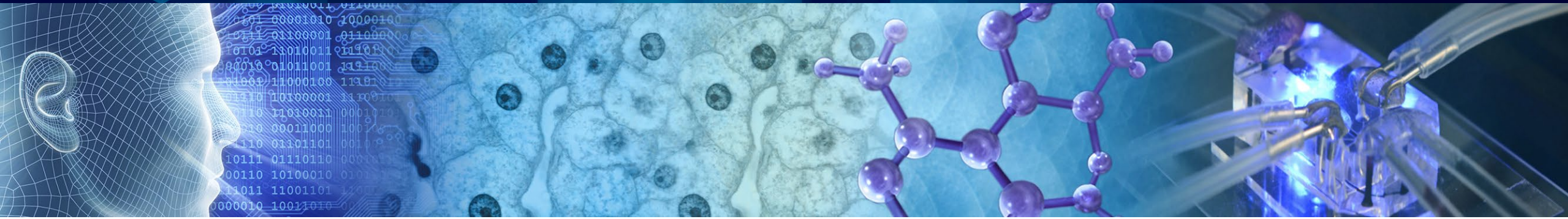
National Institute of Environmental Health Sciences
*Division of Translational Toxicology*



# PROject for Military Exposures and Toxin History Evaluation in US service members (PROMETHEUS)


**Warren Casey, PhD, DABT**

**Director, Strategic Partnerships / NIEHS Division of Translational Toxicology**


**ICCVAM Public Forum, 20 May 2024**



PROMETHEUS
PROject for Military Exposures and Toxin History Evaluation in US servicemembers

# Mission of DTT

The NIEHS Division of Translational Toxicology (DTT) aims to improve public health through the development of data and knowledge that are *translatable, predictive and timely*."

Human Relevant

Impactful

# DTT Strategic Framework


## Strengthening Capabilities Programs

This strategic area of focus aligns with DTT's intent to enhance toxicology toward becoming a more predictive science through the development and application of new technologies and includes the following program areas:

- Novel Tools and Approaches
- Scientific Cyberinfrastructure


## Responsive Research Programs

This strategic area of focus aligns with DTT's intent to respond proactively to public health concerns related to novel environmental exposures and includes the following program areas:

- Emerging Contaminants and Issues of Concern
- Safe and Sustainable Alternatives


## Exposure-based Research Programs

This strategic area of focus aligns with DTT's intent to solve contemporary public health problems related to environmental exposures and includes the following program areas:

- Combined Exposures and Mixtures
- Consumer Products and Therapeutics
- Occupational and Inhalation Exposure


## Health Effects Innovation Programs

This strategic area of focus aligns with DTT's intent to develop disease-focused environmental toxicology and includes the following program areas:

- Carcinogenicity Health Effects Innovation
- Cardiovascular Health Effects Innovation
- Developmental Neurotoxicity Health Effects Innovation

https://www.niehs.nih.gov/research/atniehs/dtt/strategic-plan

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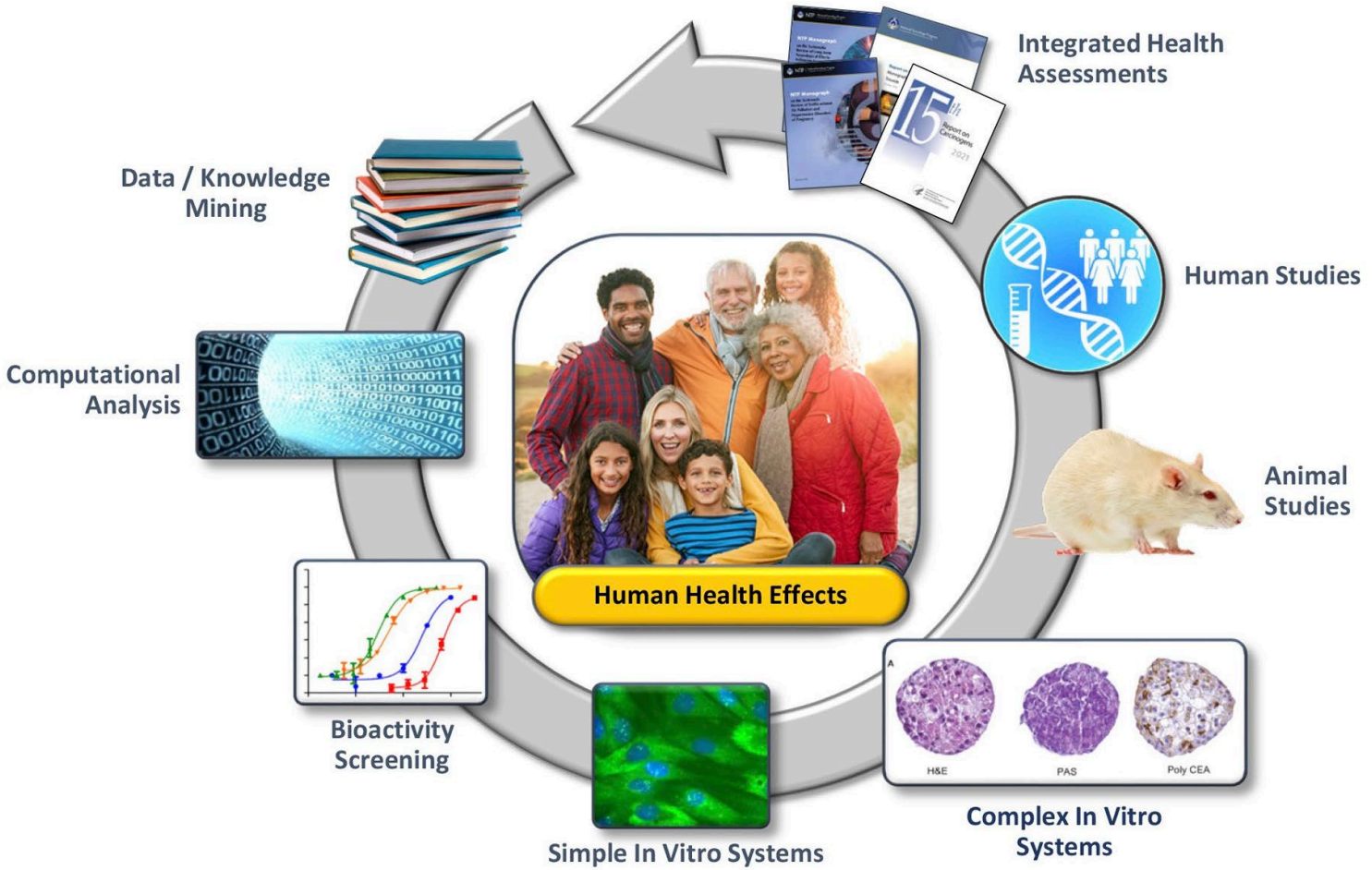
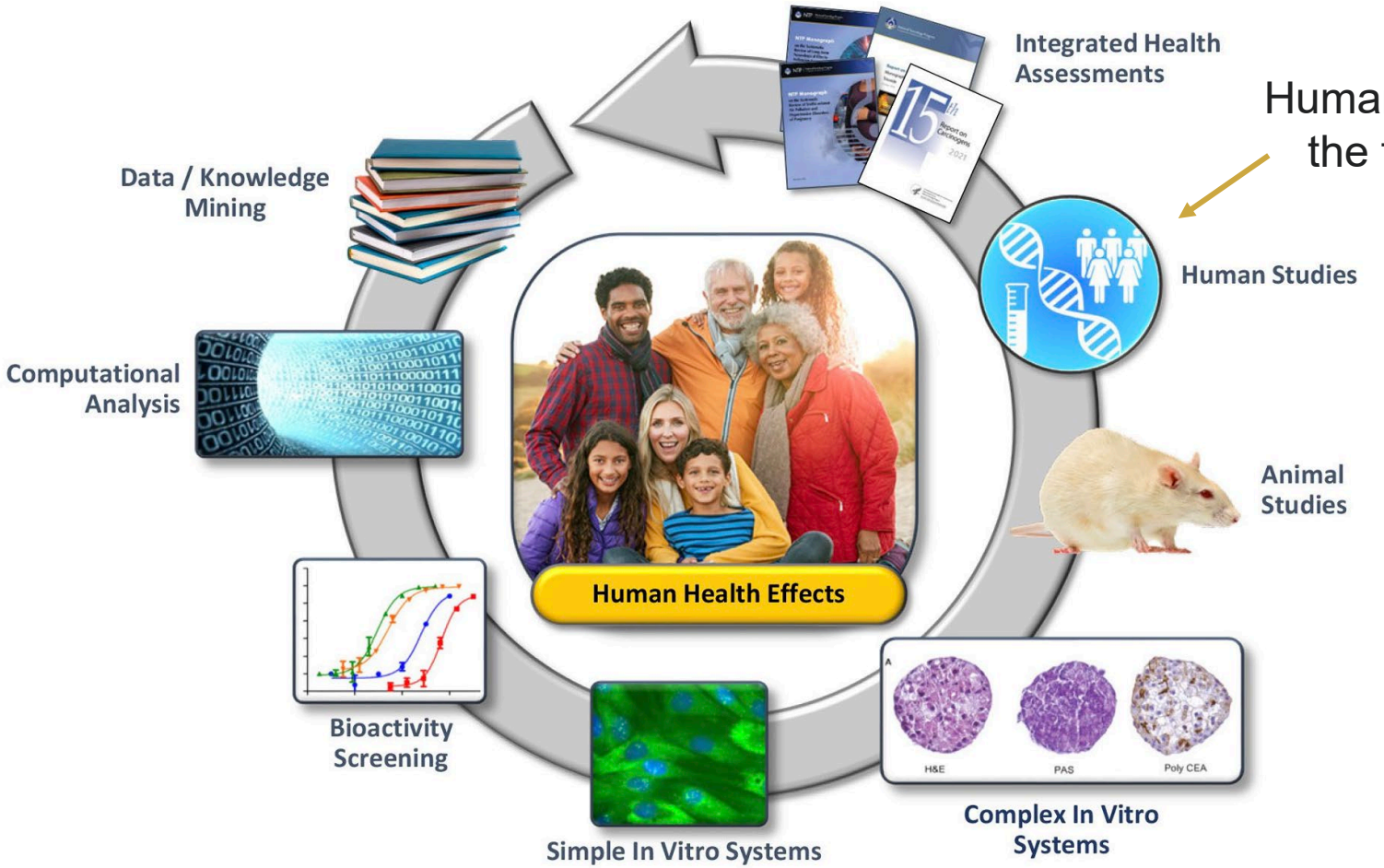
# Translational Toxicology Pipeline

