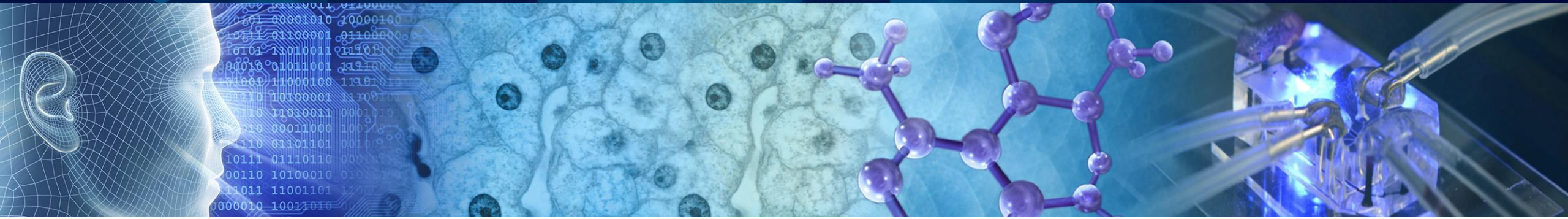
National Institute of Environmental Health Sciences
Division of Translational Toxicology



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

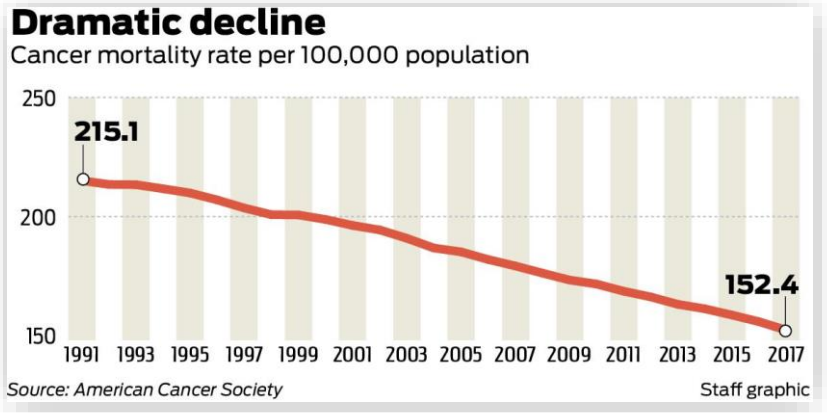
The NIEHS Division of Translational Toxicology (DTT) aims to improve public health through the development of data and knowledge that are *translatable, predictive and timely*."

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

Human Relevant

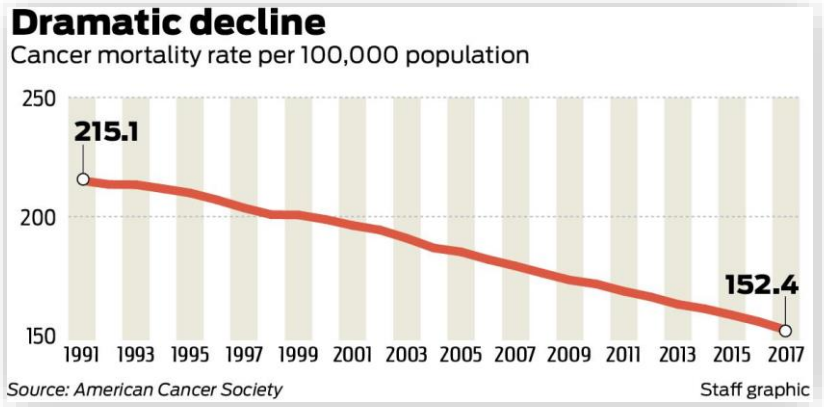


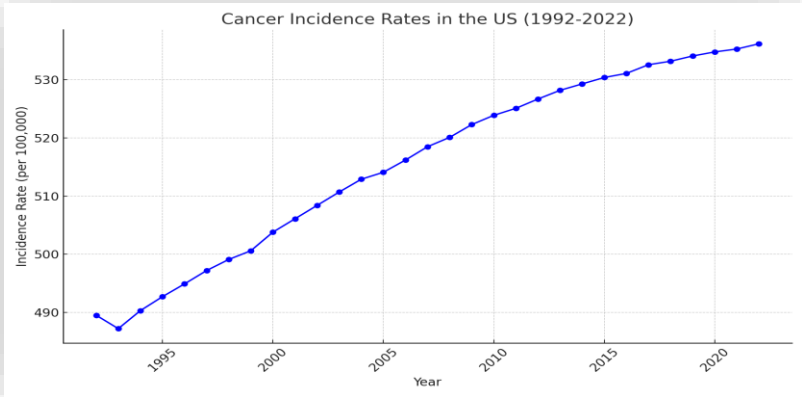
Mission of DTT

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

Human Relevant





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

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

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

National Institute of Environmental Health Sciences
Division of Translational Toxicology

