

Clinical Trials Basics and Beyond

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Susan G. Komen's OC MBC Clinical Trials Symposium

November 2, 2019



7 things you should know about joining a clinical trial

1. In some clinical trials, you could wind up receiving a standard FDA-approved treatment for metastatic breast cancer plus a placebo (sugar pill).
2. You might find that you appreciate the increased medical attention and the close monitoring of side effects during a clinical trial.
3. It's best to learn as much as possible in advance about the schedule of the trial and any costs that might be involved.
4. During the screening process or during the trial itself, speak up if you're concerned about some aspect of your care.

Why should I participate? 7 things you should know

5. Remember that you can drop out (or “withdraw consent”) at any time.
6. The experimental treatment you receive during a clinical trial could make a big difference in your health.
7. You may not regret participating in a clinical trial even if it doesn’t work out the way you hope

Why should I participate in a clinical trial?

- You may be among the first to benefit from a new treatment.
- Many trials involve targeted therapies with the goal of improved effectiveness and decreased side effects.
- You expand the number of treatment options you have.
- You have the chance to help others.

What is a clinical trial?

- NIH Definition of a Clinical Trial

A research study in which one or more human subjects are **prospectively assigned** to one or more **interventions** (which may include placebo or other control) to evaluate the effects of those interventions on **health-related biomedical or behavioral outcomes**.

Prospective Assignment

- The term "prospectively assigned" refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

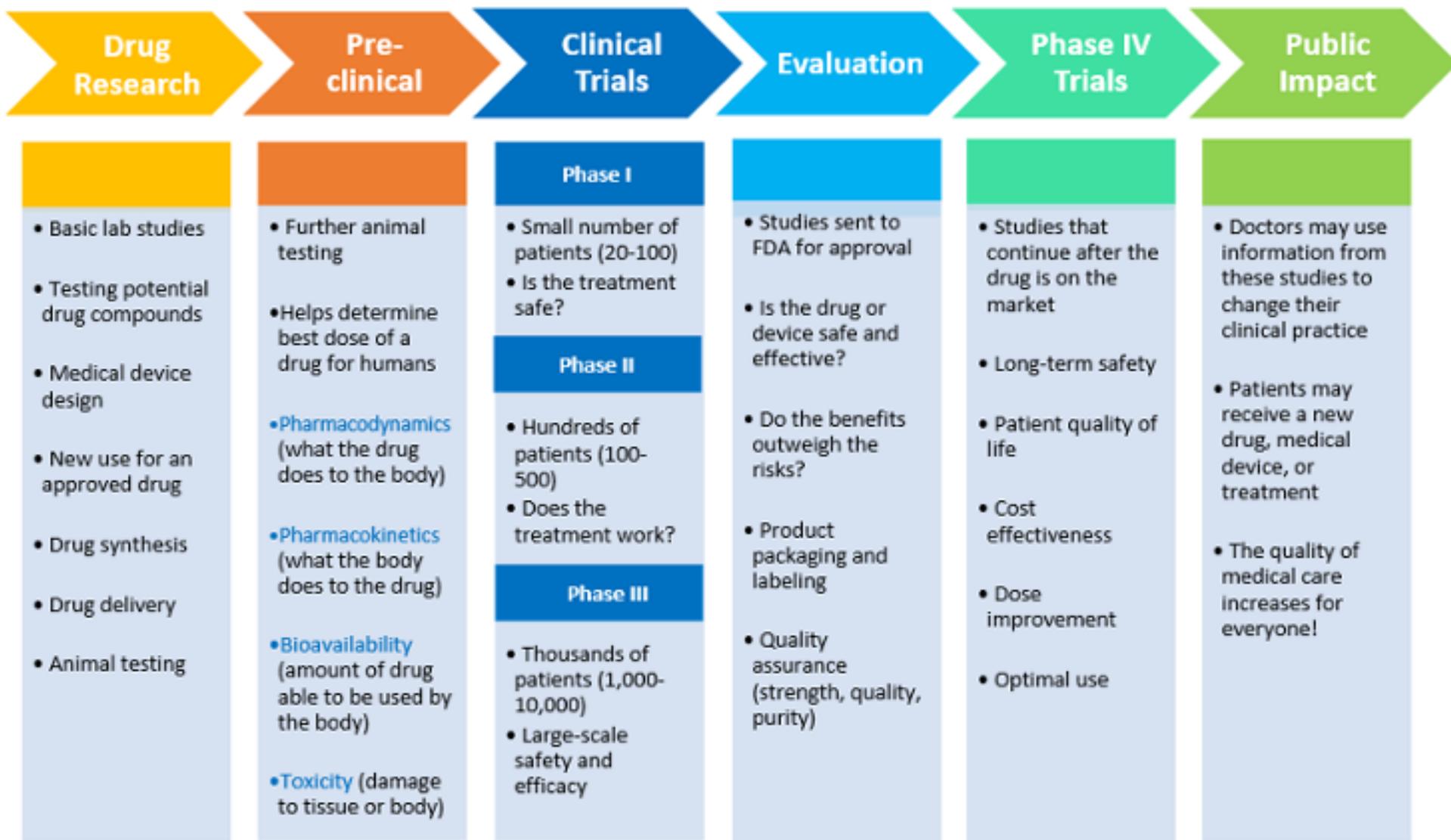
Intervention

- An "intervention" is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints.
- Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

Health-related biomedical or behavioral outcome

- A "health-related biomedical or behavioral outcome" is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life.
- Examples include: **positive or negative** changes to **physiological** or **biological parameters** (e.g., improvement of lung capacity, gene expression); positive or negative changes to **psychological** or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to **disease processes**; positive or negative changes to **health-related behaviors**; and, positive or negative changes to **quality of life**.

Clinical Trial Basics



Ethics in Clinical Research

- The goal of clinical research is to develop generalizable knowledge that improves human health or increases understanding of human biology.
- People who participate in clinical research make it possible to secure that knowledge.
- The path to finding out if a new drug or treatment is safe or effective is to test it on patient volunteers.
- Clinical research has the potential to exploit patient volunteers by placing some people at risk of harm for the good of others.
- The purpose of ethical guidelines is both to protect patient volunteers and to preserve the integrity of the science.
- The ethical guidelines in place today were primarily a response to past abuses, the most notorious of which in America was an experiment in Tuskegee, Alabama, in which treatment was withheld from 400 African American men with syphilis so that scientists could study the course of the disease. Various ethical guidelines were developed in the 20th century in response to such studies.

