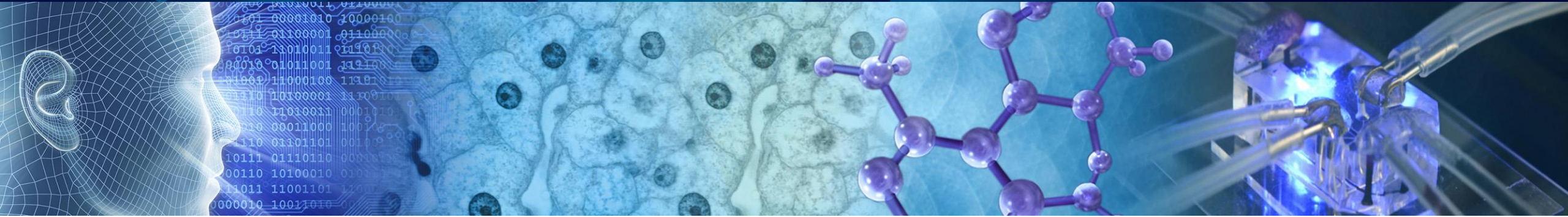




National Institute of
Environmental Health Sciences
Division of Translational Toxicology



DTT work in U.S. Active Duty and Veteran Populations

Warren Casey, PhD, DABT

Director, Strategic Partnerships / NIEHS Division of Translational Toxicology
warren.casey@nih.gov

NAEHS, 4 June 2024

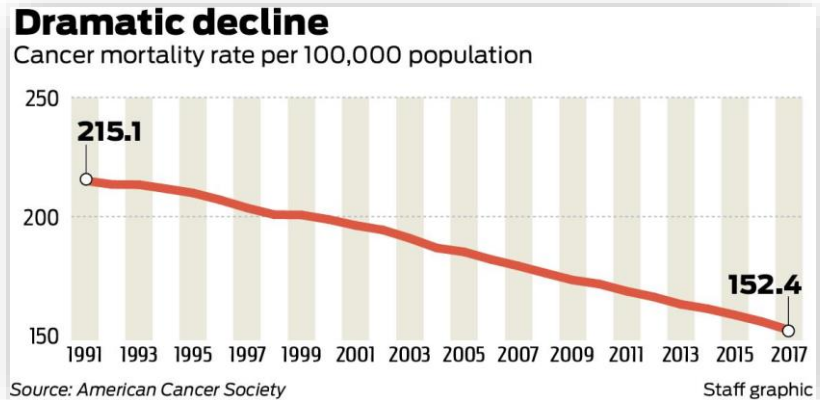
Mission of DTT

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.*”

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Impactful



Human Relevant



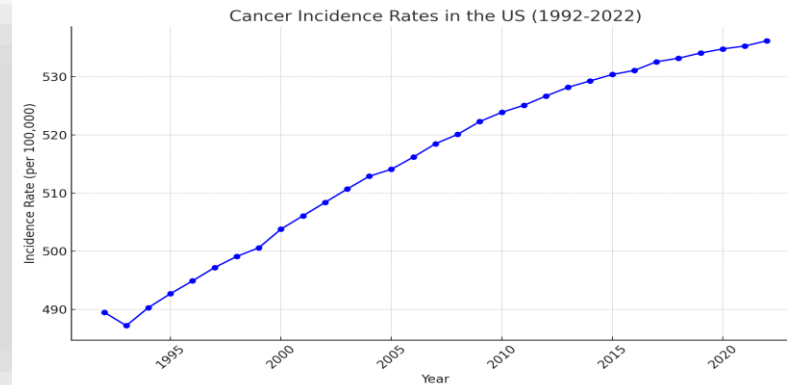
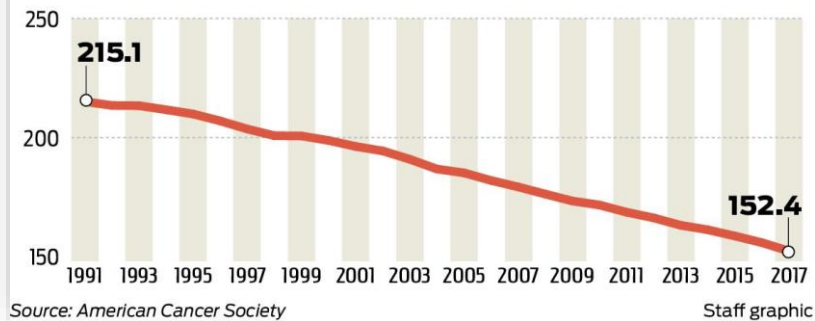
Mission of DTT

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.

Impactful

Dramatic decline

Cancer mortality rate per 100,000 population



Human Relevant



DTT Strategic Framework

Strengthening Capabilities Programs



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



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



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



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

DTT Strategic Framework

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- Cardiovascular Health Effects Innovation
- Developmental Neurotoxicity Health Effects Innovation