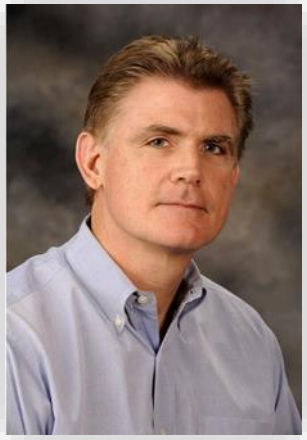
Carci-HEI Program Management Team Members

Amy Wang
Integrative Health Assessments Branch

Julie Foley
Mechanistic Toxicology Branch

Arun Pandiri
Comparative and Molecular Pathogenesis Branch

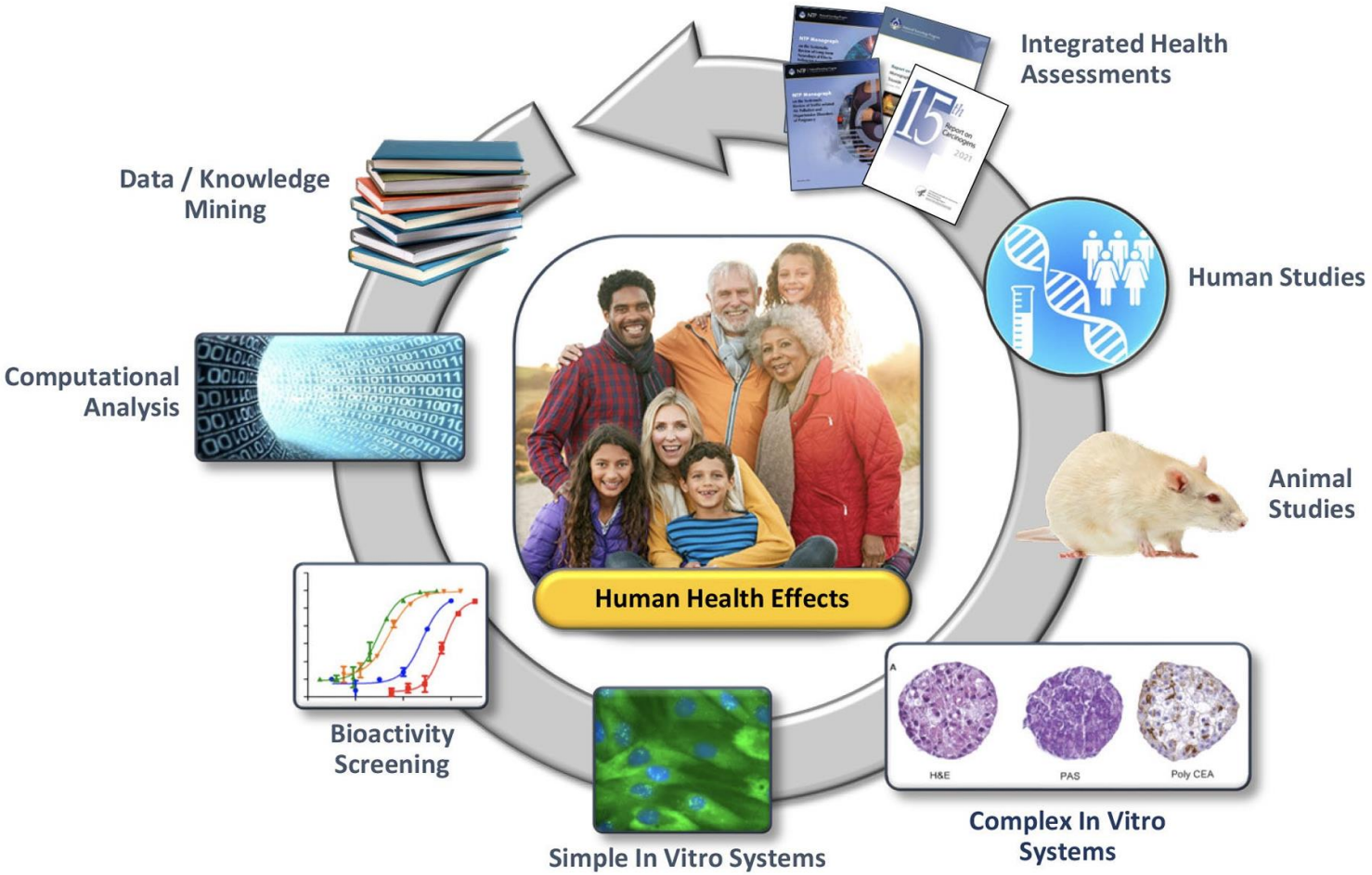
Erik Tokar
Mechanistic Toxicology Branch