Influential codes of ethics and regulations that guide ethical clinical research include

- Nuremberg Code (1947)
- Belmont Report (1979)
- U.S. Common Rule (1991)
- Declaration of Helsinki (2000)
- CIOMS (2002)

Seven principles for guiding the conduct of ethical research

- Social and clinical value
- Scientific validity
- Fair subject selection
- Favorable risk-benefit ratio
- Independent review
- Informed consent
- Respect for potential and enrolled subjects

1. Social and clinical value

- Every research study is designed to answer a specific question.
- Answering certain questions will have **significant value for society** or for present or future patients with a particular illness.
- An answer to the research question should be important or valuable enough to **justify asking people to accept some risk** or inconvenience for others.
- In other words, answers to the research question should contribute to scientific understanding of health or **improve our ways of preventing, treating, or caring for people with a given disease**. Only if society will gain useful knowledge — which requires sharing results, both negative and positive — can exposing human subjects to the risk and burden of research be justified.

2. Scientific validity

- A study should be designed in a way that will get an understandable answer to the **valuable research question**.
- This includes considering whether the question researchers are asking is answerable, whether the research methods are **valid and feasible**, and whether the study is designed with a clear scientific objective and using accepted principles, methods, and reliable practices.
- It is also important that **statistical plans** be of sufficient power to definitively test the objective, for example, and for data analysis. Invalid research is unethical because it is a waste of resources and exposes people to risk for no purpose

3. Fair subject selection

- Who does the study need to include, to answer the question it is asking?
- The primary basis for recruiting and enrolling groups and individuals should be the scientific goals of the study — not vulnerability, privilege, or other factors unrelated to the purposes of the study. Consistent with the scientific purpose, people should be chosen in a way that minimizes risks and enhances benefits to individuals and society. Groups and individuals who accept the risks and burdens of research should be in a position to enjoy its benefits, and those who may benefit should share some of the risks and burdens. Specific groups or individuals (for example, women or children) should not be excluded from the opportunity to participate in

4. Favorable risk-benefit ratio

- Uncertainty about the degree of risks and benefits associated with a drug, device, or procedure being tested is inherent in clinical research — otherwise there would be little point to doing the research.
- And by definition, there is more uncertainty about risks and benefits in early-phase research than in later research.
- Depending on the particulars of a study, research risks might be trivial or serious, might cause transient discomfort or long-term changes.
- **Risks** can be **physical** (death, disability, infection), **psychological** (depression, anxiety), **economic** (job loss), or **social** (for example, discrimination or stigma from participating in a certain trial).
- Has everything been done to minimize the risks and inconvenience to research subjects, to maximize the potential benefits, and to determine that the potential benefits to individuals and society are proportionate to, or outweigh, the risks?
- Research volunteers often receive some health services and benefits in the course of participating, yet the purpose of clinical research is not to provide health services.

5. Independent review

- To minimize potential conflicts of interest and make sure a study is ethically acceptable before it even starts, an independent review panel with no vested interest in the particular study should review the proposal and ask important questions, including: Are those conducting the trial sufficiently free of bias?
- Is the study doing all it can to protect research volunteers?
- Has the trial been ethically designed and is the risk–benefit ratio favorable? In the United States, independent evaluation of research projects is done through granting agencies, local institutional review boards (IRBs), and data and safety monitoring boards. These groups also monitor a study while it is ongoing.

6. Informed consent

- For research to be ethical, most agree that individuals should make their own decision about whether they want to participate or continue participating in research.
- This is done through a process of informed consent in which individuals (1) are accurately informed of the purpose, methods, risks, benefits, and alternatives to the research, (2) understand this information and how it relates to their own clinical situation or interests, and (3) make a voluntary decision about whether to participate.
- There are exceptions to the need for informed consent from the individual — for example, in the case of a child, of an adult with severe Alzheimer's, of an adult unconscious by head trauma, or of someone with limited mental capacity. Ensuring that the individual's research participation is consistent with his or her values and interests usually entails empowering a proxy decision maker to decide about participation, usually based on what research decision the subject would have made, if doing so were possible.

7. Respect for potential and enrolled subjects

- Individuals should be treated with respect from the time they are approached for possible participation—even if they refuse enrollment in a study—throughout their participation and after their participation ends.

