

Patient Education- Peer-based Approach

- **P**atient **A**dvocates for **L**upus **S**tudies (PALS)

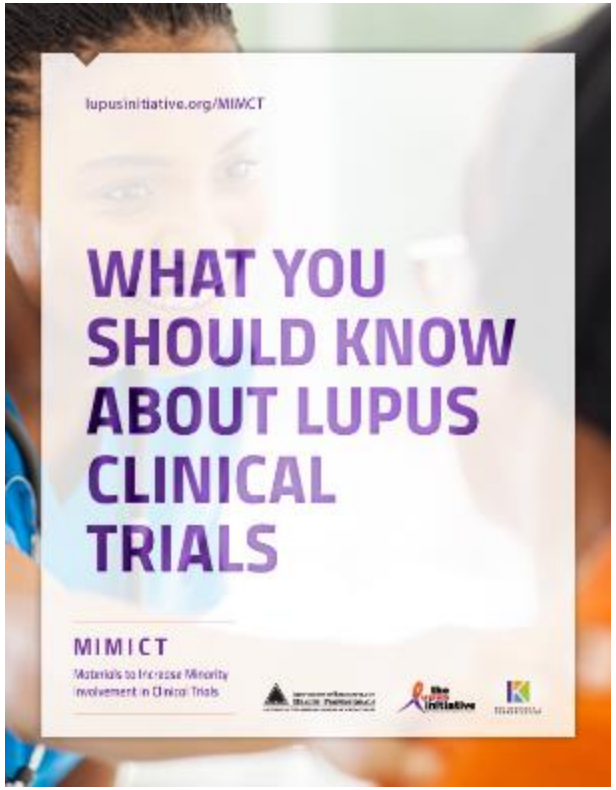
Technology-based Applications

- **P**rograms to address **U**nmet needs and promote **R**epresentation of **P**articipants in **L**upus clinical trials using mobile technology for **E**ngagement" (PURPLE)

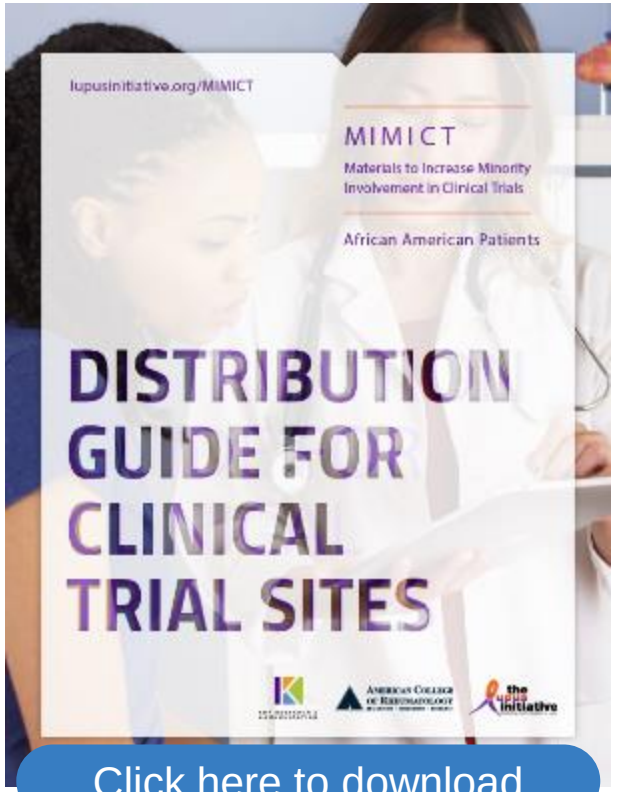
MIMICT MODEL BUILDS ON THREE INTERVENTION CATEGORIES

Educational modules for providers

Educational materials for patients



Outreach tools for clinical trial sites



Click here to download

https://thelupusinitiative.org/wp-content/uploads/MIMICT-Distribution-Guide_2018_FINALsm.pdf

WHAT WOULD MOTIVATE YOU TO PARTICIPATE IN A CLINICAL TRIAL?