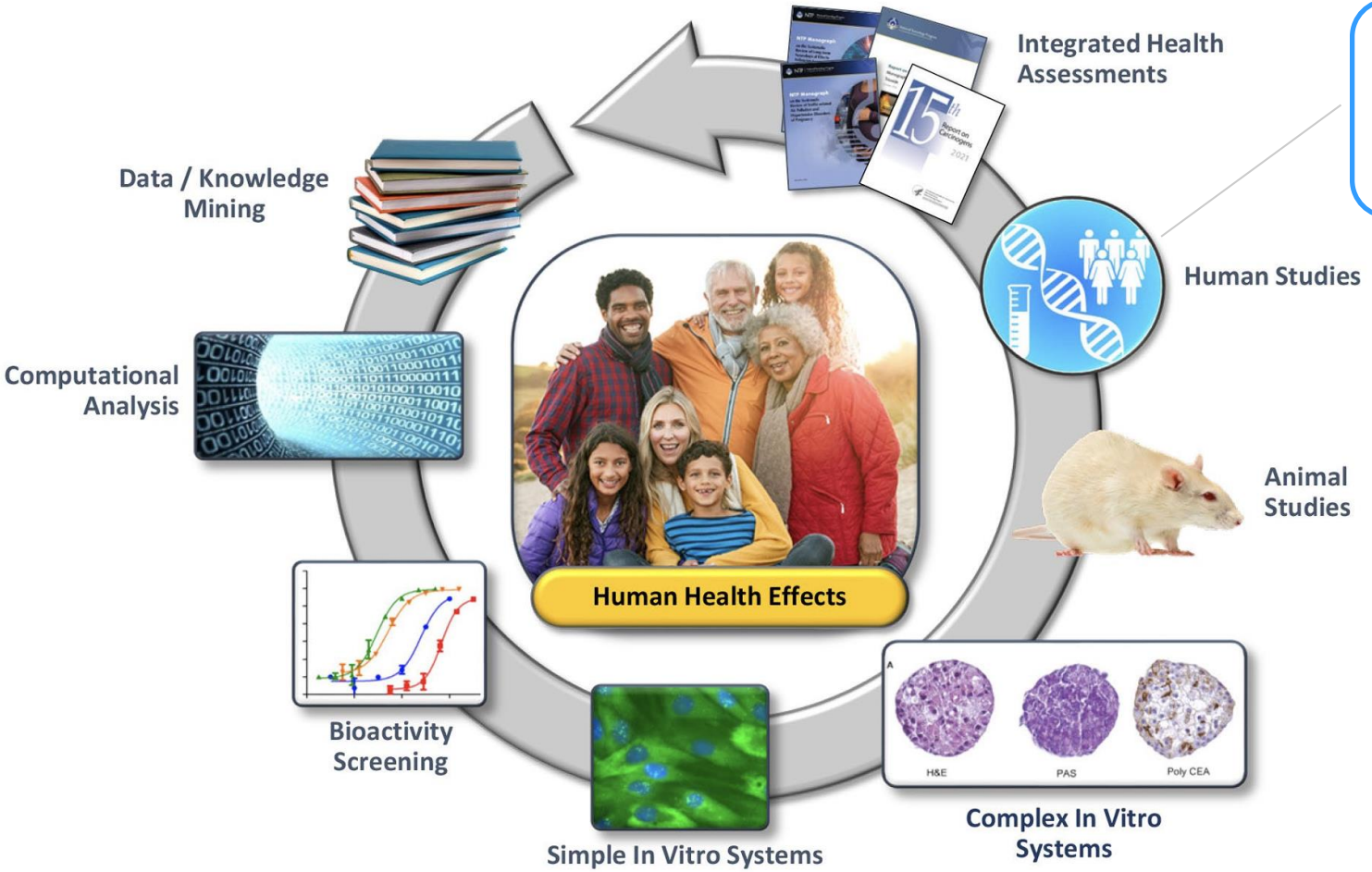
Warren Casey
Office of the Director

Kristine Witt
Predictive Toxicology Branch, Retired (Special Volunteer)

