LUPUS RESEARCH PROGRAM

WHAT IS THE PROGRAM'S CONGRESSIONAL INTENT?

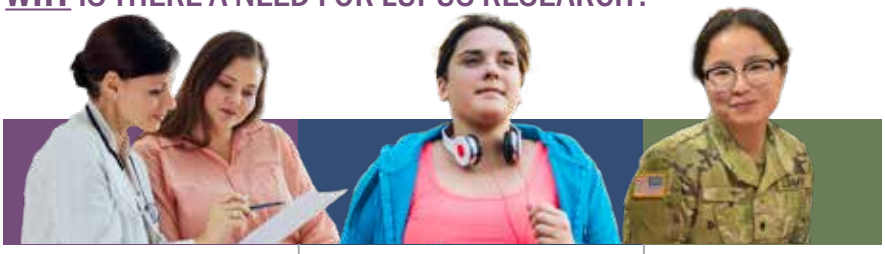
Established in 2017, the Lupus Research Program (LRP) supports innovative, high-risk, high-reward studies that offer the promise of shifting current paradigms with the hope of improving treatments and quality of life.

FY22 Congressional Appropriations	
$10M	
FY22 Research Investment	
Idea Award	$1,198,883
Impact Award	$5,249,969
Transformative Vision Award	$2,499,628
Total:	$8,948,480
FY22 Withholds and Management Costs	
USAMRDC	$150,000
SBIR/STTR	$334,000
Mgt Costs (5.96%)	$567,520
Total:	$1,051,520

"Participating in the first-ever Lupus Research Program for the DOD proved not only exhilarating but hopeful. What I came away with is that there is reason to believe that the 'cruel mystery' of lupus will be solved, and that by research, this devastating disease will no longer be misunderstood. Though irreversible lupus damage plagues my own life, I am immeasurably grateful to help our younger community look forward to quick diagnosis, appropriate medications, quality of life, a longer life expectancy, and maybe even the cure."

Kyra Miller, Lupus Foundation of America, Consumer Peer Reviewer, FY17 and FY19

WHY IS THERE A NEED FOR LUPUS RESEARCH?



Between ~161,000 to 1.5 million Americans are estimated to be living with lupus[1]

Lupus affects women at a rate ~10 times higher than men and is the 11th leading cause of death in females ages 25-44[2]

Similarly, female Service Members are 12.3X more likely to develop lupus compared to their male counter-parts[3]

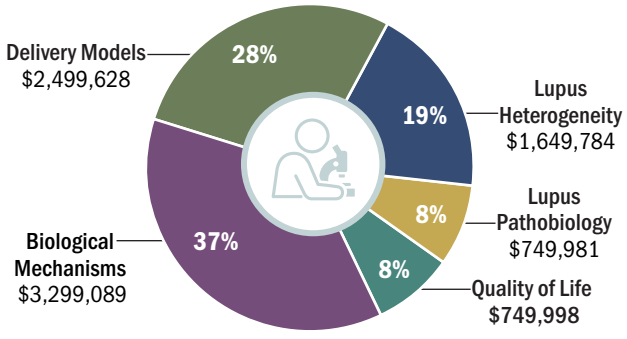
Minorities are at a **2-3X higher risk** of developing lupus[4]

Over a 10-year period within the MHS,[5] lupus medical encounters for Service Members and beneficiaries included:

- **67,372 patients**
- **705,352 out-patient encounters**
- **287,442 hospital bed days**

HOW IS THE PROGRAM ADVANCING LUPUS RESEARCH?

The LRP directed FY22 investments into 10 focus areas.



[1] Sharif, Abdullah. 2021. New CDC Study Estimates 204,295 Americans Have Lupus - Lupus Research. *Lupus Research*. www.lupusresearch.org/new-cdc-study-estimates-204295-americans-have-lupus/. | [2] Yen E and Singh R. 2018. Brief Report: Lupus – An Unrecognized Leading Cause of Death in Young Females: A Population-Based Study Using Nationwide Death Certificates, 2000-2015. *Arthritis & Rheumatology* 70(8):1251-1255. https://doi.org/10.1002/art.40512. | [3] Denagamage P, Mabila S, McQuistan AA. 2023. Trends and Disparities in Systemic Lupus Erythematosus Incidence Among U.S. Active Component Service Members, 2000-2022. *Medical Surveillance Monthly Report* 30(12):2-5. | [4] Advancing Health Equity in Lupus. 2023. Lupus Foundation of America. | [5] Military Health System (MHS) Data from the Defense Medical Surveillance System, 2009-2018. 2020. The Armed Forces Health Surveillance Division, Defense Health Agency (DHA).