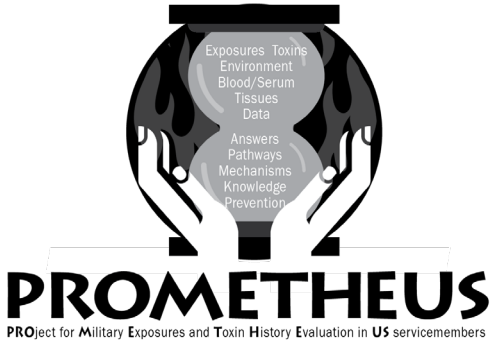


# Translational Toxicology Pipeline




Human-based toxicology is the future of toxicology

# **PRO**ject for **M**ilitary **E**xposures and **T**oxin **H**istory **E**valuation in **U.S**. service members (**PROMETHEUS**)

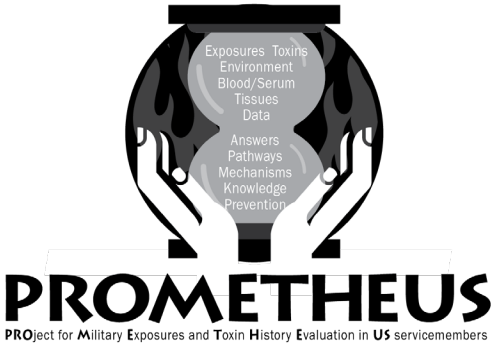



- The PROMETHEUS project was established to bring federal assets together with public-private partners to further study how exposure to toxic chemicals in the environment impact service member's health and future potential for development of conditions such as cancer

- Focused on developing actionable tools for prevention of exposure-related cancer and understanding mechanisms of disease development that may enable early detection or enhanced precision treatments.

https://medschool.usuhs.edu/sur/research/murtha-cancer-center/research

- **2022 Cancer Moonshot 2.0** initiative under the **DoD's Murtha Cancer Center (MCC) Research Program**
  - Monthly updates to Pres. Biden's Cancer Cabinet
  - $47M FY24 Funding from White house




CANCER MOONSHOT

THE WHITE HOUSE

**Progress Of The Cancer Moonshot**

The Cancer Moonshot has spurred tremendous action across the federal government and from the public and private sectors, building a strong foundation for the work ahead. To date, the Cancer Moonshot has announced more than 95 new programs, policies, and resources to address five priority actions. 170 private companies, non-profits, academic institutions, and patient groups have also stepped up with new actions and collaborations.