Translational Toxicology Pipeline



Translational Toxicology Pipeline



PROject 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

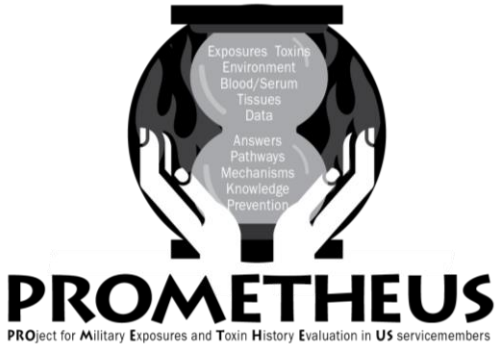
- Focused on developing actionable tools for prevention of exposure-related cancer and understanding mechanisms of disease development that may enable early detection or enhanced precision treatments.

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

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

CANCER MOONSHOT

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

- **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

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

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.

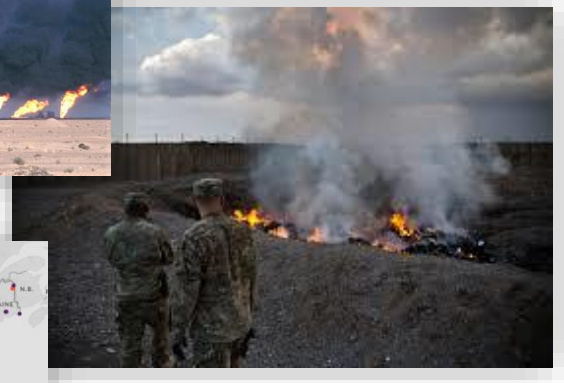
Expand Access to Cancer Screenings

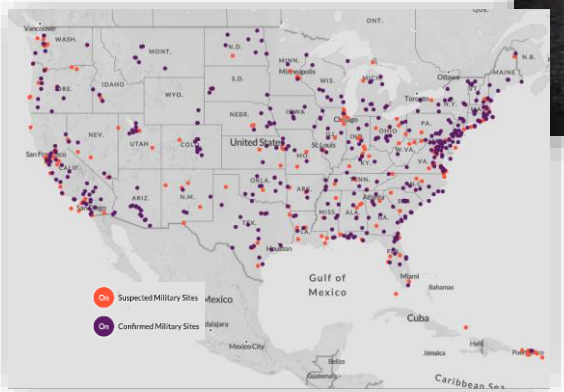
Understand and Prevent Toxic and Environmental Exposures

- $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**





- **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**
- **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