>80%

of respondents said that talking with other patients who have taken part in a clinical trial would make them very likely or likely to participate

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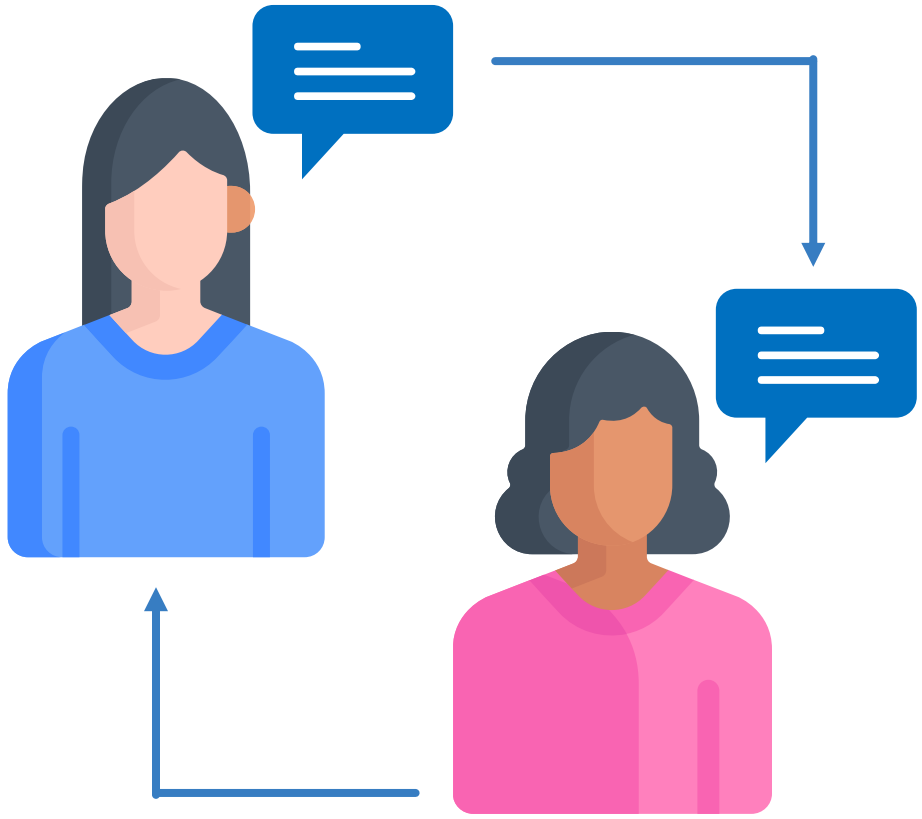
Lupus THERAPEUTICS
an affiliate of LUPUS RESEARCH ALLIANCE

LuCIN
Lupus Clinical Investigators Network



Individuals living with lupus are trained to serve as trial agnostic resource for patients

Peer to Peer Communication

PALS Patient Advocates for Lupus Studies

Early education to introduce clinical trials to individuals

Co-PIs: Saira Sheikh, MD & Sam Lim, MD
UNC, Emory, Columbia, Northwestern, UMiss

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LUPUS RESEARCH ALLIANCE

Lupus THERAPEUTICS an affiliate of LUPUS RESEARCH ALLIANCE

LuCIN Lupus Clinical Investigators Network

KDH RESEARCH & COMMUNICATION

EMORY UNIVERSITY SCHOOL OF MEDICINE

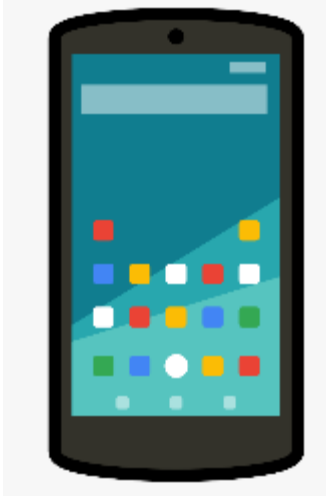
Intervention group had higher scores across all outcome measures than the control group after participating in the PALS intervention