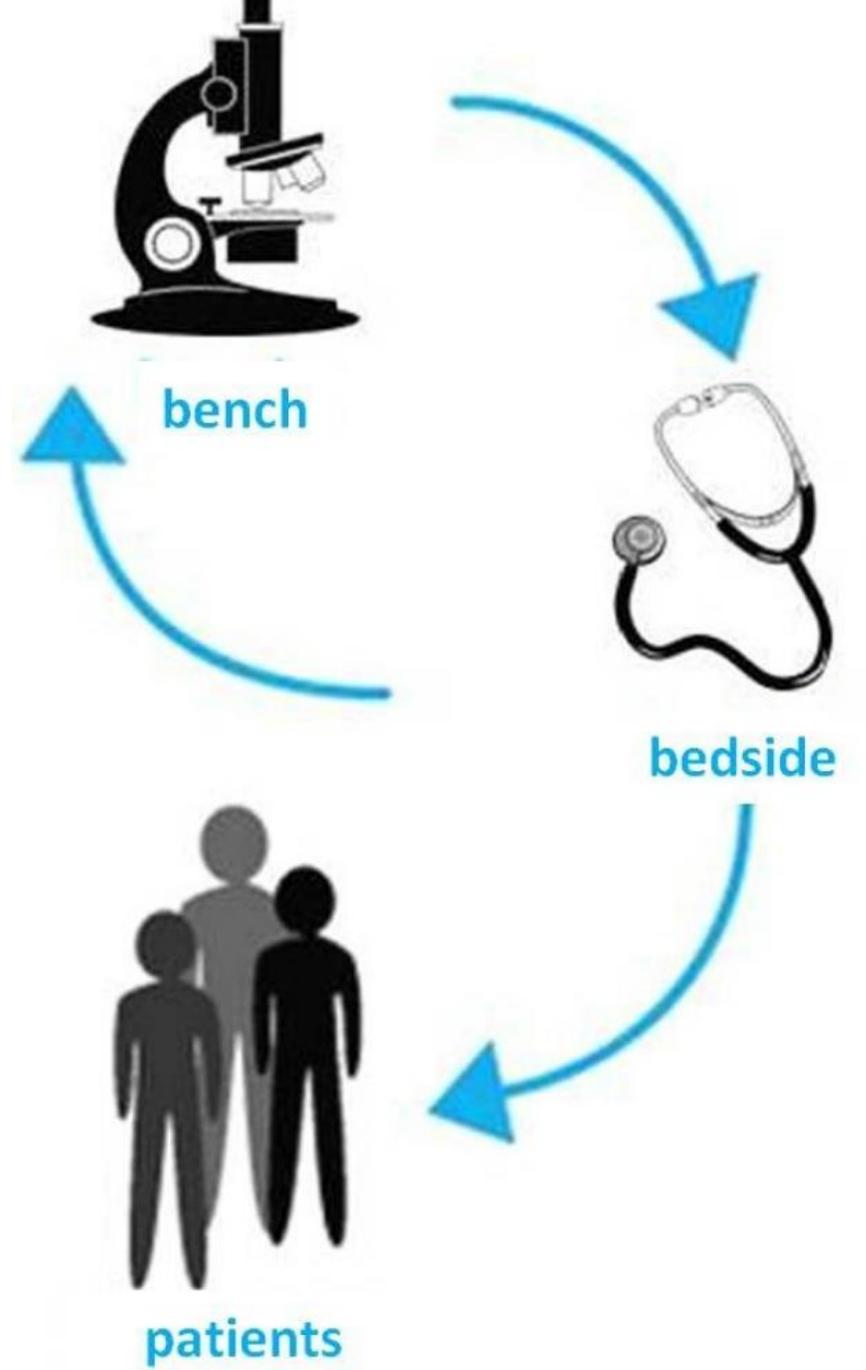
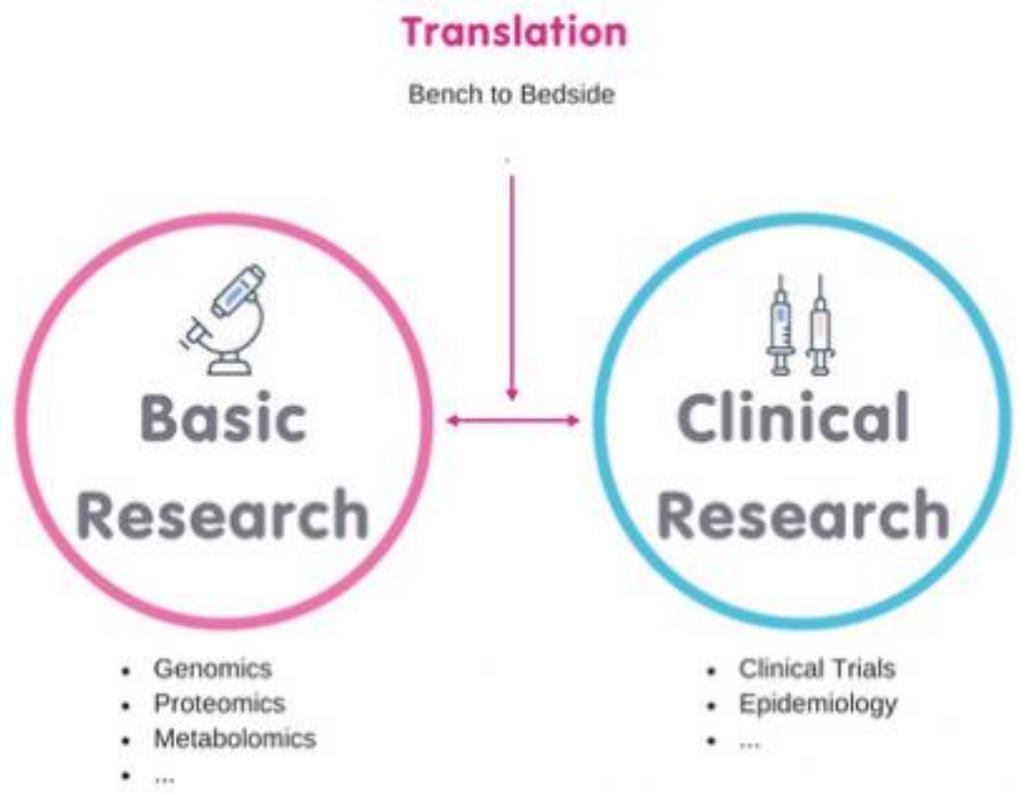
This includes:

- Respecting their privacy and keeping their private information confidential.
- Respecting their right to change their mind, to decide that the research does not match their interests, and to withdraw without penalty.
- Informing them of new information that might emerge in the course of research, which might change their assessment of the risks and benefits of participating.
- Monitoring their welfare and, if they experience adverse reactions, untoward events, or changes in clinical status, ensuring appropriate treatment and, when necessary, removal from the study.
- Informing them about what was learned from the research. Most researchers do a good job of monitoring the volunteers' welfare and making sure they are okay. They are not always so good about distributing the study results. If they don't tell you, ask

Other Essential components

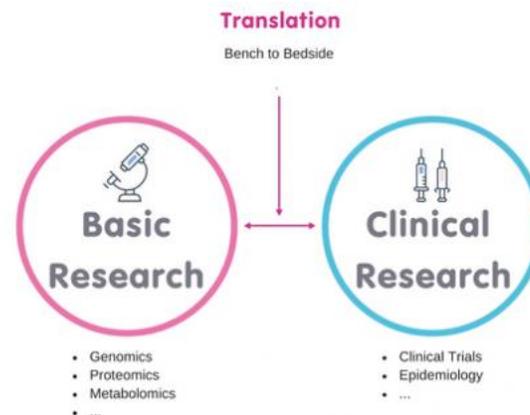
- support trials investigating high priority questions
- avoid needlessly duplicating previously conducted trials
- exercise proper stewardship over precious public resources, in part by developing and maintaining robust data about the trials we support
- respect ethical obligations to participants who give their time and sometimes put themselves at risk for the sake of advancing science
- promote broad, transparent, timely, and responsible dissemination of information from NIH-funded clinical trials

From Bench to Bedside and Back Again



Translational Research – Bench to Bedside

- **Translational research** is the process of applying knowledge from basic biology and clinical trials to techniques and tools that address critical medical needs. Unlike applied sciences, **translational research** is specifically designed to improve health outcomes.



1) Translational Research Requires Biospecimens

- Collecting Biospecimens is critical for translational research and advancing knowledge at the molecular level and leads to increased treatment options and biomarkers
- The only way this field can progress is through the generosity of individuals who donate their specimens for research purposes

Patients on clinical trials are likely to donate tissue if asked

- Eastern Cooperative Group (ECOG) found an average consent rate of 88% when an optional request for biologic specimens was made to 30,496 patients participating on an ECOG trial between November 2000 and August 2008.
- Consent rate varied by disease type and ranged from 63%-93.8%.
- Most frequent consenters are patients with leukemia (93.8%), breast cancer (93.5%), GI cancers (91%).
- Less frequent consenters are patients with thoracic cancer (75.7%), multiple myeloma (75%) and those in prevention trials (63%).

Consider the following if you were donating a sample or participating in a clinical trial:

- Would you want to know what was done to your sample?
- Would you want to know if your sample helped the research study?
- Do you want to know what the results of the research are?
- What was learned from use of your sample and/or participation?
- Was it used efficiently?
- Did something happen to it?
- Shouldn't you have the right to know if you so choose?

Research lacks transparency!!!

Informed consent

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- This is done through a process of informed consent in which individuals (1) are accurately informed of the purpose, methods, risks, benefits, and alternatives to the research, (2) understand this information and how it relates to their own clinical situation or interests, and (3) make a voluntary decision about whether to participate.

Consent Forms do not permit/require sharing of data with study participants

Genetic Research

“You are being asked to participate in genetic research. Results of this genetic research will not be used in your medical care. **The results will not be given to you, the study doctor, or your personal doctor**”.