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

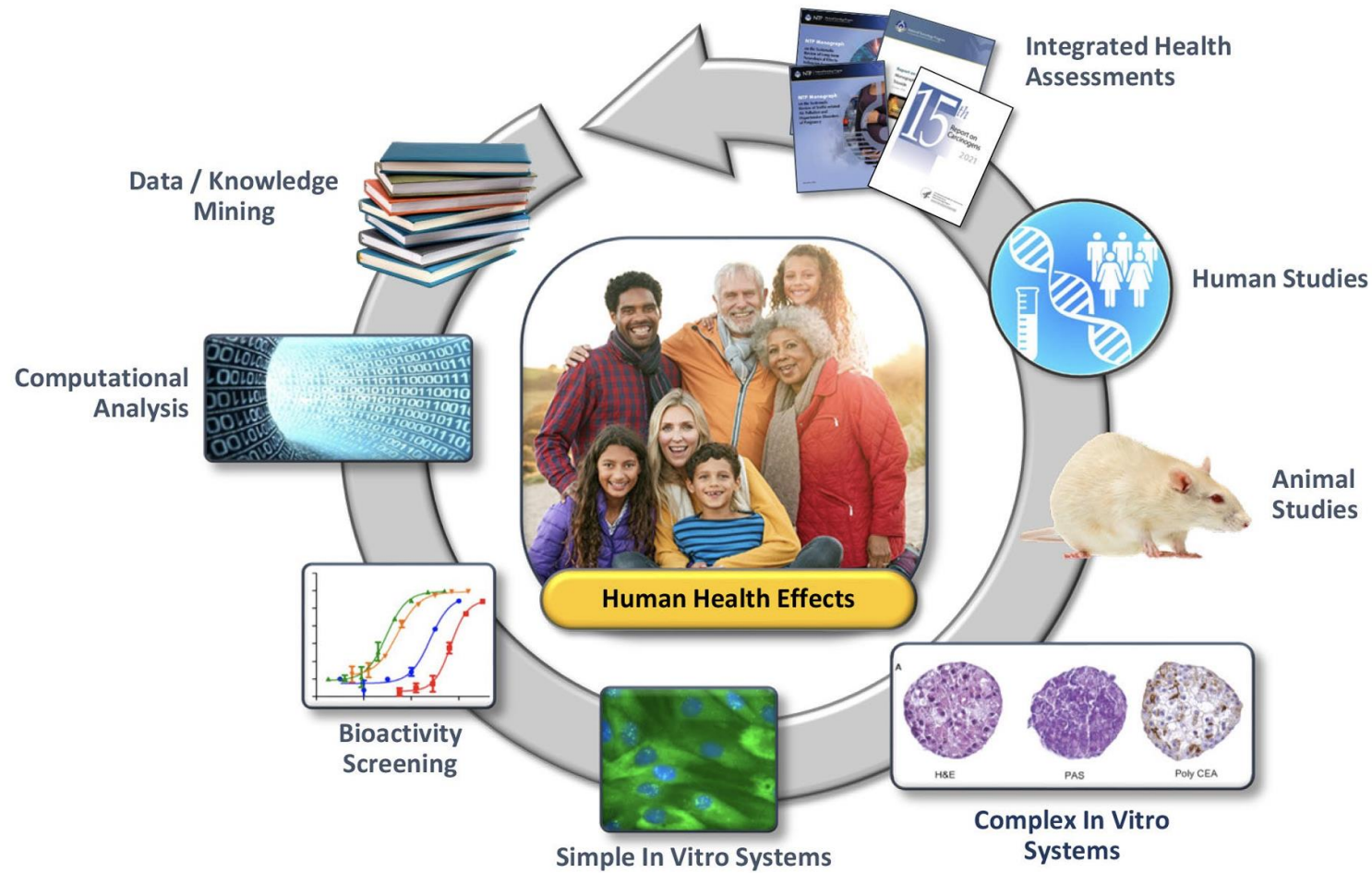


Warren Casey
Office of the Director

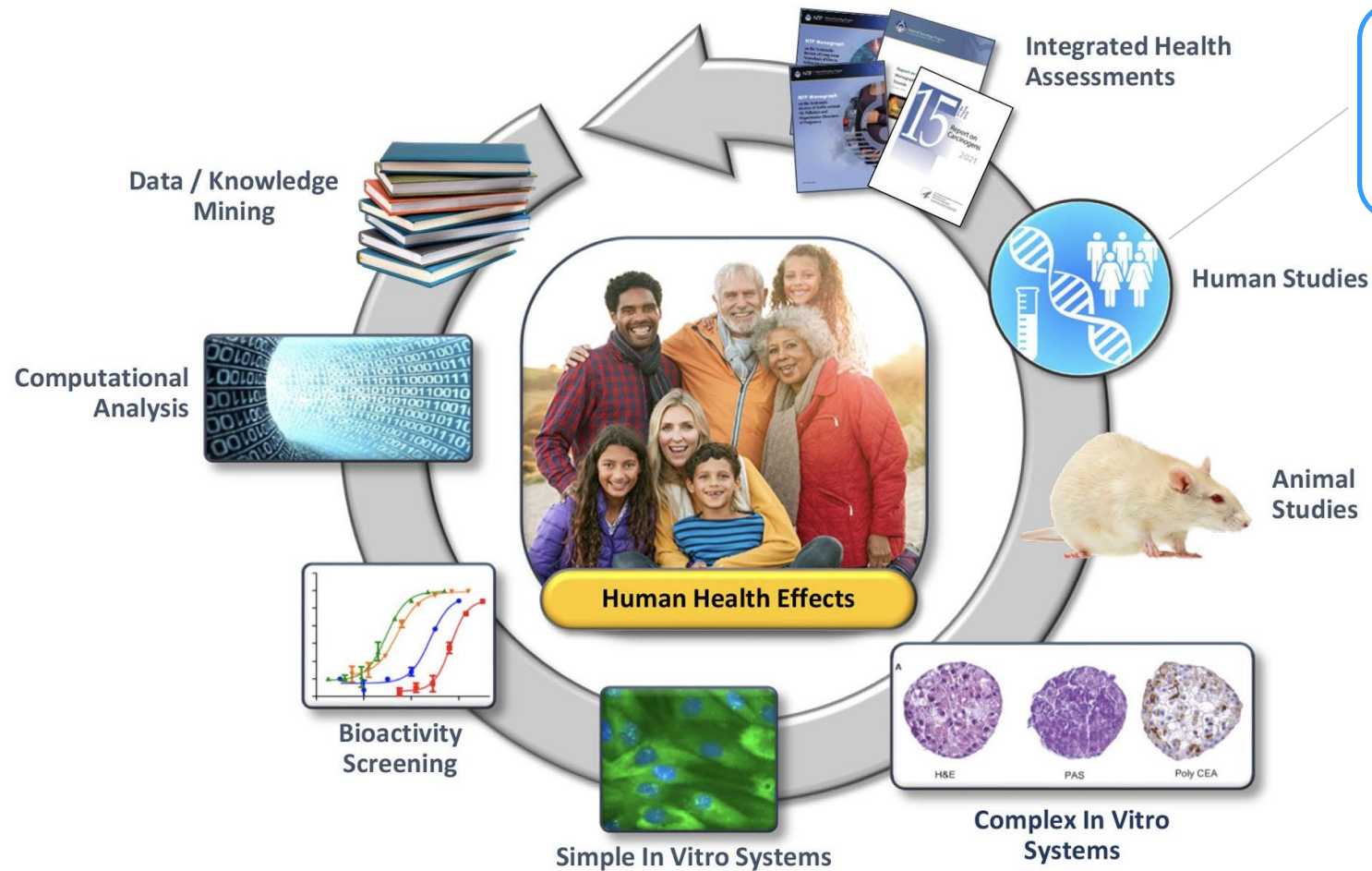


Kristine Witt
Predictive Toxicology
Branch, Retired (Special
Volunteer)

Translational Toxicology Pipeline



Translational Toxicology Pipeline



PROject for Military Exposures and Toxin History Evaluation 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.



Craig D. Shriver, MD FACS

Surgical Oncologist

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)

The Clinical Breast Care Project (CBCP)

Framingham / APOLLO / PROMETHEUS



- **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



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



Prevent More Cancers Before They Start



Drive New Innovation and Deliver the Latest Progress to Patients and Communities



Support and Center Patients and Caregivers



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Expand Access to Cancer Screenings



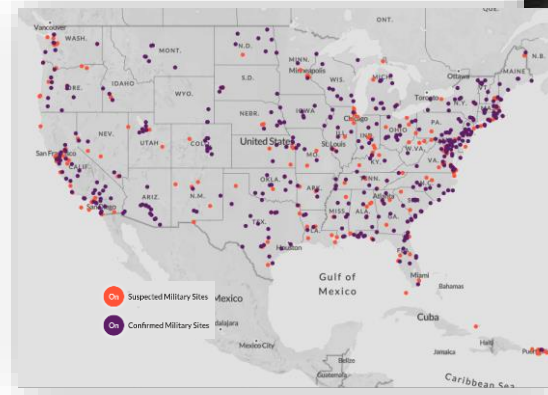
Understand and Prevent Toxic and Environmental Exposures



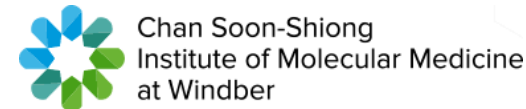
- \$47 million for the Department of Defense (DoD) Murtha Cancer Center to support the tri-agency Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) project and its related research initiatives; and investment in a new DoD program, PROject for Military Exposures and Toxin History Evaluation 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 **Promise to Address Comprehensive Toxics (PACT) Act of 2022**



- **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 **Promise to Address Comprehensive Toxics (PACT) Act of 2022**
- **Umbrella of collaborative efforts under DoD's Murtha Cancer Research Program (MCRC) with 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





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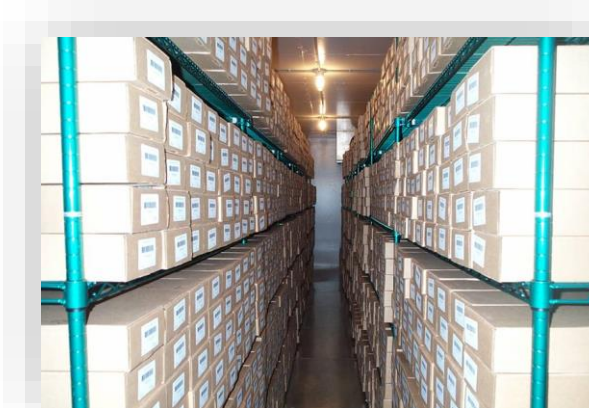
Resources