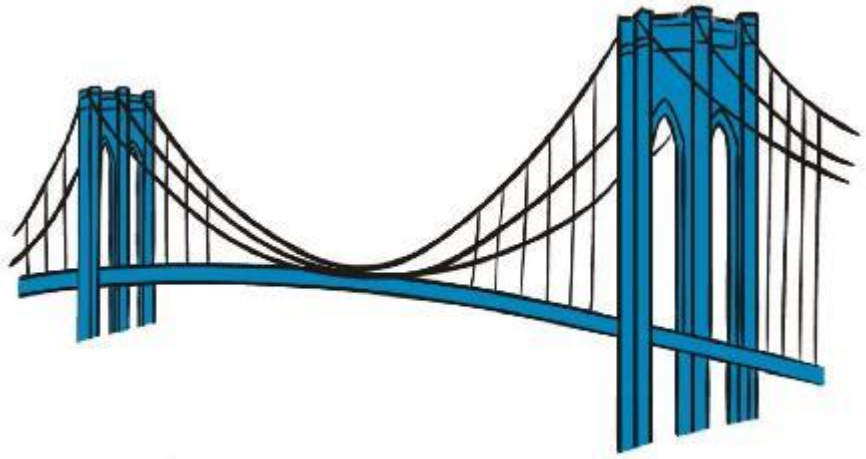
Composite Score	Intervention group scored higher than control at posttest on all outcomes
Knowledge	↑
Attitudes	↑
Self-efficacy	↑
Intentions	↑

↑ Statistically significant increase

↑ Increase (not statistically significant)