THE BENCH WITH BEDSIDE INITIATIVE™

EMPOWERING WITH KNOWLEDGE, HOPE, AND TRANSPARENCY

An unconventional collaborative approach between scientists and patients

“Lab to Life”

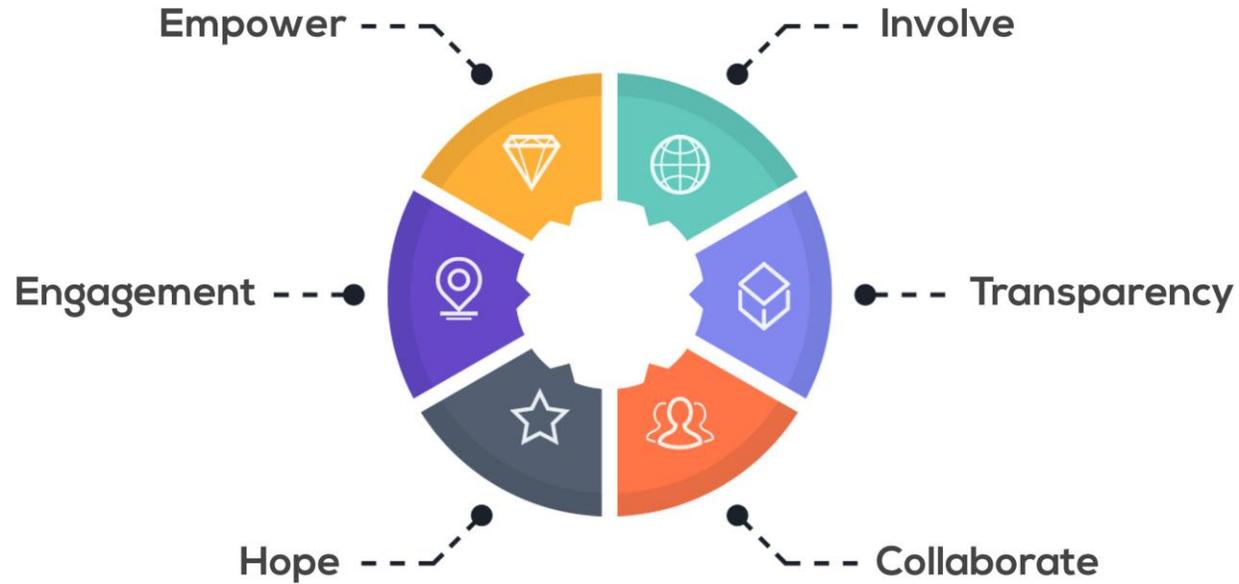
<https://thebenchwithbedsideinitiative.usc.edu/>

The Bench with Bedside Initiative is a
Trans-relational Approach to Translational
Research

Trans-Relational Research: Bench with Bedside

- A new research model whereby the researcher at the Bench **collaborates with** the patient at the Bedside.
- Augment patient/researcher relationship
- Increase the transparency and accountability of research by providing patients with research results
- Send a strong message of hope to patients
- Conduct a highly translational research project where all stakeholders speak into it
- Increase participation across underrepresented (not just minorities) populations

Benefits of The Bench with Bedside Initiative™



- Mutual learning
- Mutual empathy
- Humanizing research
- Augment Patient/Researcher relationship



The Bench with Bedside Initiative fills a big gap in patient research involvement

- Researchers rarely interact with research participants outside of scheduled events
- Lack of transparency in research
- Patient and public engagement in science usually predominates at the beginning of a study or at major milestones
- As mandated by consent forms and IRBs, most patients never learn of the fate of their sample and most researchers never learn who the patient is or what happens to them
- Patients are recruited in clinics by physicians
- Under-enrollment for people of color