PROGRAM MISSION: *Fund research to understand, prevent, and diagnose lupus and to improve treatments and quality of life of patients, including Service Members, Veterans, and beneficiaries*

HOW IS THE PROGRAM MAKING AN IMPACT?

Machine Learning-Based Algorithms

Machine Learning to Quantify Adaptive Immunity for the Treatment of Lupus Nephritis

Marcus Clark, M.D., The University of Chicago

Dr. Clark and his team developed **machine learning-based algorithms for characterizing the immune response** observed in lupus nephritis from images of kidney tissue samples.[6] After acquiring high-resolution images of cells, the team trained a machine learning neural network, known as Cell Distance Mapping 4, to accurately identify complex cell features and classify cells by type. Clark found specific **inflammatory markers within the kidneys associated with the progression towards end-stage renal disease and renal failure** that showed promise for **better predictors of progressive renal disease** and **potential new therapeutic targets**.

Precision Medicine

Multi-Ancestral Genomic Approach to Precision Medicine

Carl Langefeld, Ph.D., Wake Forest University Health Sciences

Epigenetic modifications to DNA, such as the addition of a methyl group onto DNA bases, can alter gene expression without changing the sequence of DNA. Langefeld and his team are investigating **epigenetic risk factors** for lupus to identify pathogenic mechanisms and therapeutics to target and treat the disease. Examining **genomic DNA from three pairs of female identical twins discordant for lupus**,[7] meaning only one twin is diagnosed with the disease, the researchers identified **59 areas of differentially methylated DNA** between the unaffected and affected twins, including 11 novel locations, representing potential risk factors for the disease. Analysis of these identified areas and FDA-approved drugs predicted interaction with 41 drugs, including one known lupus therapy. The team's findings **strongly suggest there are opportunities to repurpose already FDA-approved drugs as treatments** for lupus.

Female-Biased Lupus Disease

Role for Abnormal Gene Expression from the Inactive X in Female-Biased Lupus Disease

Montserrat C. Anguera, Ph.D., University of Pennsylvania

To prevent overexpression of certain genes, one X-chromosome is naturally silenced, or turned off, in those with two X-chromosomes, a process called X-chromosome inactivation. Anguera and her team explored how this inactivation is maintained within the silenced X-chromosome to **better understand the connection between sex and autoimmune disease** in lupus. The team used an **innovative single-cell profiling technology** to examine the genetic information of individual immune cells and detected high levels of impaired X-chromosome inactivation in B-cells, a type of white blood cell. Many genes that escaped X-chromosome inactivation in B-cells were immune regulatory genes, suggesting **nontypical gene silencing could lead to increased immune system activation in individuals with this disease,** and could explain a reason for **higher rates of autoimmune diseases, such as lupus, in women**. The team also assessed the impact of age on X-chromosome inactivation. In a recent publication,[8] the team reported genetic patterns correlated to patient age, but not necessarily to disease activity, indicating many of the genes affected by X-chromosome inactivation remain present despite disease remission.

[6] Abraham R, Durkee MS, et al. 2022. Specific In Situ Inflammatory States Associate with Progression to Renal Failure in Lupus Nephritis. *The Journal of Clinical Investigation* 132(13):e155350. https://doi.org/10.1172/JCI155350. | [7] Marion MC, Ramos PS, et al. 2021. Nucleic Acid-Sensing and Interferon-Inducible Pathways Show Differential Methylation in MZ Twins Discordant for Lupus and Overexpression in Independent Lupus Samples: Implications for Pathogenic Mechanism and Drug Targeting. *Genes* 12(12):1898. | [8] Pyfrom S, Paneru B, et al. 2021. The Dynamic Epigenetic Regulation of the Inactive X Chromosome in Healthy Human B Cells Is Dysregulated in Lupus Patients. *Proceedings of the National Academy of Sciences of the United States of America* 118(24):e2024624118. https://doi.org/10.1073/pnas.2024624118.