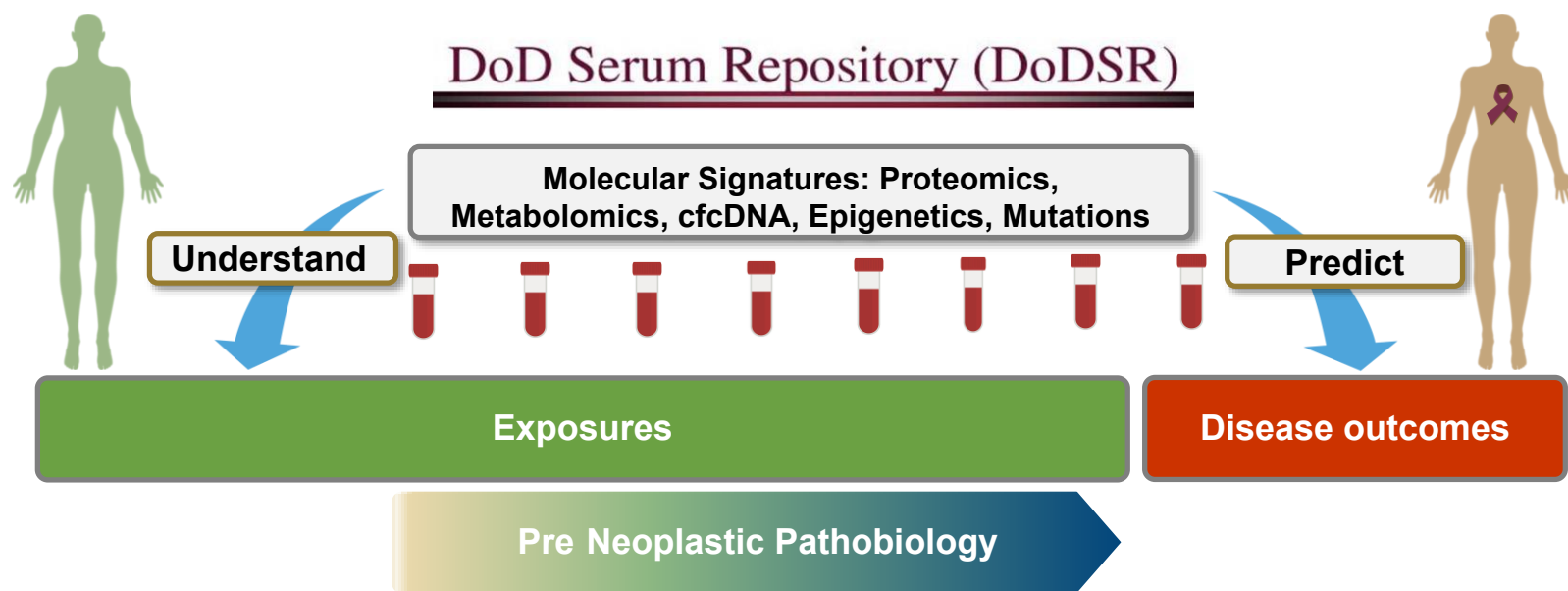
Resources

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 Etiology, Risk, and Outcomes



Resources

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.



VA

U.S. Department
of Veterans Affairs

Resources

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; Krah, 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. Krah, MD, Patricia Rohrbeck, DrPH, Young-Mi Go, PhD, and Dean P. Jones, PhD

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

Resources

Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) Network

 APOLLO HOME



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.

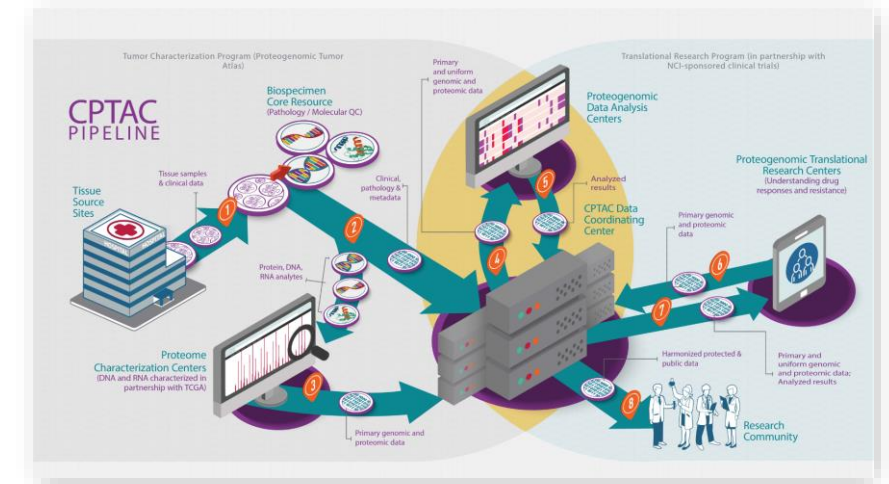
 Data Portal

 Antibody Portal

 Assay Portal

☒ CONTACT US

☒ SIGN UP FOR EMAIL UPDATES



Clinical Proteomic Tumor Analysis Consortium (CPTAC)



Resources

Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) Network

- APOLLO 1 Lung Cancer -Complete
- APOLLO 2 GYN Cancer –Early Results
- APOLLO 3 Prostate Cancer –Early Results
- APOLLO 4 Breast Cancer –Early Results

Retrospective

- **APOLLO 5 All cancers**

- APOLLO 6 Pancreatic Cancer
- APOLLO 7 Testicular Germ Cell Tumors
- APOLLO 8 Glioblastoma
- APOLLO 9 Krukenberg Tumors

Prospective



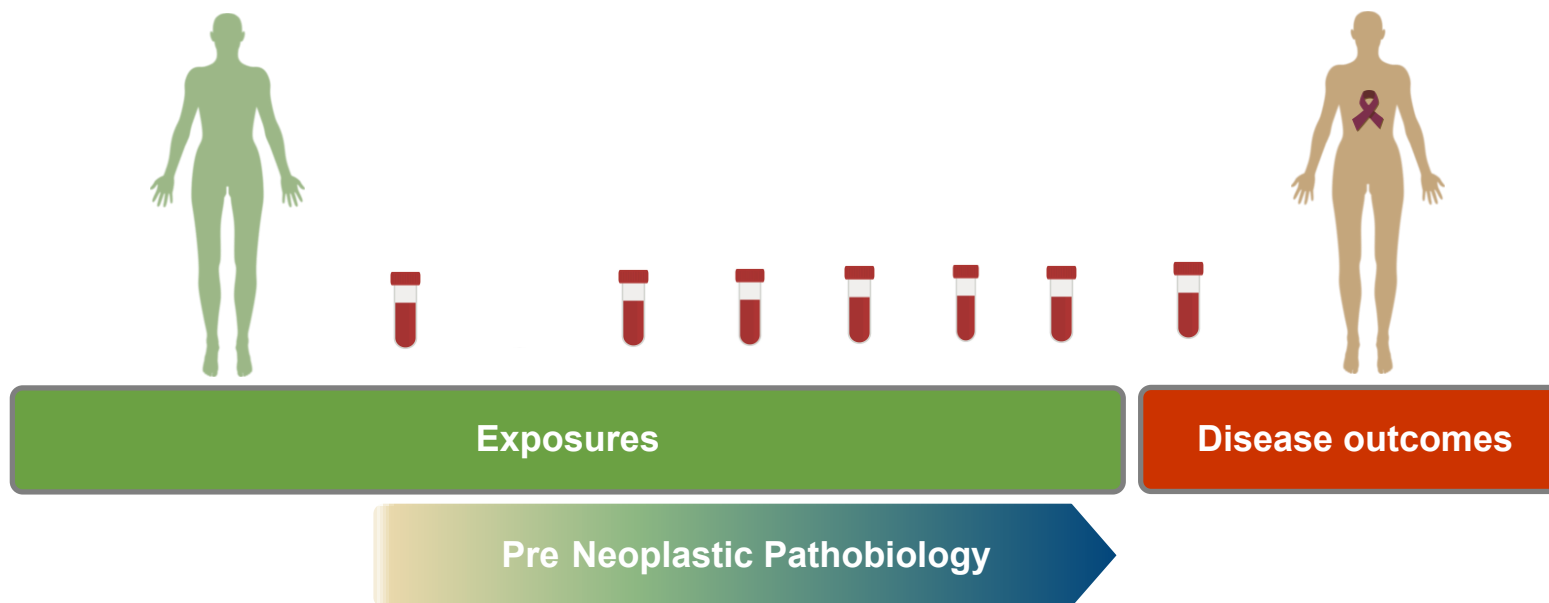
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Research Programs