Diverging Engagement



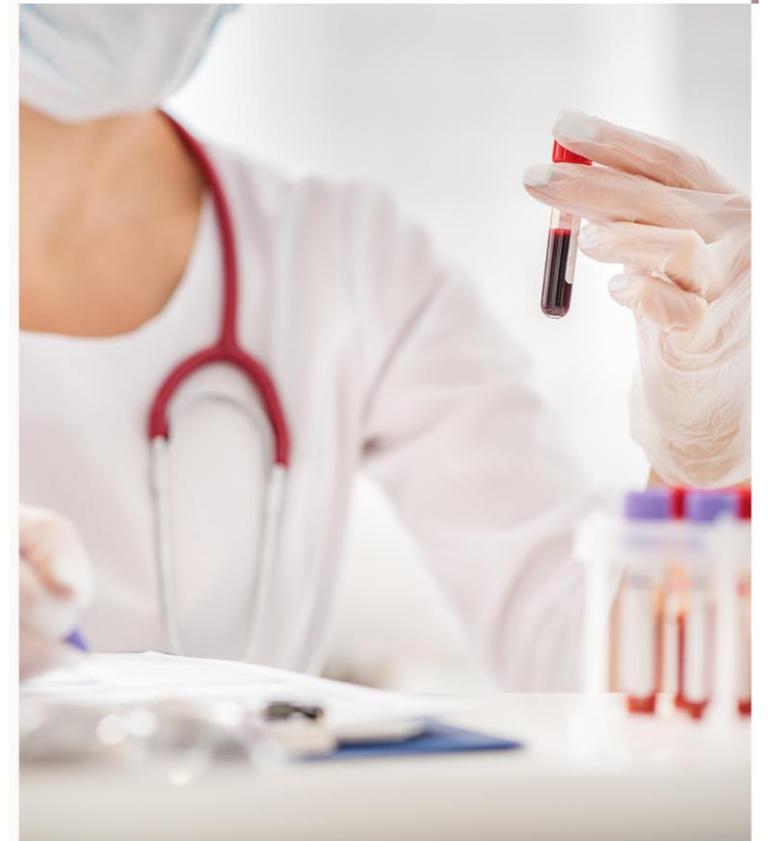
Converging Engagement



Better Biomarkers to Predict Breast Cancer Recurrence

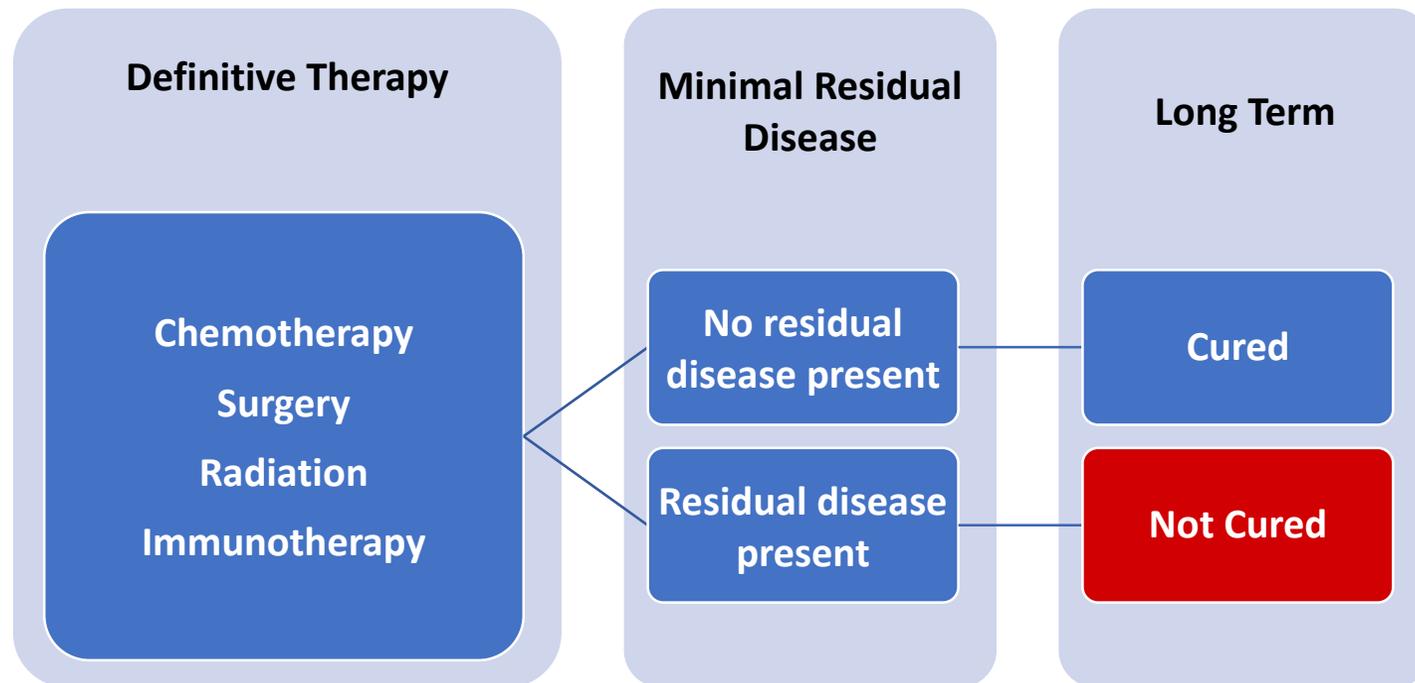
WE NEED SENSITIVE AND AFFORDABLE SCREENING STRATEGIES TO IDENTIFY PATIENTS AT HIGH-RISK OF DEVELOPING LETHAL MBC BEFORE IT OCCURS.

- At end of therapy
- Early stage breast cancer
- Cell-free DNA methylation

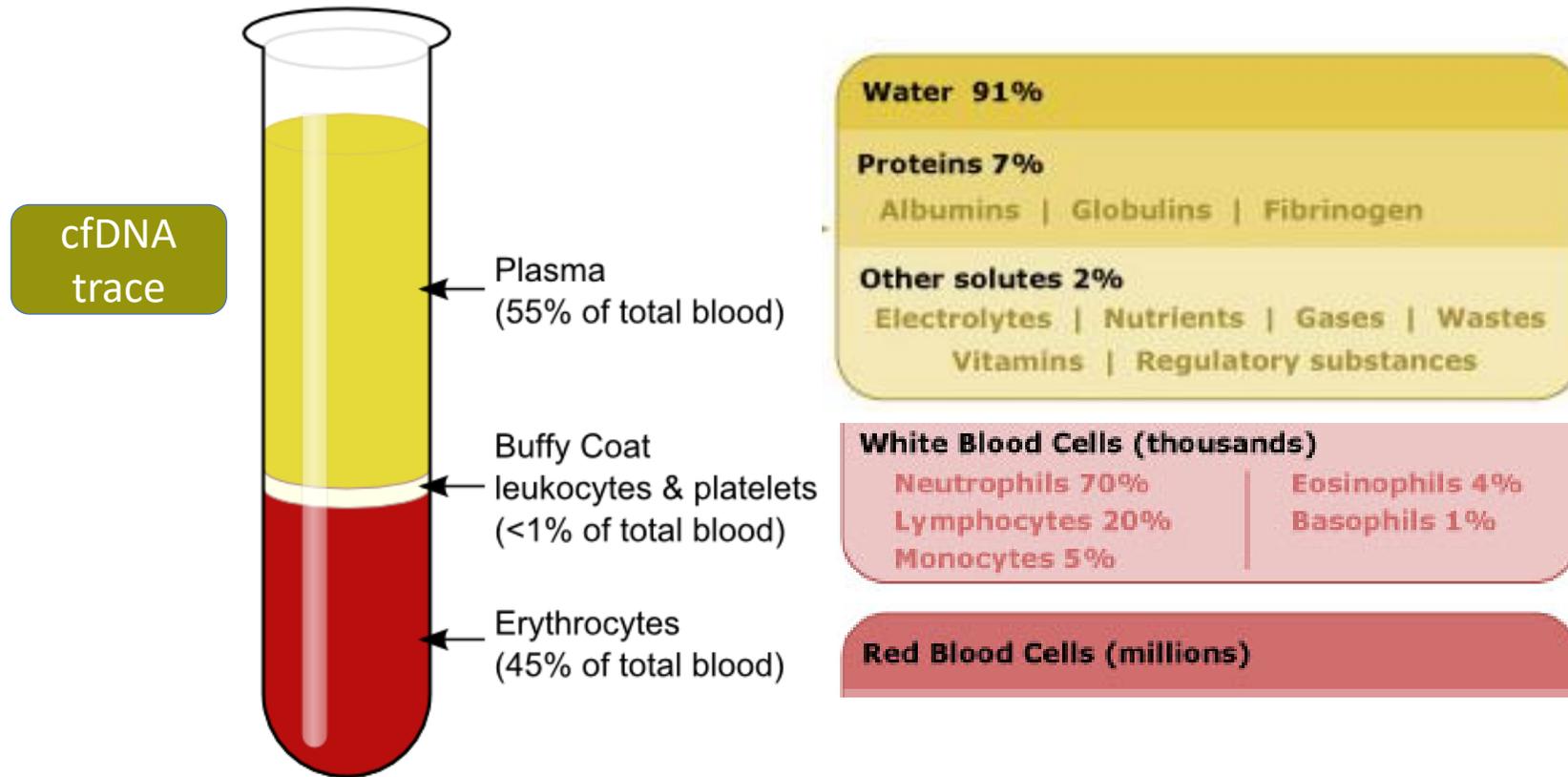


Early detection has *not eliminated* mortality due to breast cancer

- >90% of breast cancer associated mortality is due to recurrence in a distant site
- Imaging is not detecting aggressive forms of breast cancer which can occur years after initial diagnosis
- Current criteria to classify patients as high-risk are relatively crude and rely on tissue at a single time point (HR status, Her2 status, stage, grade, LN status, Oncotype DX score)