Expand Access to Cancer Screenings

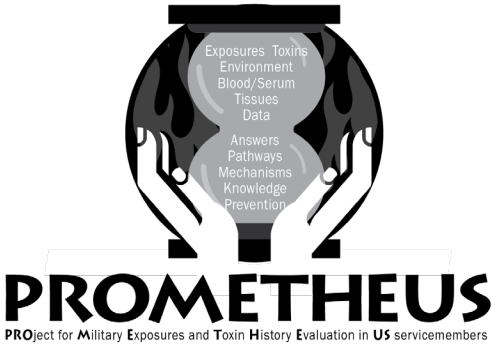
Understand and Prevent Toxic and Environmental Exposures

- $47 million for the Department of Defense (DoD) Murtha Cancer Center to support the tri-agency Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) project and its related research initiatives; and investment in a new DoD program, PROject for Military Exposures and Toxin History Evaluation in U.S. Service Members (PROMETHEUS), to understand and address cancer in exposed service members; and

- **2022 Cancer Moonshot 2.0** initiative under the **DoD's Murtha Cancer Center (MCC) Research Program**

- Responsive to the Sergeant First Class (SFC) Heath Robinson Honoring our **P**romise to **A**ddress **C**omprehensive **T**oxics (**PACT**) **Act of 2022**

PROMETHEUS
PROject for Military Exposures and Toxin History Evaluation in US servicemembers

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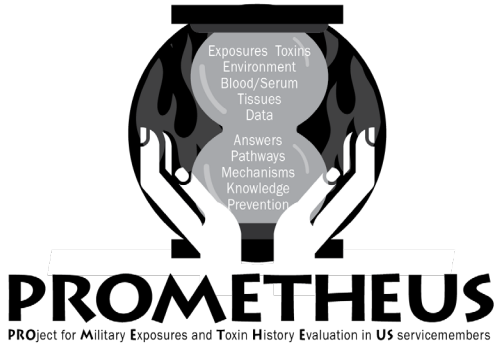
- Responsive to the Sergeant First Class (SFC) Heath Robinson Honoring our **P**romise to **A**ddress **C**omprehensive **T**oxics (**PACT**) **Act of 2022**
- **Umbrella of collaborative efforts between DoD, VA, NIEHS, NCI, and Public/Private Partners** conducting research that integrates retrospective/prospective exposure data, phenotypic data, and biospecimens unique to the DoD & VA, but relevant to civilian exposures as well
    - Over 60 strategically aligned projects

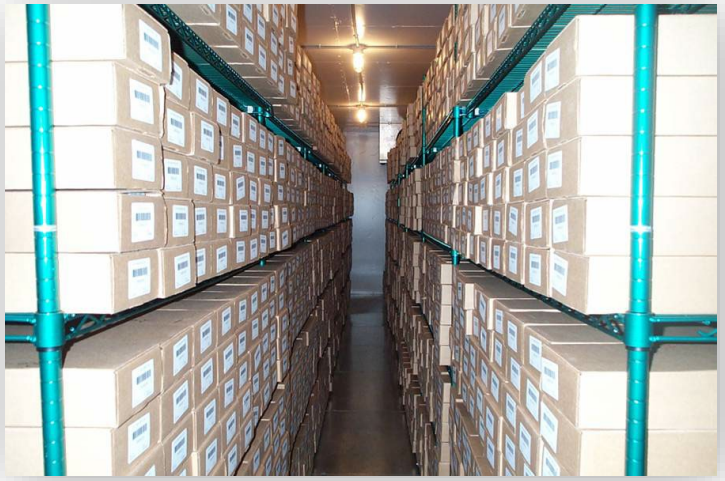
# Resources available to PROMETHES researchers



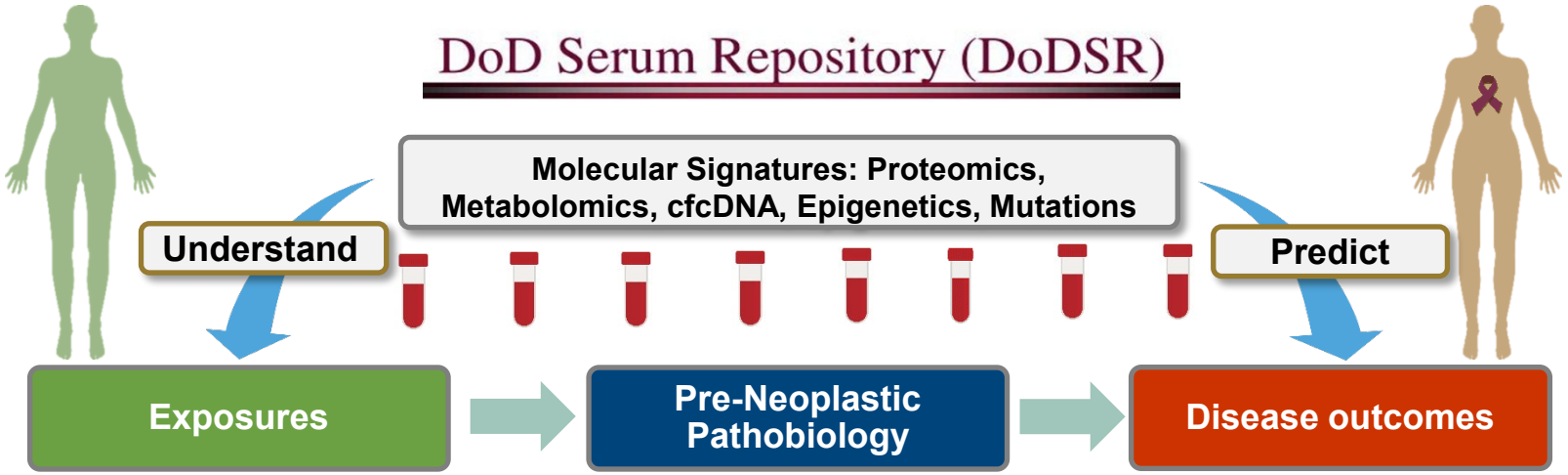
# Resources available to PROMETHES researchers

## Department of Defense Serum Repository (DoDSR)

- Over 70 million serum specimens from over 10 million service members since 1986
- Collected upon entry into service and every two years thereafter, as well as before and after each deployment (since 1996)



# Use of DoDSR Sera to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes

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# Resources available to PROMETHES researchers

## The Individual Longitudinal Exposure Record (ILER)

- Time of deployments
- Locations and events during deployments
- All-hazard occupational data
- Environmental hazards that were known or found later
- Any monitoring performed in the area(s)
- Medical encounter information (e.g., diagnosis, treatment, and laboratory data)
- Medical concerns that should be addressed regarding possible exposures

U.S. Department of Veterans Affairs

## Veteran Military Occupational & Environmental Exposure Assessment Tool (VMOAT)

- A self-report questionnaire that evaluates multiple exposure domains in a comprehensive manner
- organized into environmental exposure categories and is designed to capture pre-military, military, and post-military exposures across a Veteran's lifespan.

# Resources available to PROMETHES researchers

## Military Biomarkers Research Study (MBRS)

- Phase I was a feasibility study of stored sera
- Phase II looked at associations between exposures and biomarkers
- Phase III examined relationships of biomarkers and health outcomes
- Phase IV investigated in vitro biomarker changes associated with exposures to chemicals of interest.