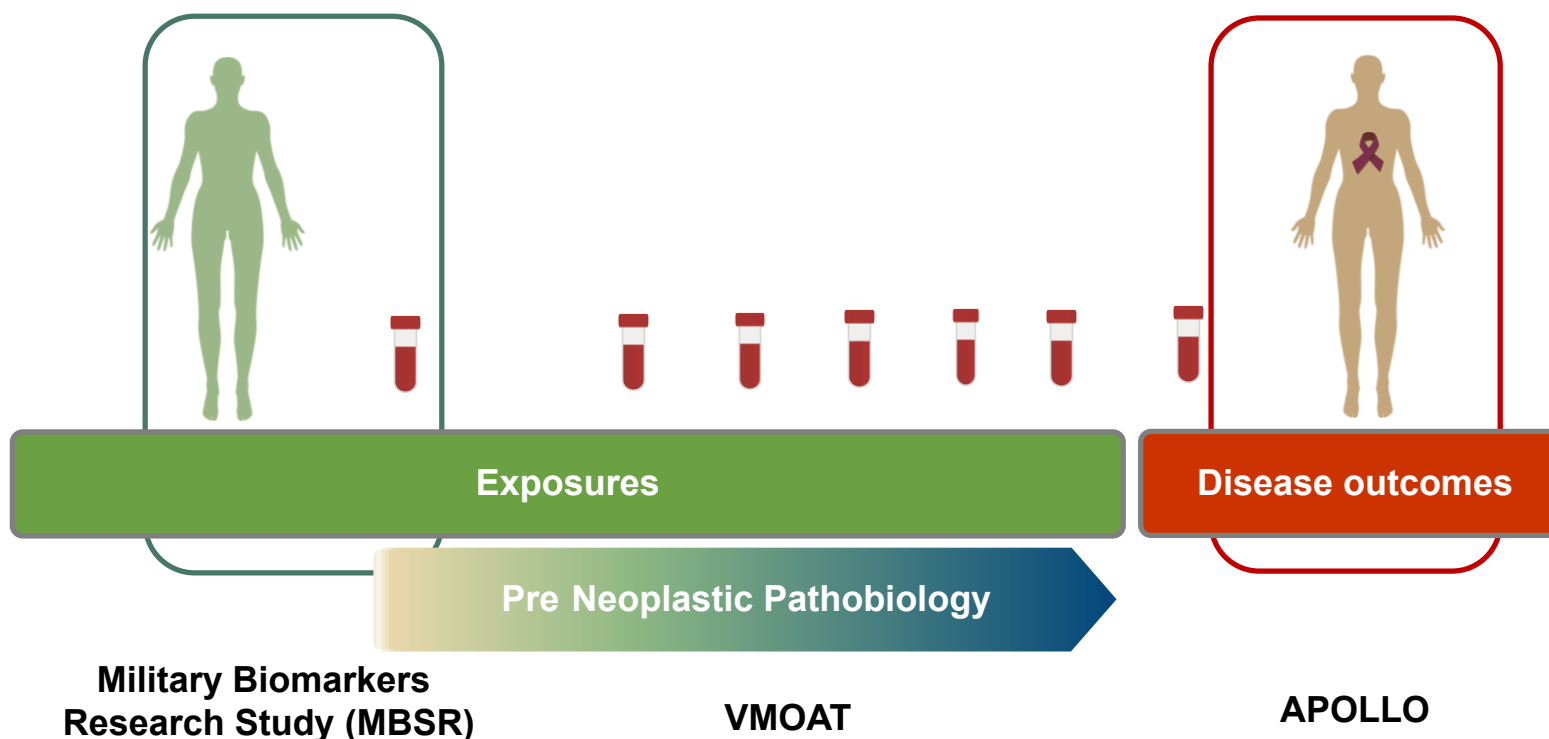
Use of DoDSR Sera and Toxin Exposure Data in APOLLO-enrolled Patients to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes

- Pan Cancer
- Focused on deployment-related exposures
- Includes cases that were Active Duty or Veterans at time of diagnosis



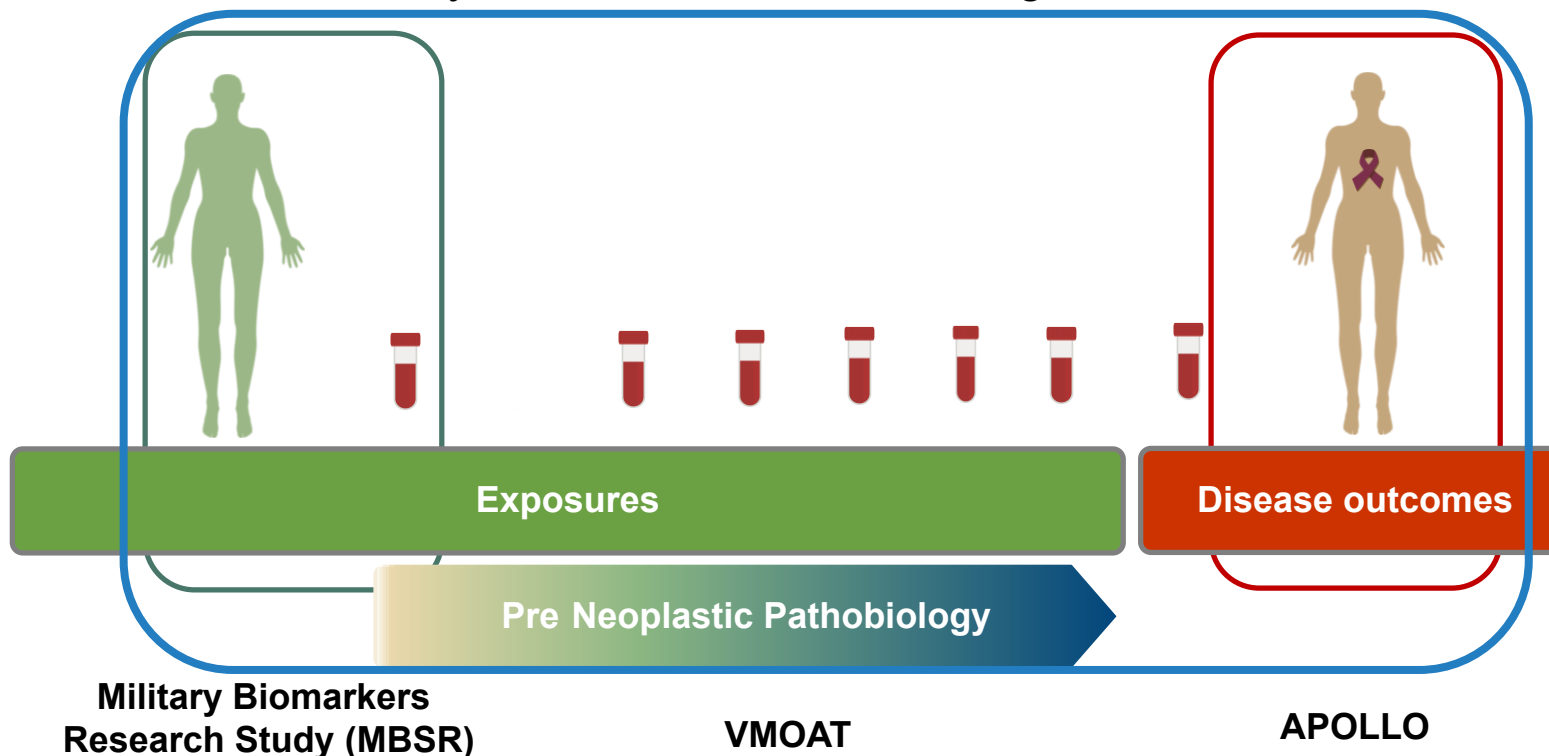
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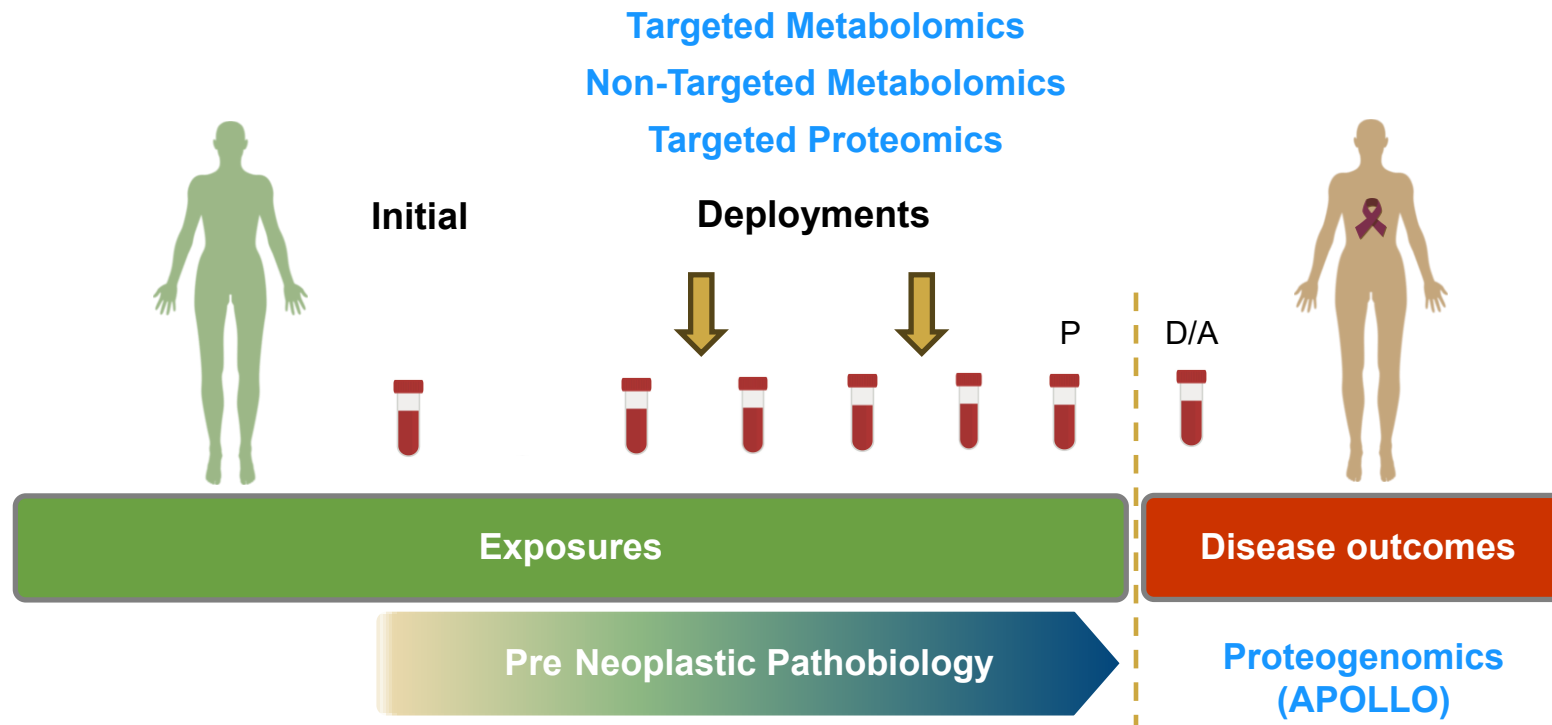