Liquid Biopsy using cell-free DNA



Applications of ctDNA in the clinical management of cancer



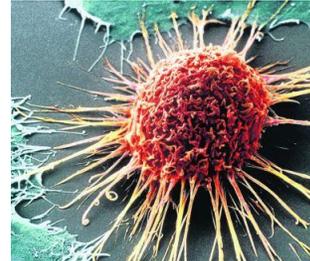
Early Detection



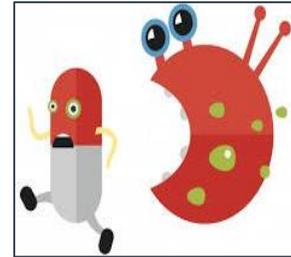
Diagnosis,
Prognosis



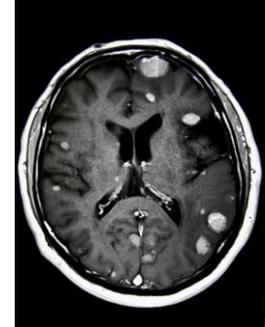
Therapy



**Minimal
Residual Disease**

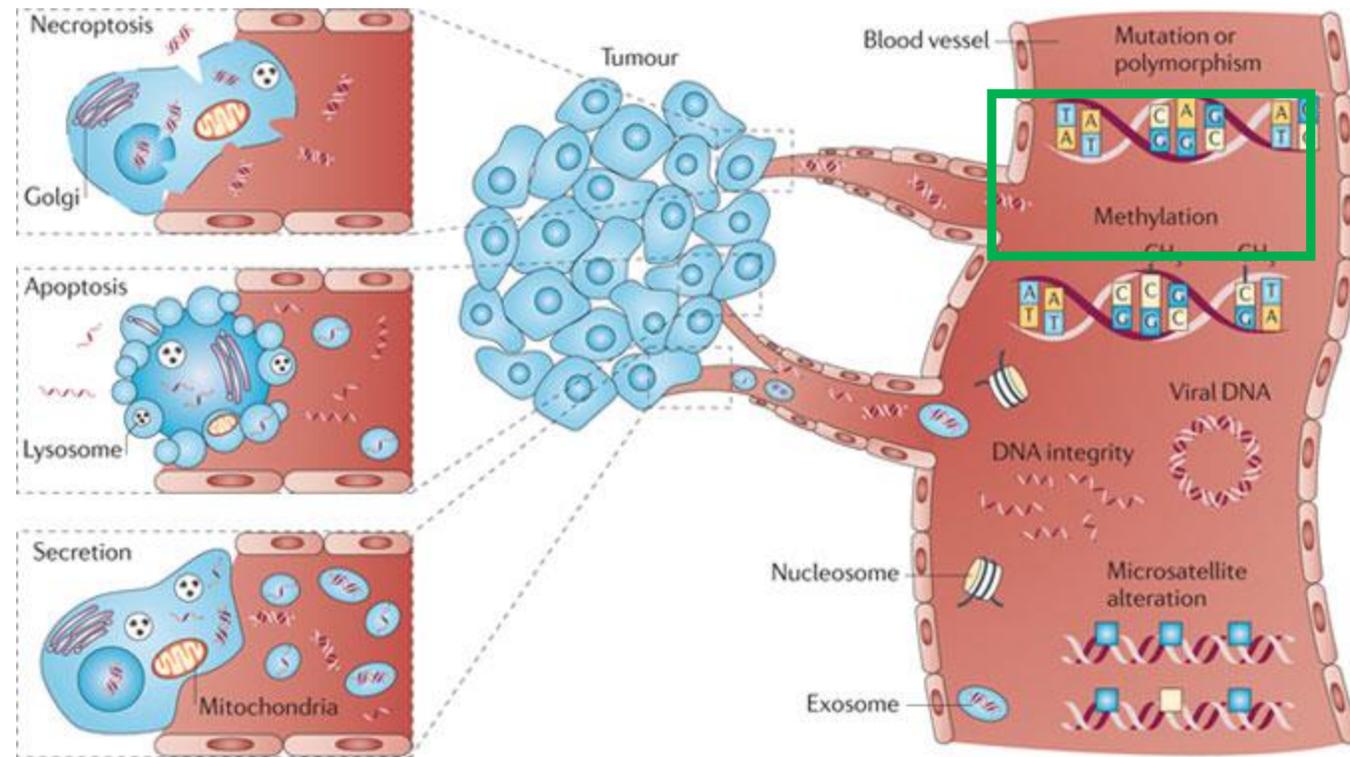


Resistance



Relapse

Circulating tumor DNA harbors genetic and epigenetic tumor changes



Central Hypothesis

Detection of **micrometastatic residual disease**

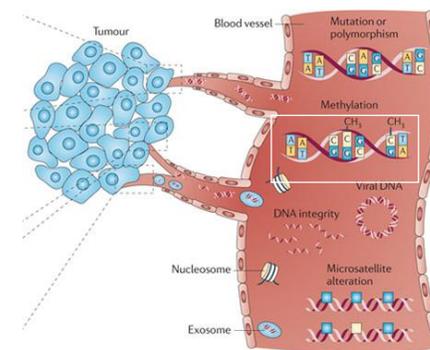


Predicts **macrometastasis**



Precision stratification of **high-risk BC** in pre-metastatic setting

- Sensitive and specific biomarker
- Non-invasive approaches (multiple time points)



cfDNA methylation



"LAB TO LIFE"

BREAST CANCER SURVIVORS

Donate Blood to Help
Advance Research

WE NEED 500 SURVIVORS:
See if you are eligible to donate blood and
join our team by taking the survey at
thebenchwithbedsideinitiative.usc.edu

November 16, 2019
9:00AM - 1:00PM

**USC Norris Comprehensive
Cancer Center and Hospital**
1450 Biggy Street, Los Angeles, CA 90089

RESEARCH PURPOSE:
To develop better and more robust
screening strategies so we can predict
which women will develop a
recurrence of breast cancer.
Check back for other dates and locations