JOEM Journal of Occupational and Environmental Medicine

JOEM V58, No. 85, 2016
JOEM V61, No. 125, 2019

DEPLOYMENT EXPOSURES, BIOMARKERS, AND HEALTH OUTCOMES

**Use of Biomarkers to Assess Environmental Exposures and Health Outcomes in Deployed Troops**

Mallon, Timothy M. MD, MPH; Krahl, Pamela K. MD, MPH; Haines, Kevin M. Jr. MS; Walker, Douglas I. PhD; Thatcher, Thomas PhD; Woeller, Collynn F. PhD; Thakar, Juilee PhD; Hopke, Philip K. PhD; Gaydos, Joel C. MD, MPH; Smith, Mathew Ryan PhD; Uppal, Karan PhD; Go, Young-Mi PhD; Jones, Dean P. PhD; Utell, Mark MD

Author Information

*Journal of Occupational and Environmental Medicine* 61():p S1-S4, December 2019. | *DOI:* 10.1097/JOM.0000000000001752

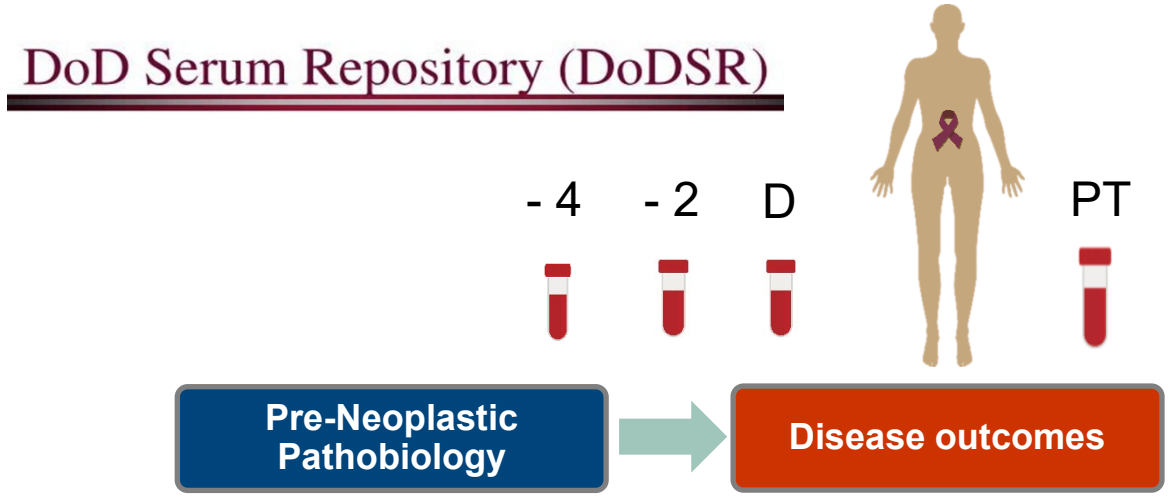
Benzo[a]pyrene Perturbs Mitochondrial and Amino Acid Metabolism in Lung Epithelial Cells and Has Similar Correlations With Metabolic Changes in Human Serum

*Matthew Ryan Smith, PhD, Douglas I. Walker, PhD, Karan Uppal, PhD, Mark J. Utell, MD, Philip K. Hopke, PhD, Timothy M. Mallon, MD, Pamela L. Krahl, MD, Patricia Rohrbeck, DrPH, Young-Mi Go, PhD, and Dean P. Jones, PhD*

JOEM V61, No. 125, S73-81, 2019

# Resources available to PROMETHES researchers

Framingham - a new longitudinal research program to transform our understanding of the biological underpinnings of cancer.



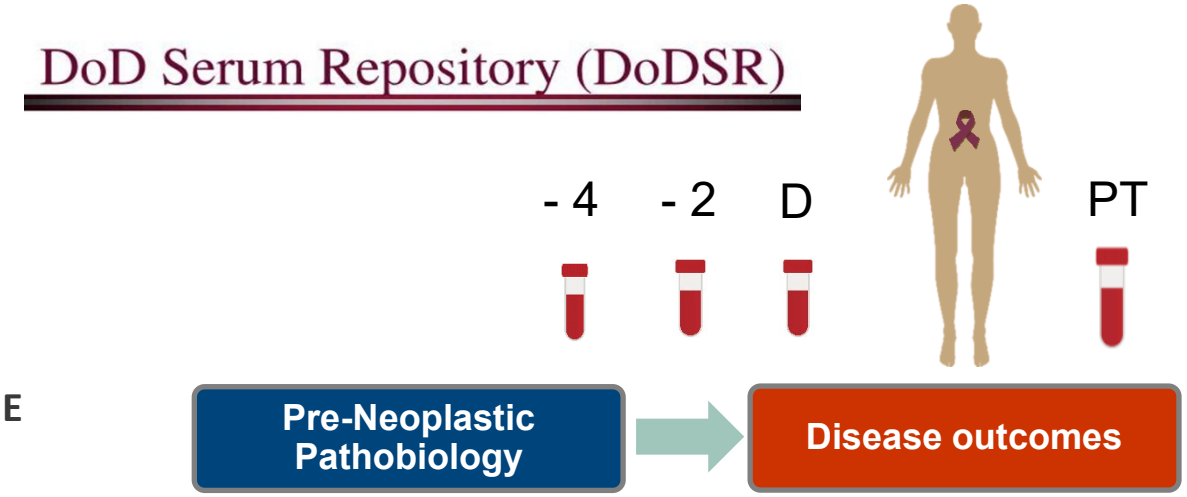

Targeted & Non-Targeted Proteomics

PROMETHEUS
PROject for Military Exposures and Toxin History Evaluation in US servicemembers