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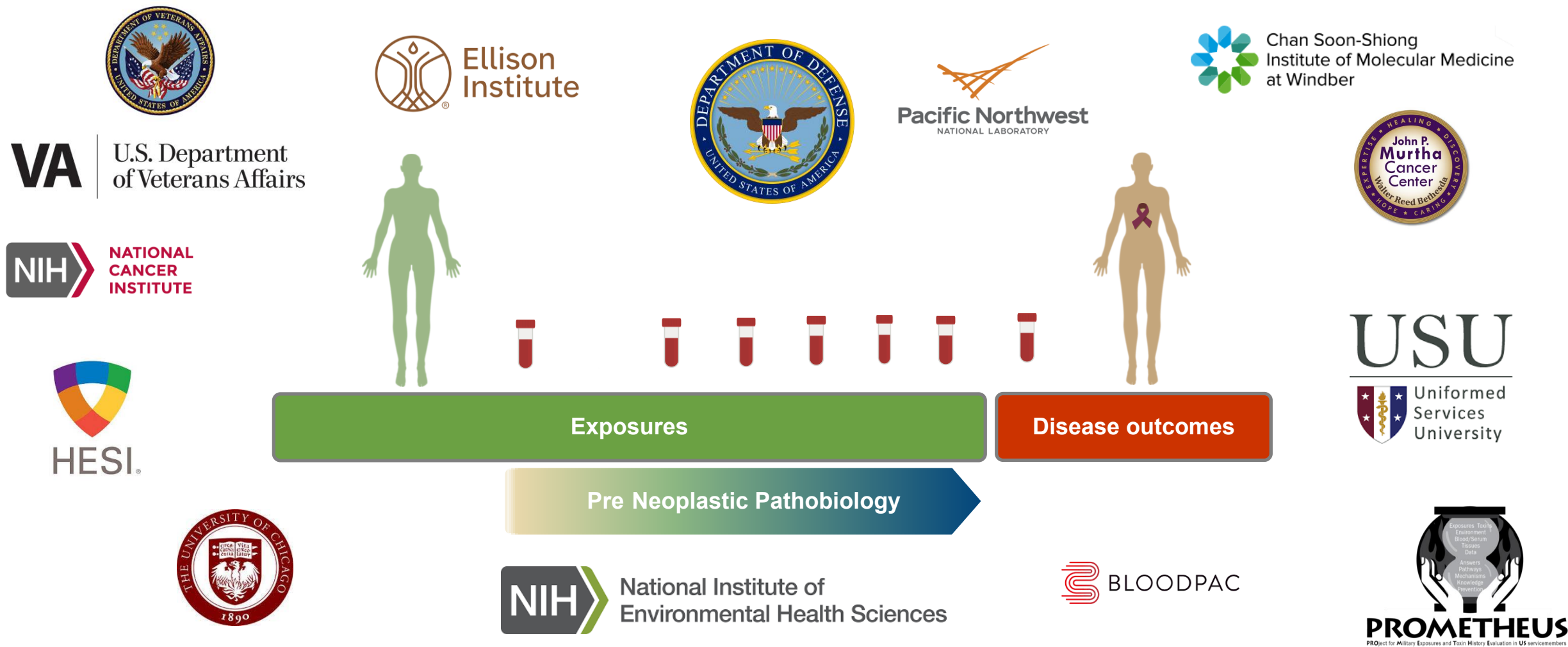


Use of DoDSR Sera and Toxin Exposure Data in APOLLO-enrolled Patients to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes



P = sample most proximal to diagnosis
D/A = Diagnostic sample from APOLLO sample taken at diagnosis

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



Conference Report

Colorectal Cancer

Early-onset colorectal cancer research: gaps and opportunities

Laura Brockway-Lunardi¹, Stefanie Nelson², Arun R Pandiri³, James V Tricoli⁴, Asad Umar⁵, Anil Wali⁶ & Phillip J Daschner^{*,7}



Greatest interest in the contribution of environmental exposures

Research gaps and opportunities include:

- Need for larger, more diverse cohorts with environmental exposures across the lifespan that include stool and serum samples and integration of consensus molecular subtype information.
- Better molecular markers of exposure are needed to measure the relative contribution of putative environmental factors of risk and to better understand how these exposures affect biological mechanisms in EO-CRC.
- Integrated multi-omic approaches in carefully stratified cohorts to agnostically determine how risk factors (e.g., obesity, diet, infection, drugs and metabolic syndromes) may effect molecular changes in EO-CRC.
- Determine the nonAPC driven Wnt/beta catenin activating mechanisms that promote intestinal epithelial cell (IEC) stem cell activation in EO-CRC (e.g., Line 1 insertions and RNF43 suppression).
- Use of artificial intelligence algorithms and novel models like organoids that link risk exposures to molecular signatures of EO-CRC and identify potential preventive and therapeutic targets.
- Additional collaborative resources such as biorepositories that include digitized tissue images to develop consensus histopathology, electronic health records (EHRs) and annotated family history and exposure data.