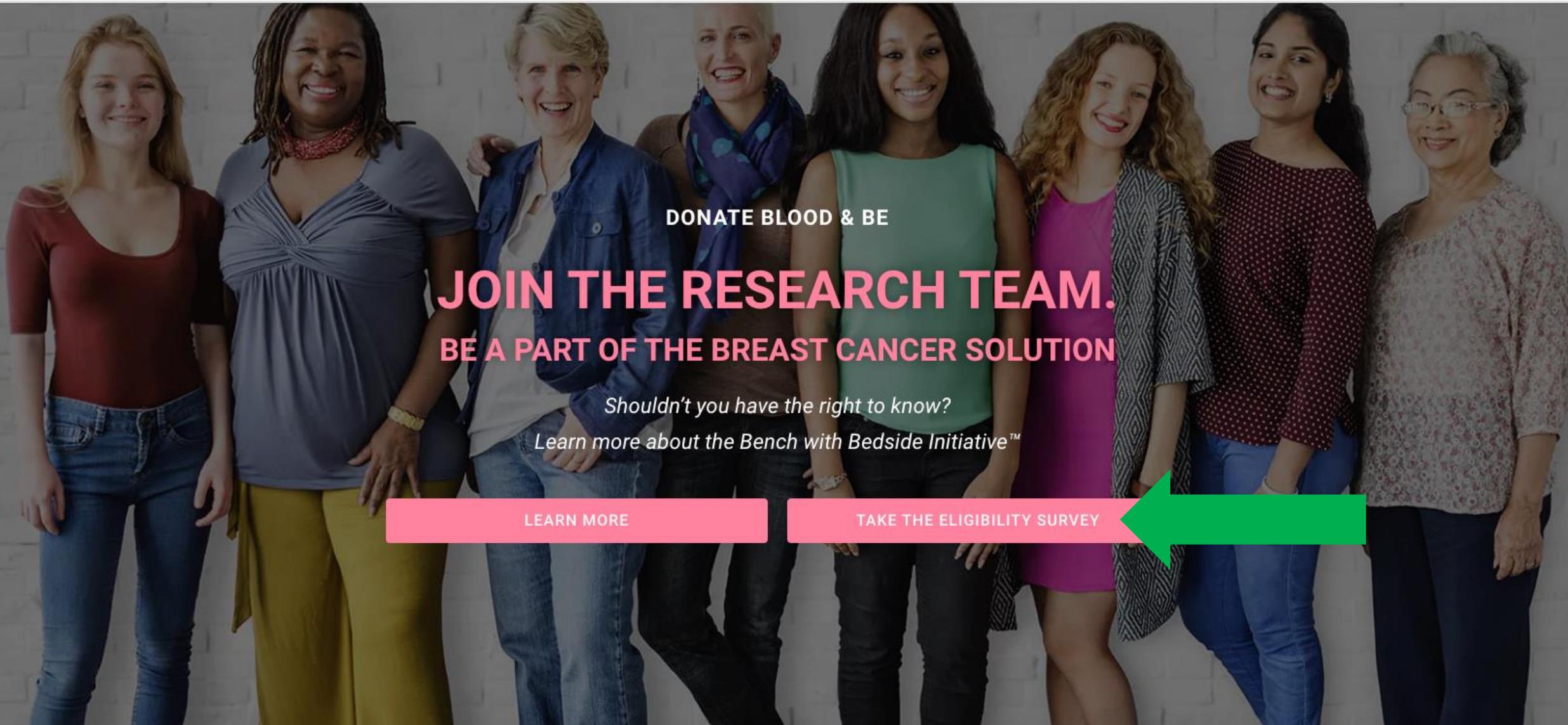
Keck School of
Medicine of **USC**



USC University of
Southern California

USC Norris Comprehensive Cancer Center
Keck Medicine of **USC**

<https://thebenchwithbedsideinitiative.usc.edu/>



DONATE BLOOD & BE

JOIN THE RESEARCH TEAM. BE A PART OF THE BREAST CANCER SOLUTION

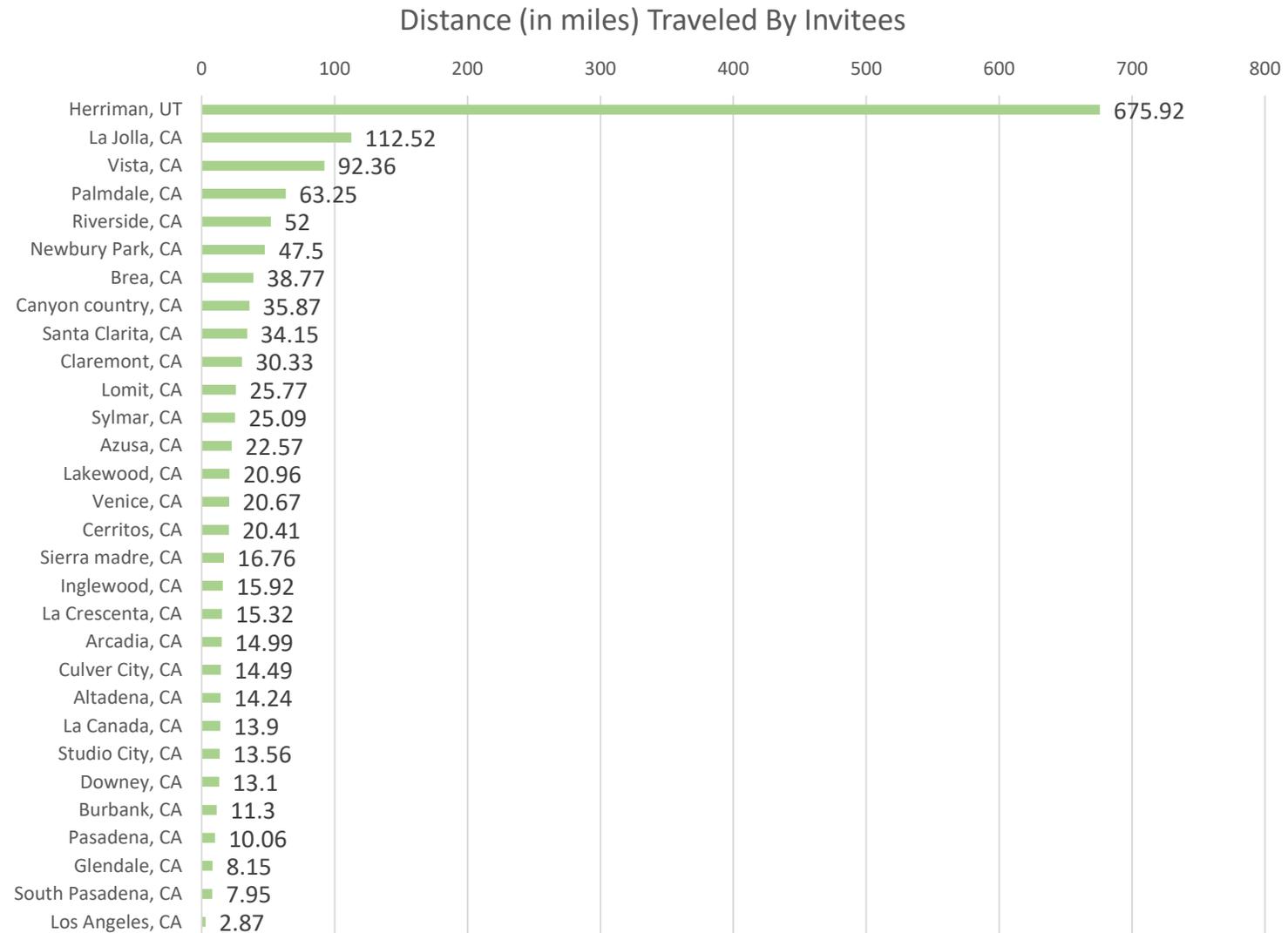
*Shouldn't you have the right to know?
Learn more about the Bench with Bedside Initiative™*