# Resources available to PROMETHES researchers

Framingham -

- OROPHARYNGEAL CANCER
- LYMPHOMA
- MELANOMA
- PANCREATIC DUCTAL ADENOCARCINOMA
- METASTATIC CANCER OF ANY TYPE TO BONE




Targeted & Non-Targeted Proteomics

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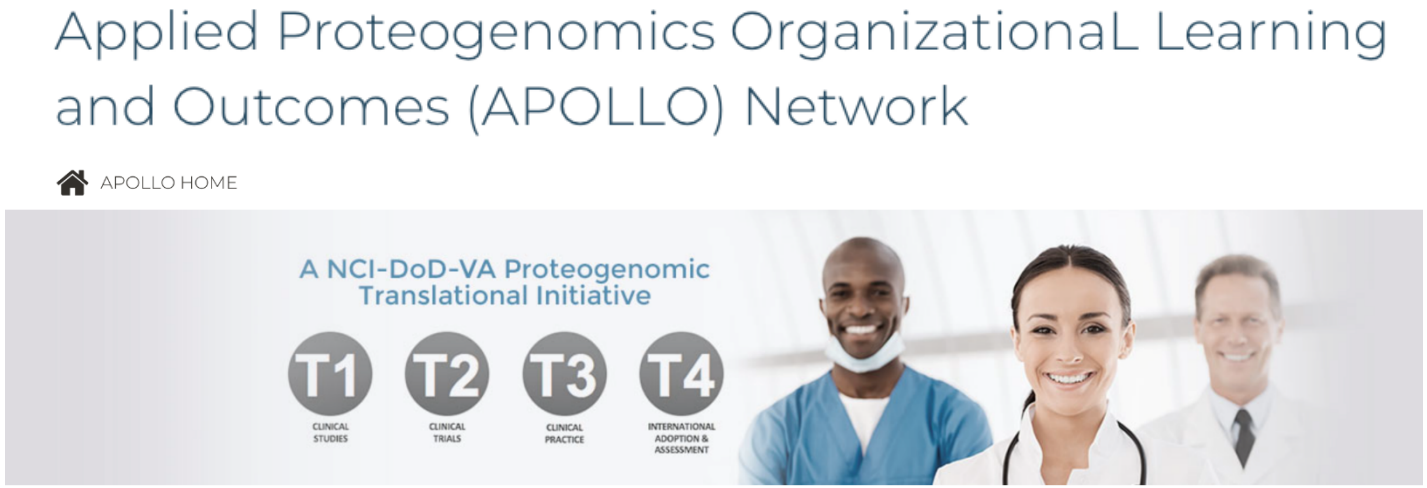
# Resources available to PROMETHES researchers

## Applied Proteogenomics OrganizationaL Learning and Outcomes (APOLLO) Network




APOLLO is analyzing the DNA, RNA, and protein expression of 8,000 annotated human tissue specimens from a wide variety of organ sites acquired from DoD, VA, and other medical facilities.

- APOLLO 1 Lung Cancer -Complete
- APOLLO 2 GYN Cancer –Early Results
- APOLLO 3 Prostate Cancer –Early Results
- APOLLO 4 Breast Cancer –Early Results
- APOLLO 5 All cancers -Underway
- APOLLO 6 Pancreatic Cancer
- APOLLO 7 Testicular Germ Cell Tumors
- APOLLO 8 Glioblastoma
- APOLLO 9 Krukenberg Tumors

https://proteomics.cancer.gov/programs/apollo-network

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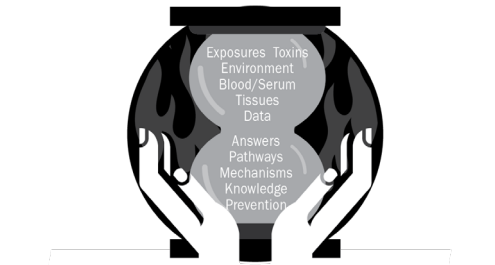


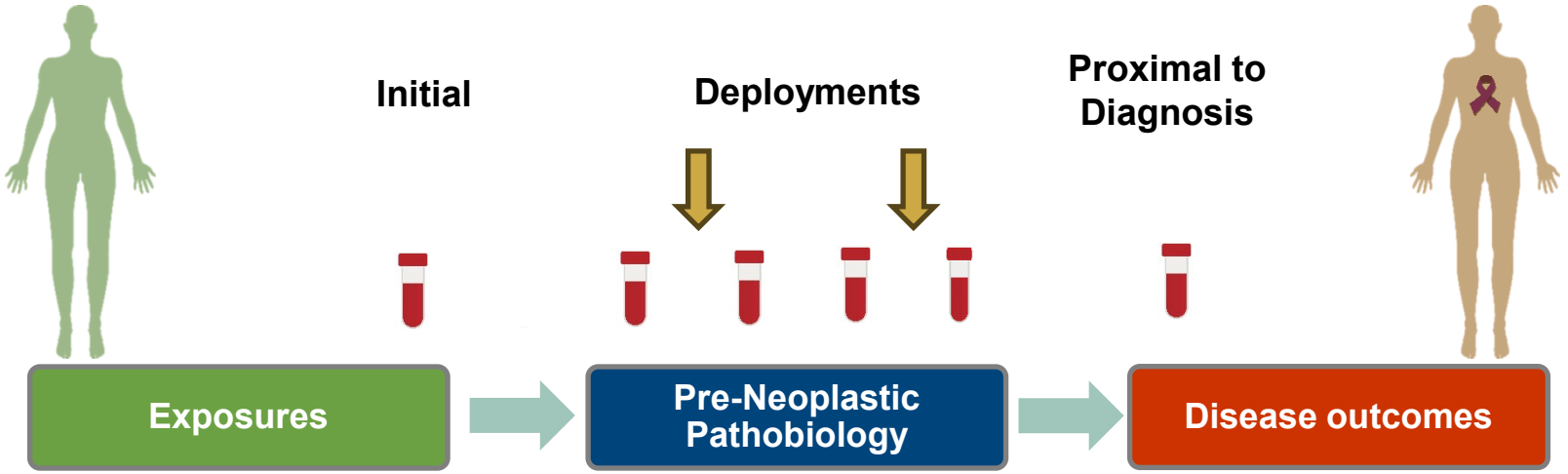

PROMETHEUS

PROject for Military Exposures and Toxin History Evaluation in US servicemembers

# Research Programs

# Use of DoDSR Sera and Toxin Exposure Data in APOLLO-enrolled Patients to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes

- Pan Cancer
- Focused on deployment-related exposures
- Includes Active Duty and Veterans at time of diagnosis




ILER
VMOAT

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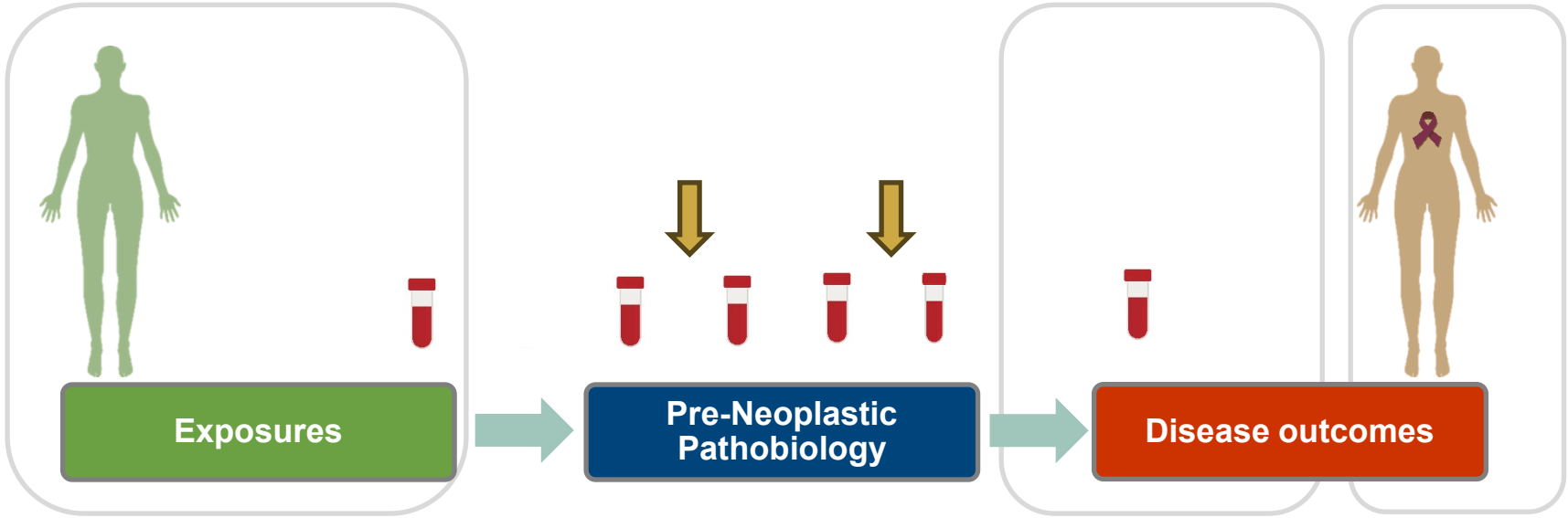