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

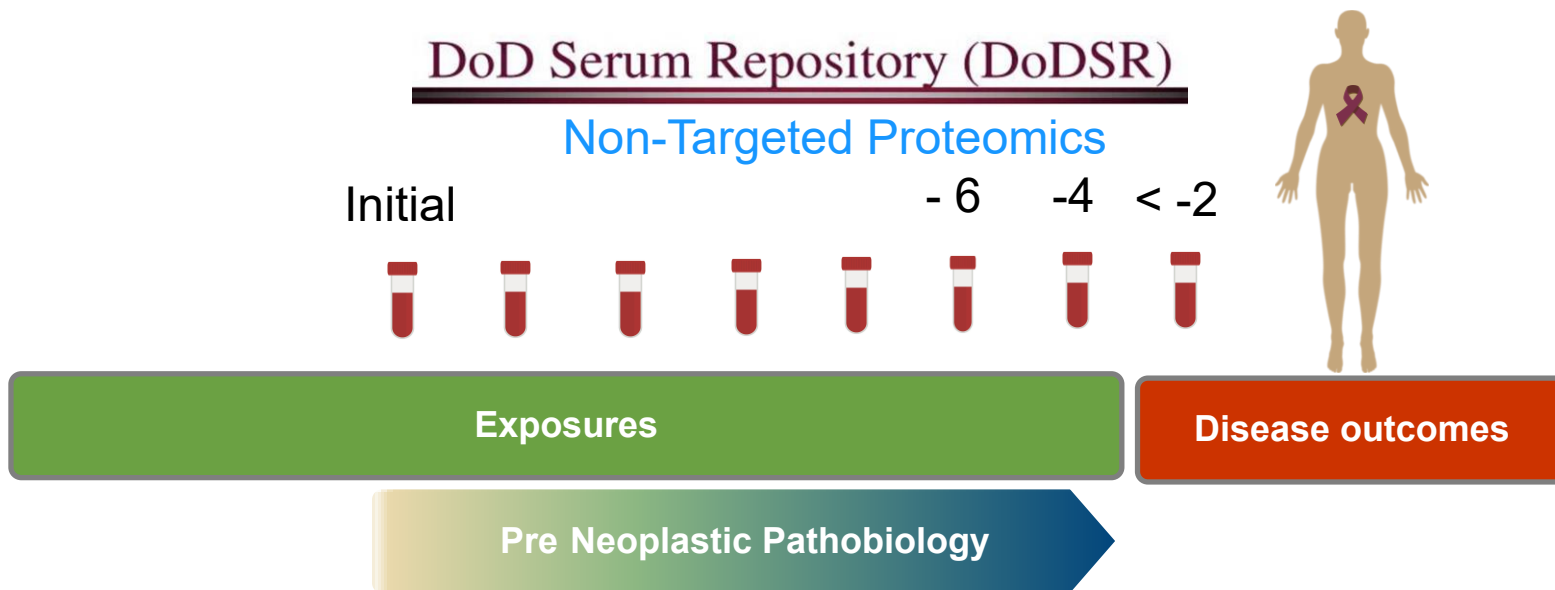
Stephanie Shao^{1,2}, Benjamin A. Neely³, Tzu-Cheg Kao¹, Janet Eckhaus¹, Jolie Bourgeois¹, Jasmin Brooks³, Elizabeth E. Jones³, Richard R. Drake³, and Kangmin Zhu^{1,2}

> [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.

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

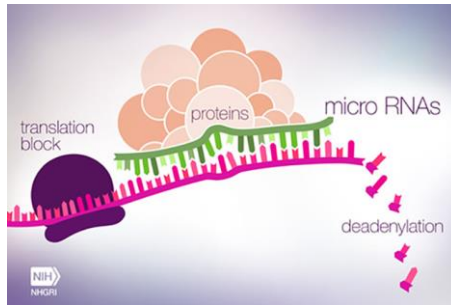
- Average age 40 years
- Nested Case-Control study with 397 Cases / 397 Controls
- Included only those on Active Duty at time of diagnosis, deployment-agnostic
- Most individuals had 4 samples available
- Epidemiologic data using self-administered questionnaires and telephone interviews



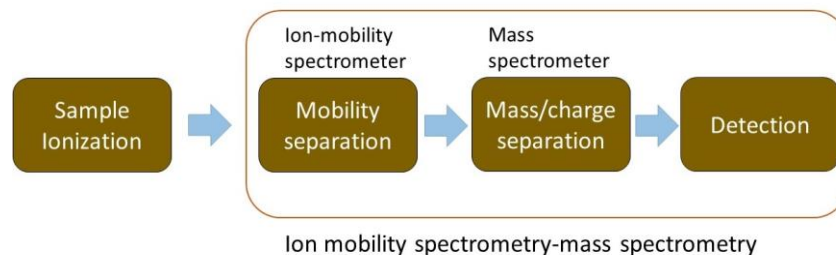
Use of DoDSR Sera and Toxin Exposure Data in to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes for Early Onset Colorectal Cancer

Now reanalyzing samples using newer technologies:

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



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



THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

Erin Baker



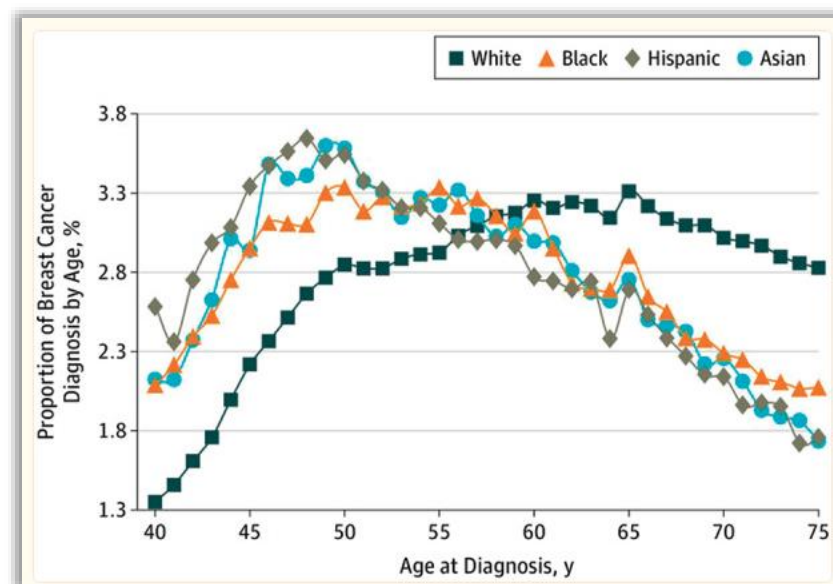
Ivan Rusyn



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

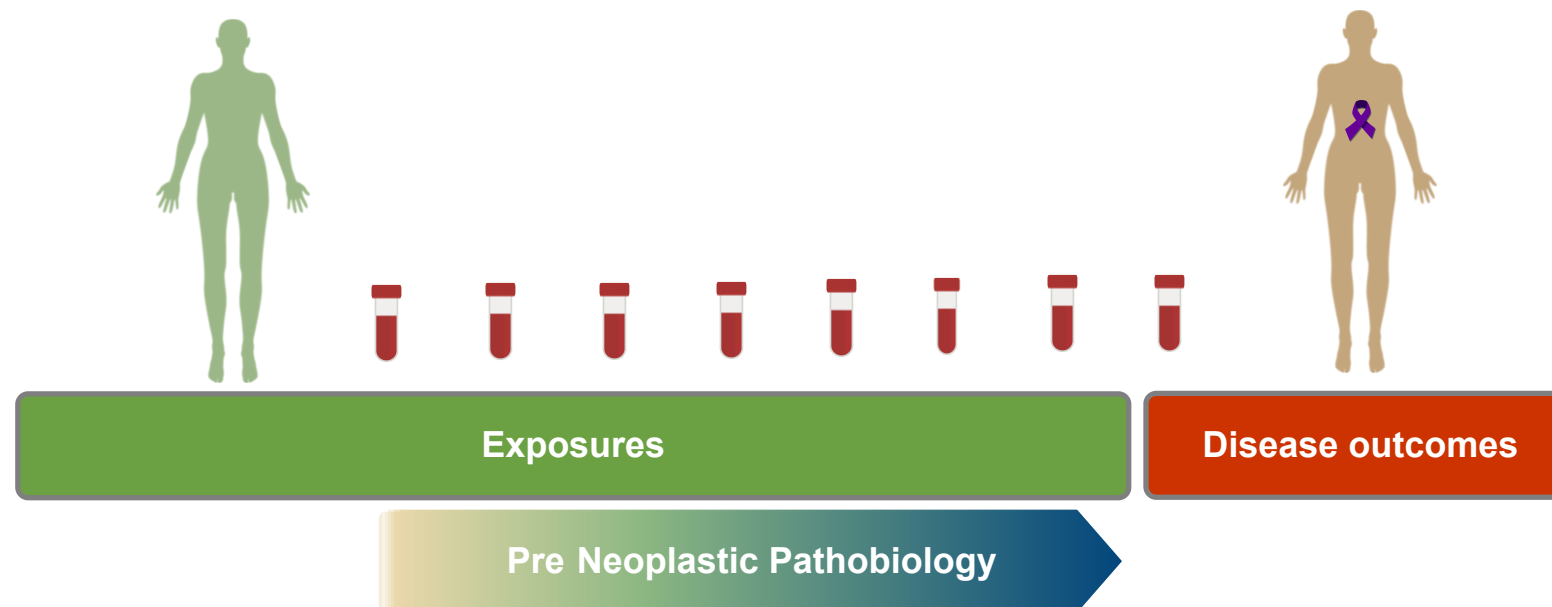
Use of DoDSR Sera and Toxin Exposure Data in to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes for Early Onset Breast Cancer

- 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)



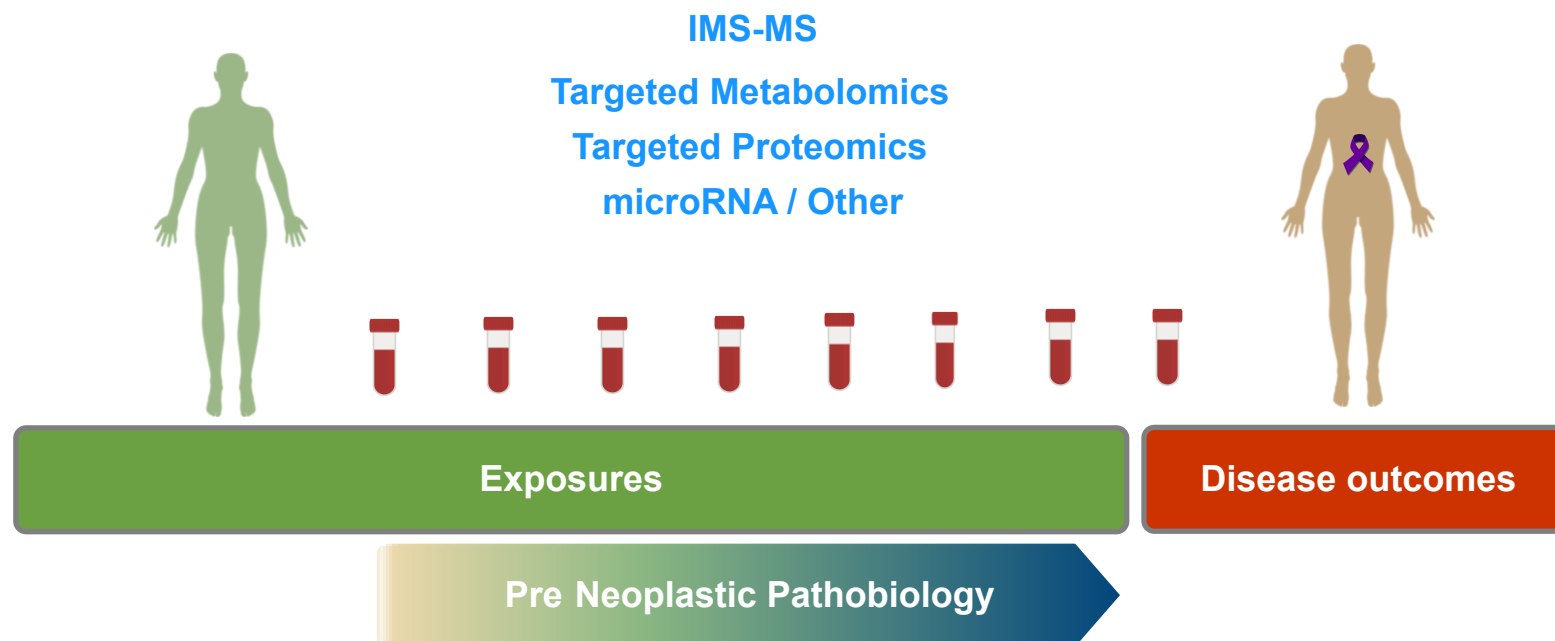
Use of DoDSR Sera and Toxin Exposure Data in to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes for Early Onset Breast Cancer

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



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
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Prospective Exposure Studies using OneDraw



- Personally administered blood collection device (Dried Blood Spot)
- 150 μ L Capillary blood (2 strips / 75 μ L ea.)
- 6,000 devices procured



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



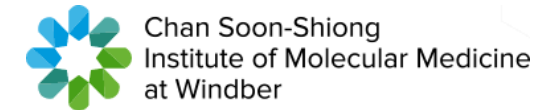
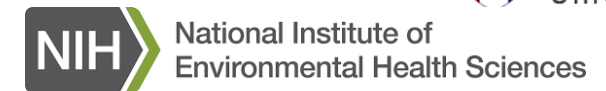
Patient-Friendly

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



Prospective Exposure Studies using OneDraw

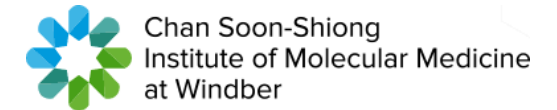
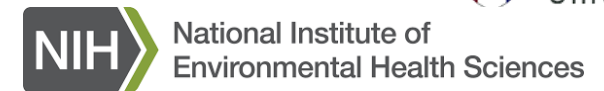
- Naval Flightline Exposures: pre/post-shift, pre-post-deployment
- Biobanking and longitudinal monitoring: Initial samples collected during Army In-Processing