[LEARN MORE](#)

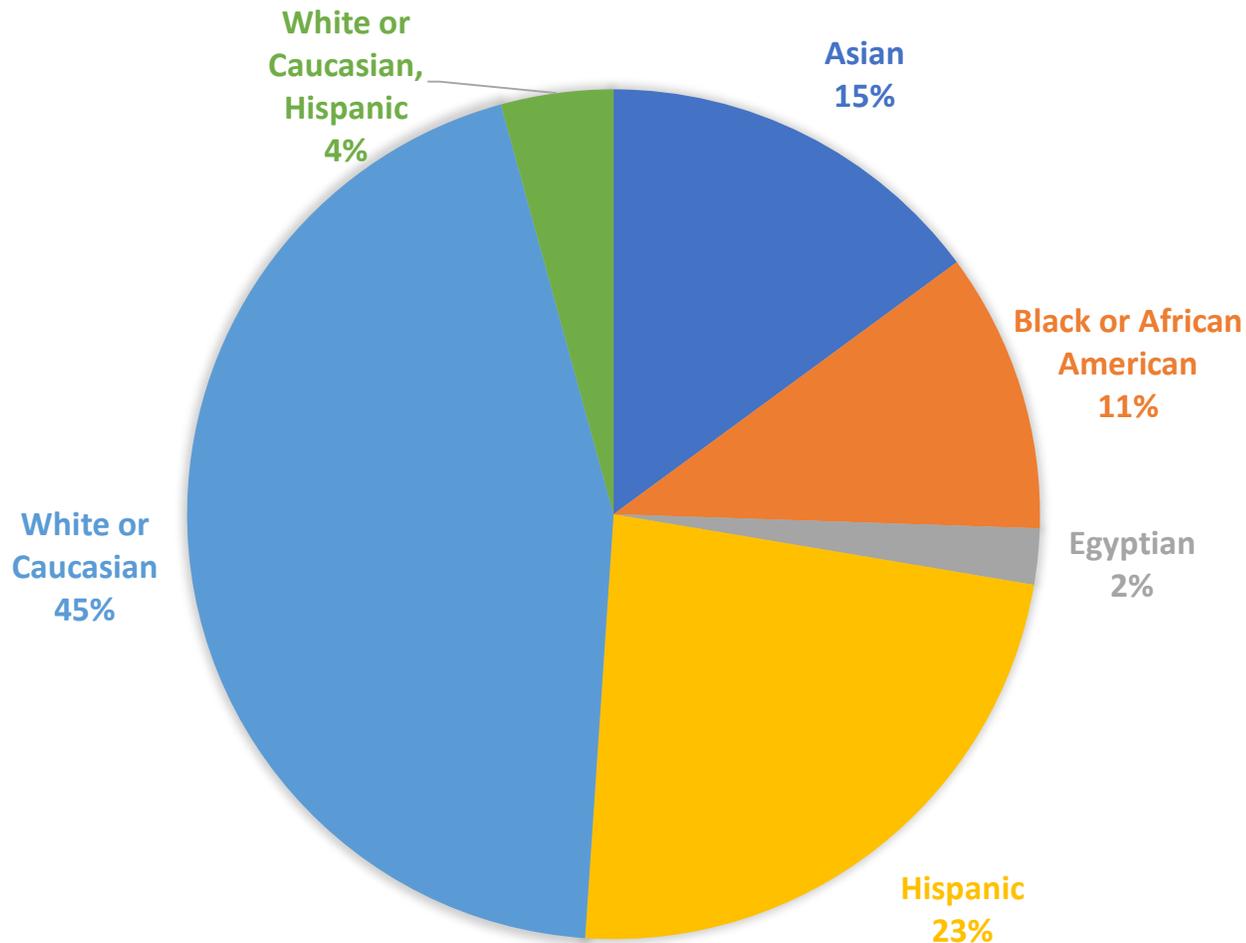
[TAKE THE ELIGIBILITY SURVEY](#)



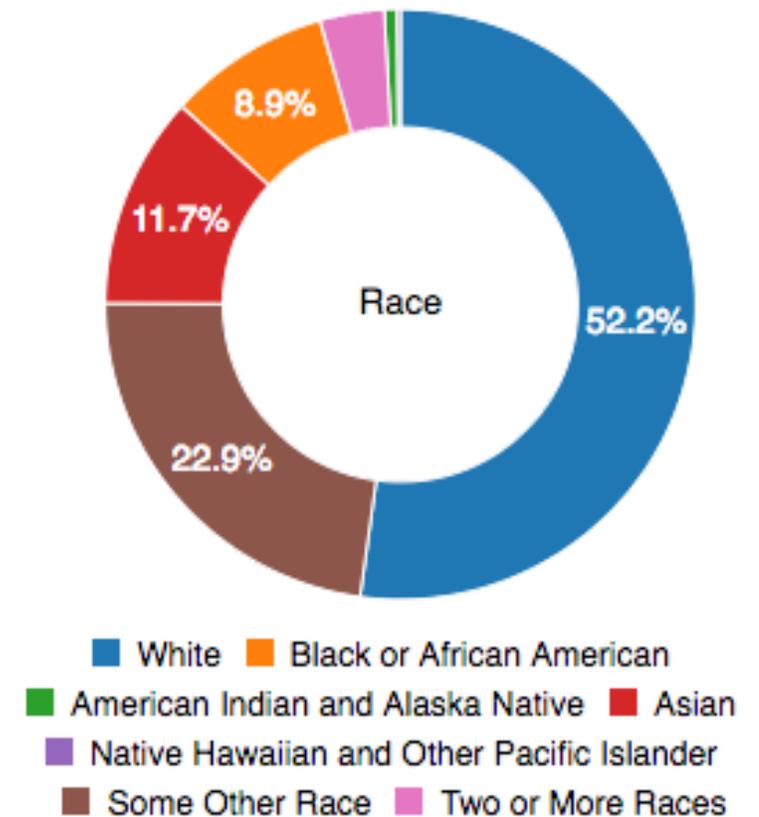
They came from near and far



Participants represented Los Angeles County Racial Demographics



Los Angeles Population by Race











Acknowledgments

- Sharon Schlesinger
- Salhia Lab (Gerald Gooden, Ben Yi Tew, David Buckley)
- Susan G. Komen (LA and Orange County Affiliates)
- Keck School of Medicine
- Keck Medicine
- Department of Translational Genomics
- SC Clinical and Translational Science Institute
- Kaufman/Levine Seed Grant
- NCI 1R01CA201352
- Illumina Inc.
- Nugen Inc
- **All the Patient Collaborators**