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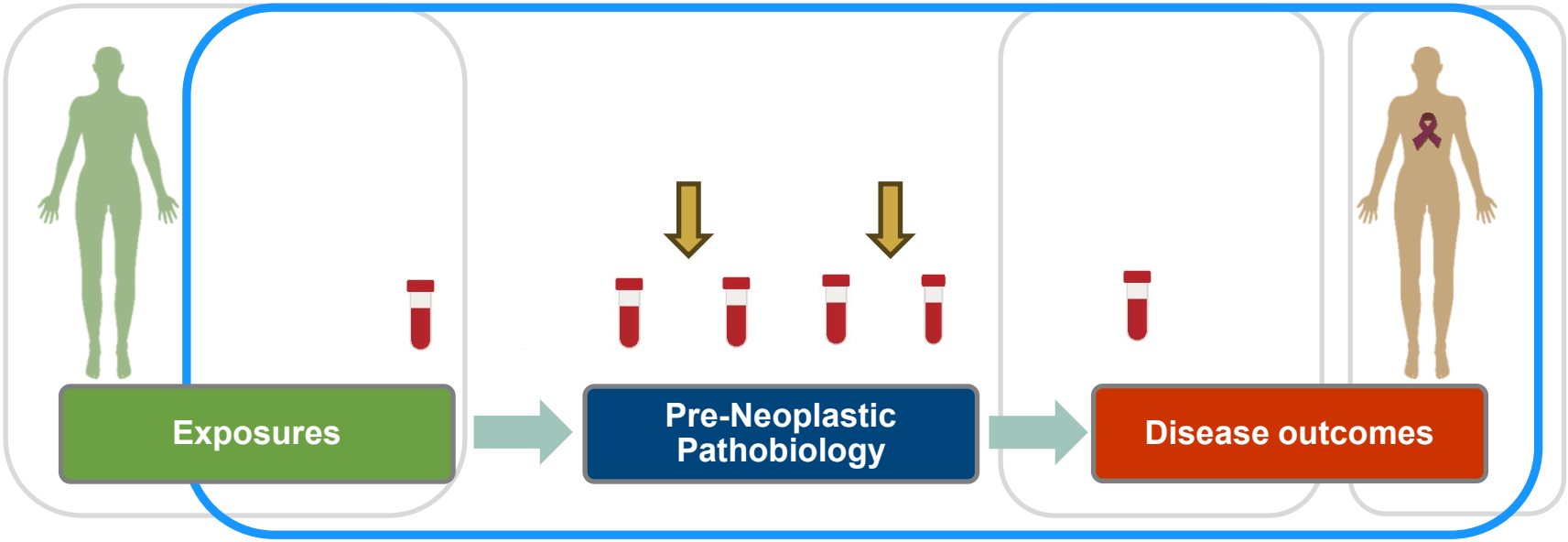
Targeted Metabolomics
Non-Targeted Metabolomics
Targeted Proteomics




Military Biomarkers Research Study (MBSR)

Framingham

APOLLO
WGS

PROMETHEUS
PROject for Military Exposures and Toxin History Evaluation in US servicemembers

# Use of DoDSR Sera and Toxin Exposure Data in APOLLO-enrolled Patients to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes

Ellison Institute

Targeted Metabolomics
Non-Targeted Metabolomics
Targeted Proteomics

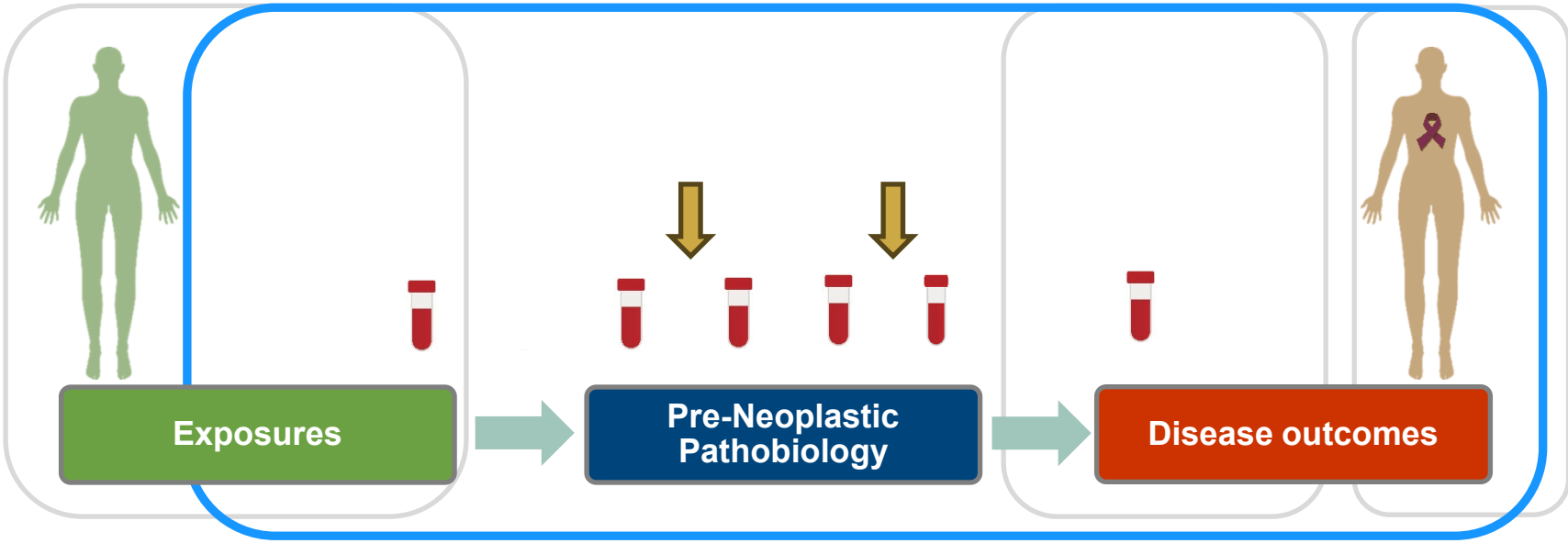
Pacific Northwest NATIONAL LABORATORY

Chan Soon-Shiong Institute of Molecular Medicine at Windber

USU Uniformed Services University

NIH NATIONAL CANCER INSTITUTE

HESI




VA U.S. Department of Veterans Affairs

BLOODPAC

Military Biomarkers Research Study (MBSR)