BRIDGING THE GAP THROUGH TECHNOLOGY



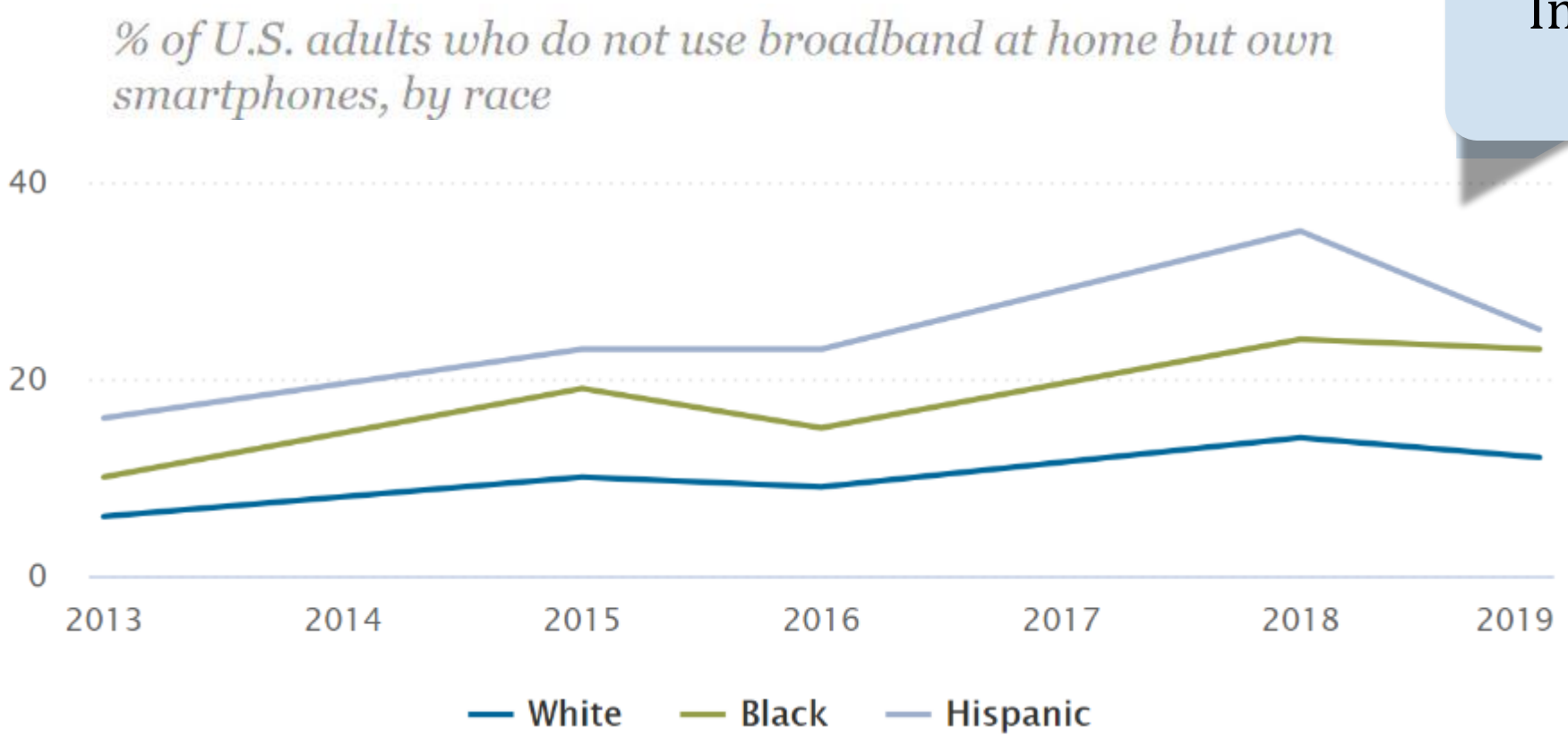


THOUGHT PROVOKING TIME IN OUR EVOLUTIONARY HISTORY

Six of the world's seven billion people have mobile phones - but only 4.5 billion have a toilet

U.N. report (2013)

BRIDGING THE GAP- SMARTPHONES HELP REACH UNDERREPRESENTED GROUPS



In 2019, **96%** of Americans owned a cell phone

Higher rates of smartphone reliance:

- Younger adults
- Black adults
- Hispanic adults
- Lower education
- Lower-income

https://www.pewresearch.org/internet/chart/smartphone-dependency-by-race/

DOCTORS ARE A TRUSTED SOURCE OF HEALTH INFORMATION

Patients consistently rate their own doctors as their most trusted source of health information, yet most physicians do not have sufficient time or resources to discuss clinical trials

First of its kind to educate patients about clinical trials through interactive content using **custom-built physician avatars modeled after patients' real-life treating physicians**

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RTI INTERNATIONAL

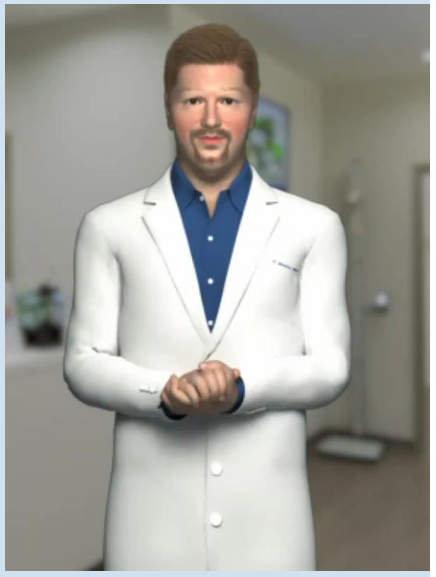
PURPLE

Programs to address Unmet needs and promote Representation of all Participants in Lupus clinical trials using mobile technology for Engagement

Culturally competent Health literate Bilingual

Animations explain complex concepts

Dr. Saira Sheikh



Dr. Alfredo Rivadeneira

Simple Interactive Engaging Evidence-based

Assess knowledge based on "teach back"

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RTI INTERNATIONAL

PATTERN HEALTH

KOH RESEARCH & COMMUNICATION

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

LET'S TAKE CHARGE

We need diverse participants in lupus clinical trials to:

- Represent the patients that will use the medical products
- Obtain better data on how well treatments work in diverse communities
- Understand how people may react differently to medical products

LET'S TAKE CHARGE! Help make lupus research more diverse

minorityhealth.hhs.gov/letstakecharge
#LetsTakeCharge

OMH U.S. Department of Health and Human Services Office of Minority Health

FDA

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https://minorityhealth.hhs.gov/letstakecharge/campaign-resources/

PARTING THOUGHTS: HOW DO WE DEFINE SUCCESS?

Dynamic state influenced by how well WE deliver information that matches patients' abilities, needs and preferences

Informed decisions = Empowered patients

szsheikh@email.unc.edu

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