Prospective Exposure 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

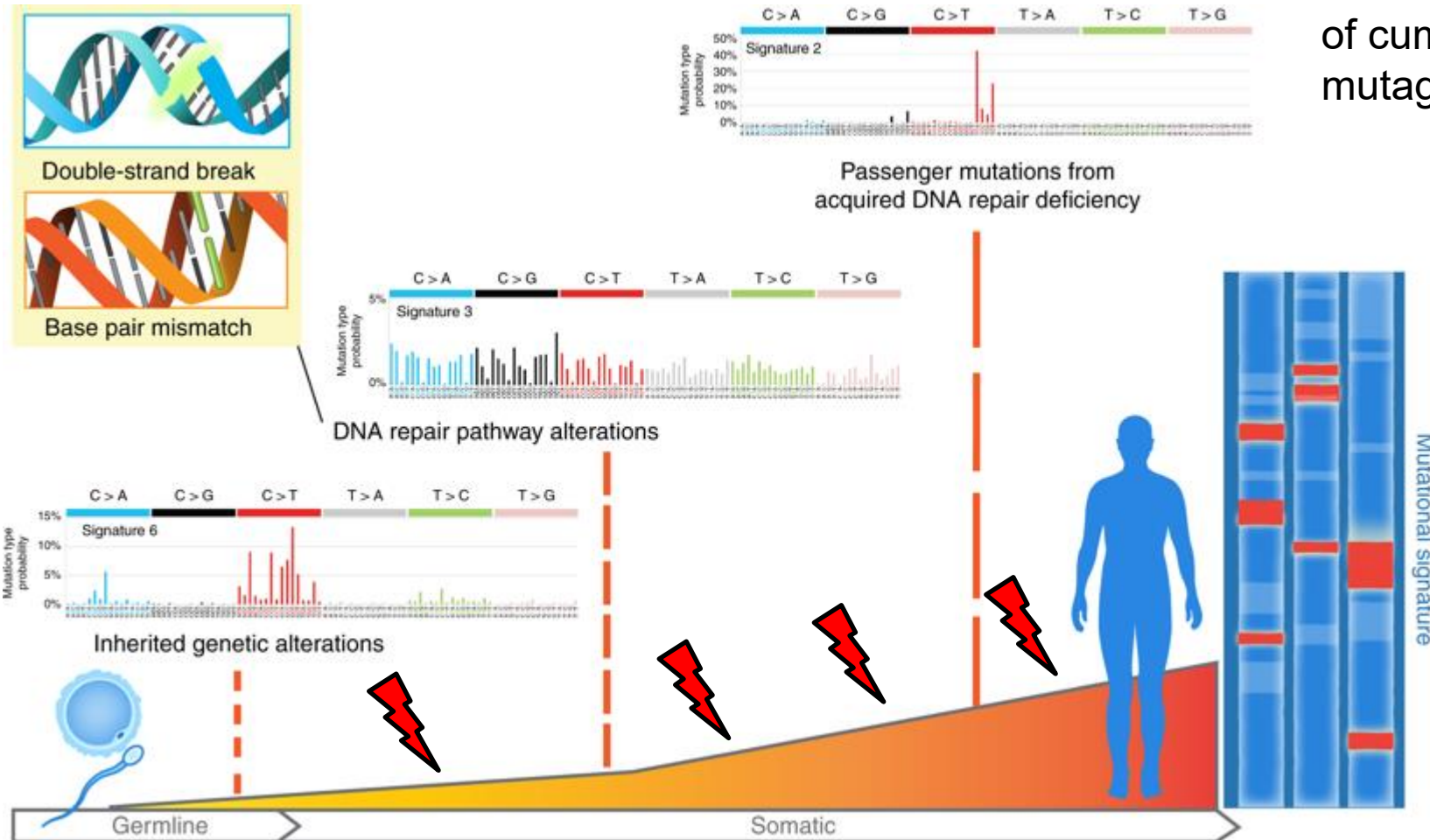
Terra Vincent Hall (VA) / Sue Fenton (NCSU)



Linking Exposures to Cancers using Mutational Signature Profiling

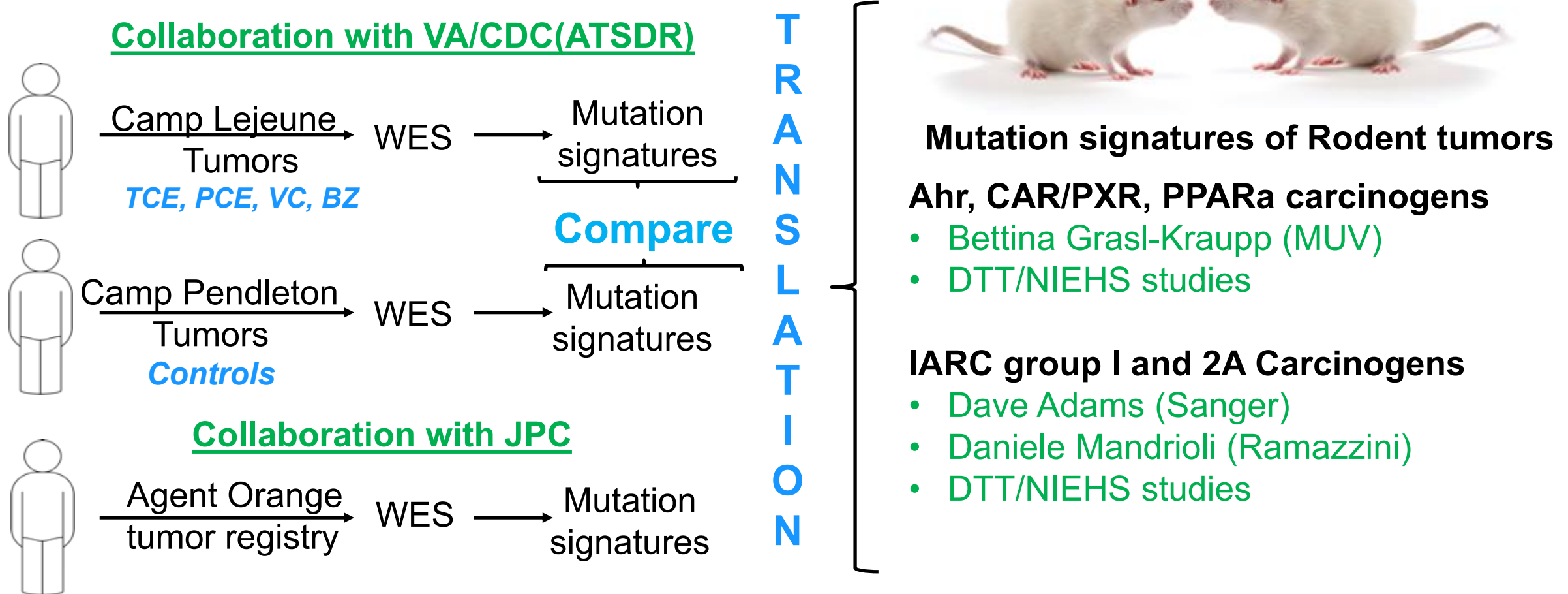
Mutational Signature – molecular footprints of cumulative endogenous and exogenous mutagenic events over a lifetime

- Insights to carcinogenic processes
- Linkages to exposures
- Potential utility in diagnosis, prognosis and treatment



Arun Pandiri
Comparative and Molecular
Pathogenesis Branch

Linking cancer mutation signatures to exposures





National Institute of
Environmental Health Sciences
Division of Translational Toxicology

Office of Program Operations



[Michelle J. Hooth, Ph.D., D.A.B.T.](#)

Deputy Director for Program Operations,
Division of Translational Toxicology;
Director, Office of Program Operations



[Matt Stout, Ph.D., D.A.B.T.](#)

Toxicologist

Project Officer/Contract Officer's Representative



PROMETHEUS RETREAT



Questions?



References

APOLLO

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

Brockway-Lunardi, L., Nelson, S., Pandiri, A. R., Tricoli, J. V., Umar, A., Wali, A., & Daschner, P. J. (2020). Early-onset colorectal cancer research: gaps and opportunities. *Colorectal Cancer*, 9(3).
<https://doi.org/10.2217/crc-2020-0028>

CPTAC Proteogenomics Program

https://proteomics.cancer.gov/news_and_announcements/magic-proteogenomics-explained-series-cptac-proteogenomics-program

DTT Mission and Strategic Framework

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

EWG PFAS Map

<https://www.ewg.org/interactive-maps/2020-military-pfas-sites/map/>

Lee JY, Shi T, Petyuk VA, Schepmoes AA, Fillmore TL, Wang YT, Cardoni W, Coppit G, Srivastava S, Goodman JF, Shriver CD, Liu T, Rodland KD. Detection of Head and Neck Cancer Based on Longitudinal Changes in Serum Protein Abundance. *Cancer Epidemiol Biomarkers Prev*. 2020 Aug;29(8):1665-1672. doi: 10.1158/1055-9965.EPI-20-0192. Epub 2020 Jun 12. PMID: 32532828.
<https://aacrjournals.org/cebp/article/29/8/1665/72401/Detection-of-Head-and-Neck-Cancer-Based-on>

Murtha Cancer Research Program (APOLLO / Framingham / PROMETHEUS)

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

Molecular Analysis Researching Carcinogenic Exposures (MARCE)

<https://www.amsus.org/wp-content/uploads/2023/03/VA-Cancer-Moonshot-AMSUS-Briefing-02132023.pdf>

Data management