Framingham

APOLLO
WGS

NIH National Institute of Environmental Health Sciences

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# Use of DoDSR Sera and Toxin Exposure Data in to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes for Early Onset Colorectal Cancer

Research Article

Cancer Epidemiology, Biomarkers & Prevention

## Proteomic Profiling of Serial Prediagnostic Serum Samples for Early Detection of Colon Cancer in the U.S. Military

Stephanie Shao[1,2], Benjamin A. Neely[3], Tzu-Cheg Kao[1], Janet Eckhaus[1], Jolie Bourgeois[1], Jasmin Brooks[3], Elizabeth E. Jones[3], Richard R. Drake[3], and Kangmin Zhu[1,2]

› Cancer Epidemiol Biomarkers Prev. 2017 May;26(5):711-718.
doi: 10.1158/1055-9965.EPI-16-0732. Epub 2016 Dec 21.

**Conclusions:** Proteomic profiles in the year before cancer diagnosis have the potential to discriminate colon cancer patients from controls, and the addition of epidemiologic information may increase the sensitivity and specificity of discrimination.

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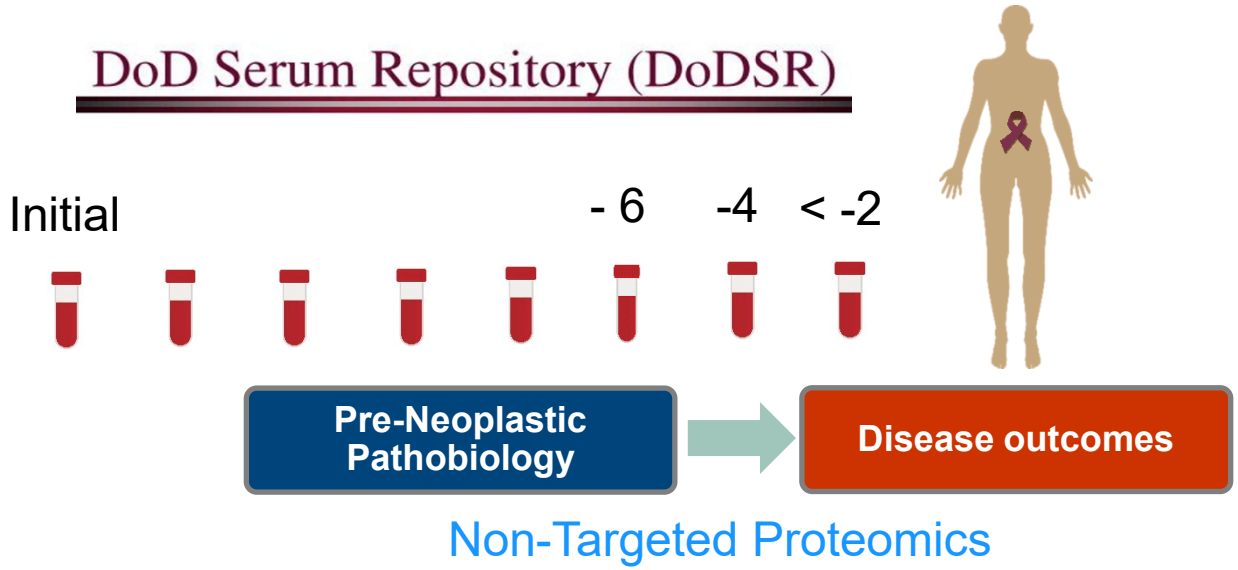
# Use of DoDSR Sera and Toxin Exposure Data in to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes for Early Onset Colorectal Cancer

- Average age 40 years
- Nested Case-Control study with 397 Cases / 397 Controls
- Included only those on Active Duty at time of diagnosis, deployment-agnostic
- Most individuals had 4 samples available
- Epidemiologic data using self-administered questionnaires and telephone interviews

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# Use of DoDSR Sera and Toxin Exposure Data in to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes for Early Onset Colorectal Cancer

Now reanalyzing samples using newer technologies:

- **microRNA Profiling** being conducted by The American Genome Center (TAGC)

USU Uniformed Services University

- Analysis of exposome via **Ion Mobility Spectrometry MS (IMS-MS)**

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL & TEXAS A&M UNIVERSITY

Erin Baker

Ivan Rusyn

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# Use of DoDSR Sera and Toxin Exposure Data in to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes for Early Onset Breast Cancer

- Average age of breast cancer diagnosis for active-duty service members is 40 years, the cutoff typically used to define early-onset breast cancer (EOBC)


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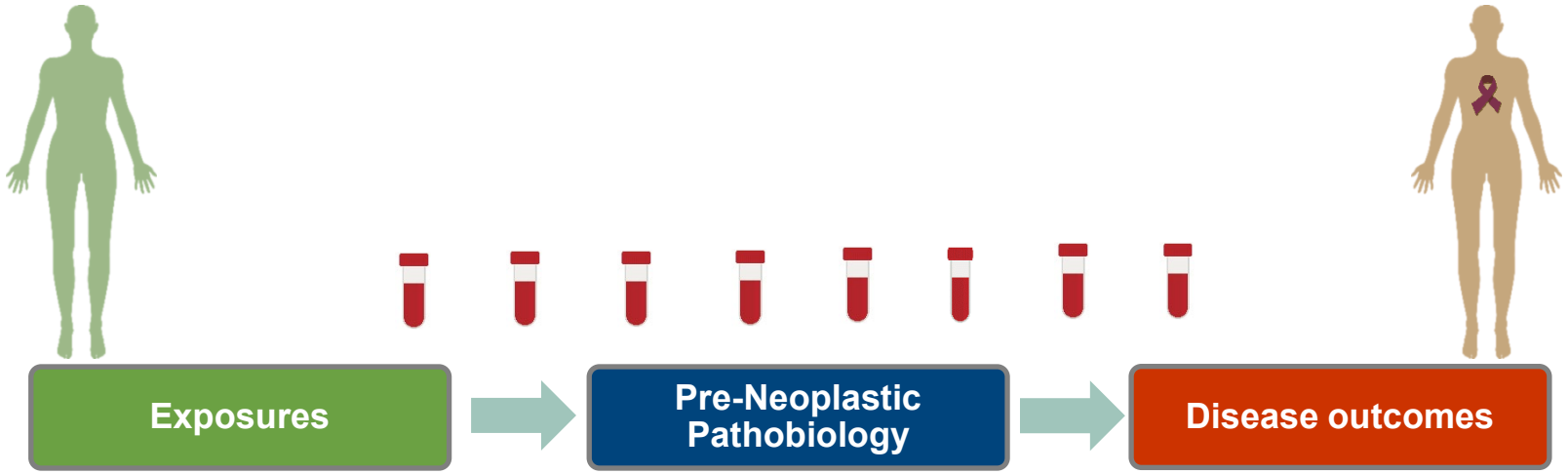
# Use of DoDSR Sera and Toxin Exposure Data in to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes for Early Onset Breast Cancer

- Include only those on Active Duty at time of diagnosis
- Deployment-agnostic
- Requesting all available samples (~10-12 / per individual)

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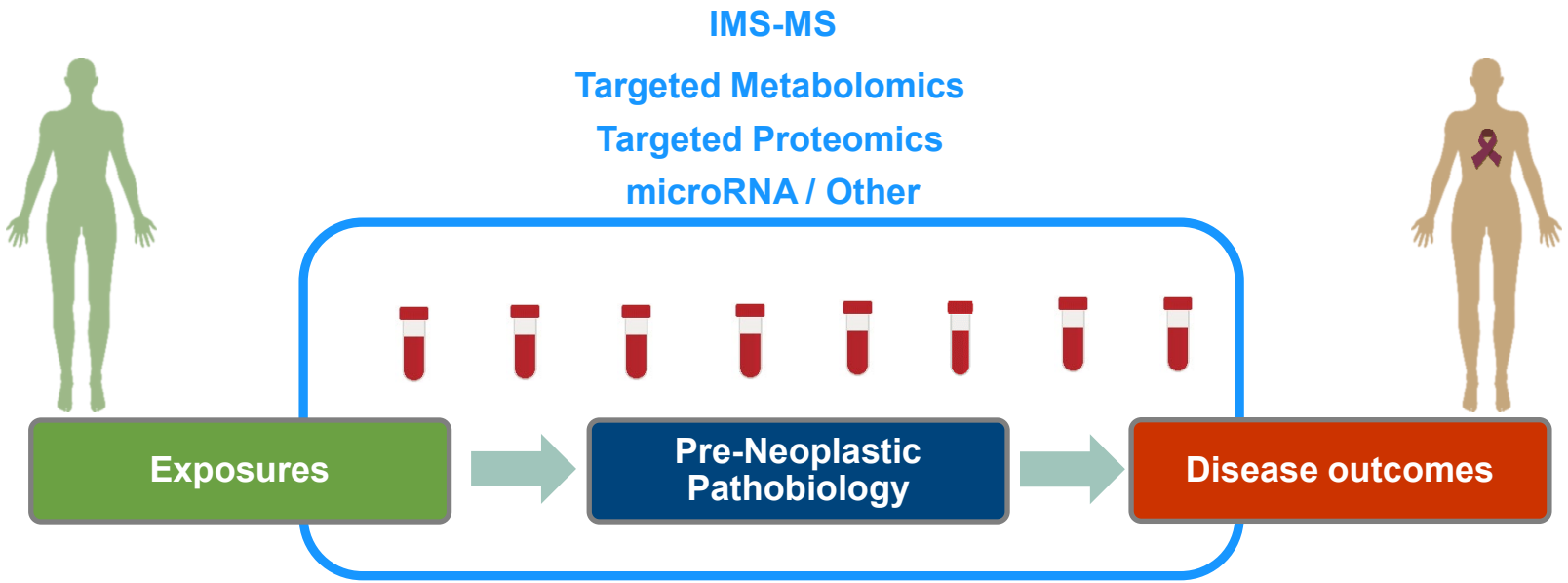


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# Prospective Exposure Studies using OneDraw

- Personally administered blood collection device (Dried Blood Spot)
- 150 µL Capillary blood (2 strips / 75µL ea.)

OneDraw™

**FDA-Cleared**

OneDraw received FDA clearance for the collection of capillary blood for quantitative measurement of HbA1c on August 15, 2019.[1]

**High-Quality Samples**

HbA1c levels in blood collected by OneDraw were comparable to those in blood collected with standard venipuncture.[2]

**Patient-Friendly**

Study participants preferred OneDraw to venipuncture and fingerstick blood collection methods for HbA1c testing.[2]

Drawbridge™ HEALTH

PROMETHEUS
PROject for Military Exposures and Toxin History Evaluation in US servicemembers

# Prospective Studies using OneDraw

- Naval Flightline Exposures: pre/post-shift, pre-post-deployment
- Biobanking and longitudinal monitoring: Initial samples collected during Army In-Processing

Pacific Northwest NATIONAL LABORATORY

Ellison Institute

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# Prospective Studies using OneDraw

- Naval Flightline Exposures: pre/post-shift, pre-post-deployment
- Biobanking and longitudinal monitoring: Initial samples collected during Army In-Processing
- Exposure monitoring in veteran firefighters

Terra Vincent Hall (VA) / Sue Fenton (NCSU)

Pacific Northwest National Laboratory

Ellison Institute

USU Uniformed Services University

NIH National Institute of Environmental Health Sciences

Chan Soon-Shiong Institute of Molecular Medicine at Windber

VA U.S. Department of Veterans Affairs

PROMETHEUS
PROject for Military Exposures and Toxin History Evaluation in US servicemembers

# How did this start?

**Jerry Lee, PhD**

Associate Professor of Clinical Medicine, Chemical Engineering, and Material Sciences | Chief Science and Innovation Officer, Ellison Institute | University of Southern California

Biden/Harris transition team

APOLLO Exec. Committee

VP Biden's task force for the Cancer Moonshot

Previously NCI Health Sciences Director , helping direct the NCI's Center for Strategic Scientific Initiatives (CSSI)

**Craig D. Shriver, MD FACS**

Colonel, Medical Corps, United States Army
Director, John P. Murtha Cancer Center / DoD Center of Excellence for Cancer Care
Walter Reed National Military Medical Center

Uniformed Services University of the Health Sciences (USUHS)

National Institute of Environmental Health Sciences
*Division of Translational Toxicology*

# Carci-HEI Program Management Team Members

**Amy Wang**
**Integrative Health Assessments Branch**

**Julie Foley**
**Mechanistic Toxicology Branch**

**Arun Pandiri**
**Comparative and Molecular Pathogenesis Branch**

**Erik Tokar**
**Mechanistic Toxicology Branch**

**Warren Casey**
**Office of the Director**

**Kristine Witt**
**Predictive Toxicology Branch, Retired (Special Volunteer)**

National Institute of Environmental Health Sciences
*Division of Translational Toxicology*


MCCRP Uniformed Services University

# PROMETHEUS RETREAT

July 26th, 2024

PROMETHEUS
PROject for Military Exposures and Toxin History Evaluation in US servicemembers