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

USU Murtha Cancer Center Research Program

NIH National Institute of Environmental Health Sciences

NIH National Cancer Institute

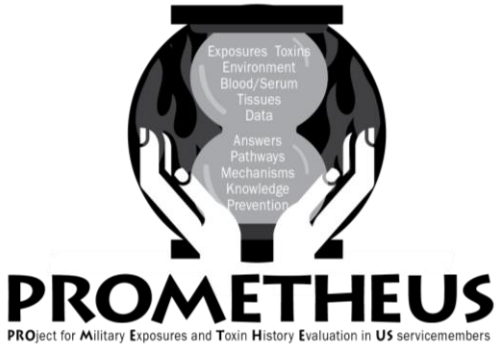
Pacific Northwest National Laboratory

VA U.S. Department of Veterans Affairs

Ellison Institute

Chan Soon-Shiong Institute of Molecular Medicine at Windber

Resources

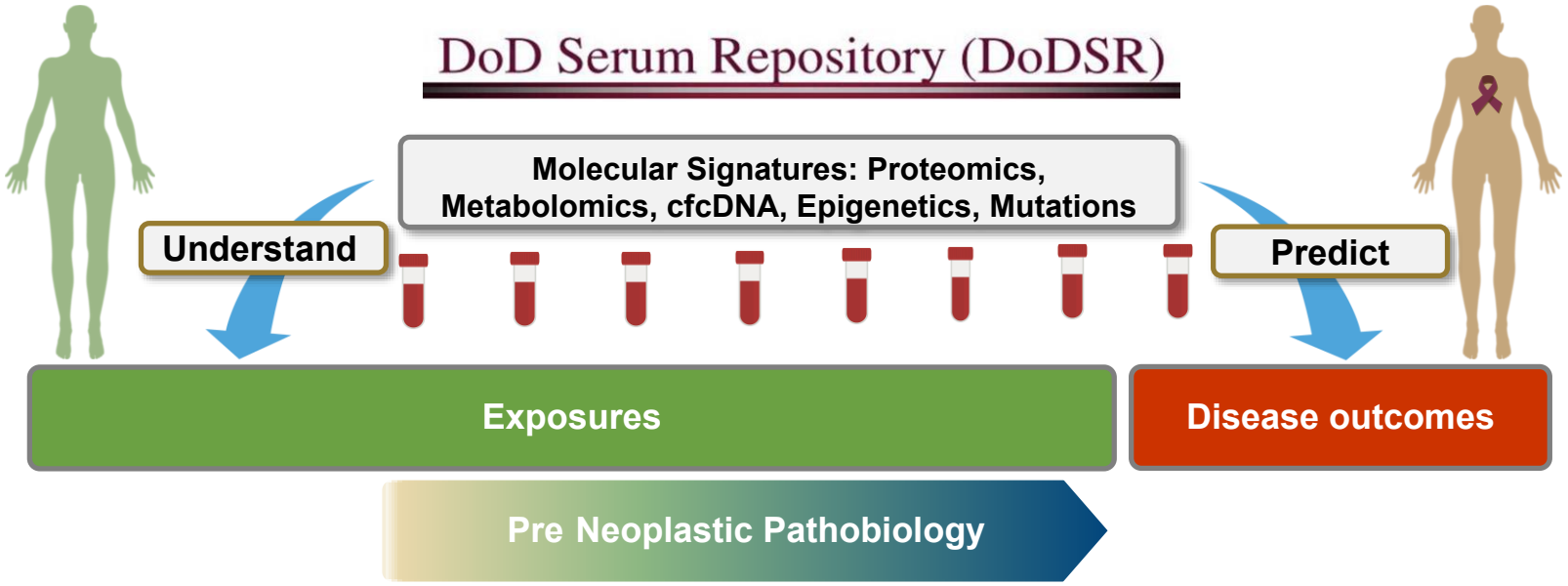

Exposures Toxins
Environment
Blood/Serum
Tissues
Data
Answers
Pathways
Mechanisms
Knowledge
Prevention
PROMETHEUS
PROject for Military Exposures and Toxin History Evaluation in US servicemembers

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



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

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.

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; 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

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.

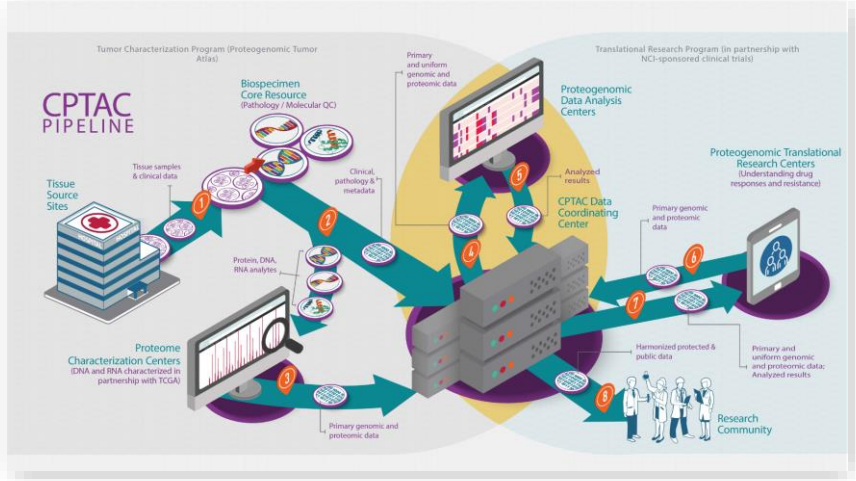
Data Portal

Antibody Portal

Assay Portal

CONTACT US

SIGN UP FOR EMAIL UPDATES



Clinical Proteomic Tumor Analysis Consortium (CPTAC)

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

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

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

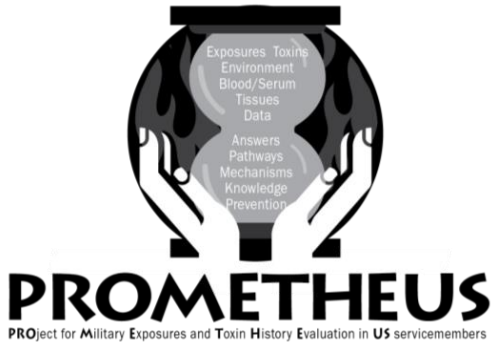
Retrospective

- APOLLO 5 All cancers
- APOLLO 6 Pancreatic Cancer
- APOLLO 7 Testicular Germ Cell Tumors
- APOLLO 8 Glioblastoma
- APOLLO 9 Krukenberg Tumors

Prospective

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

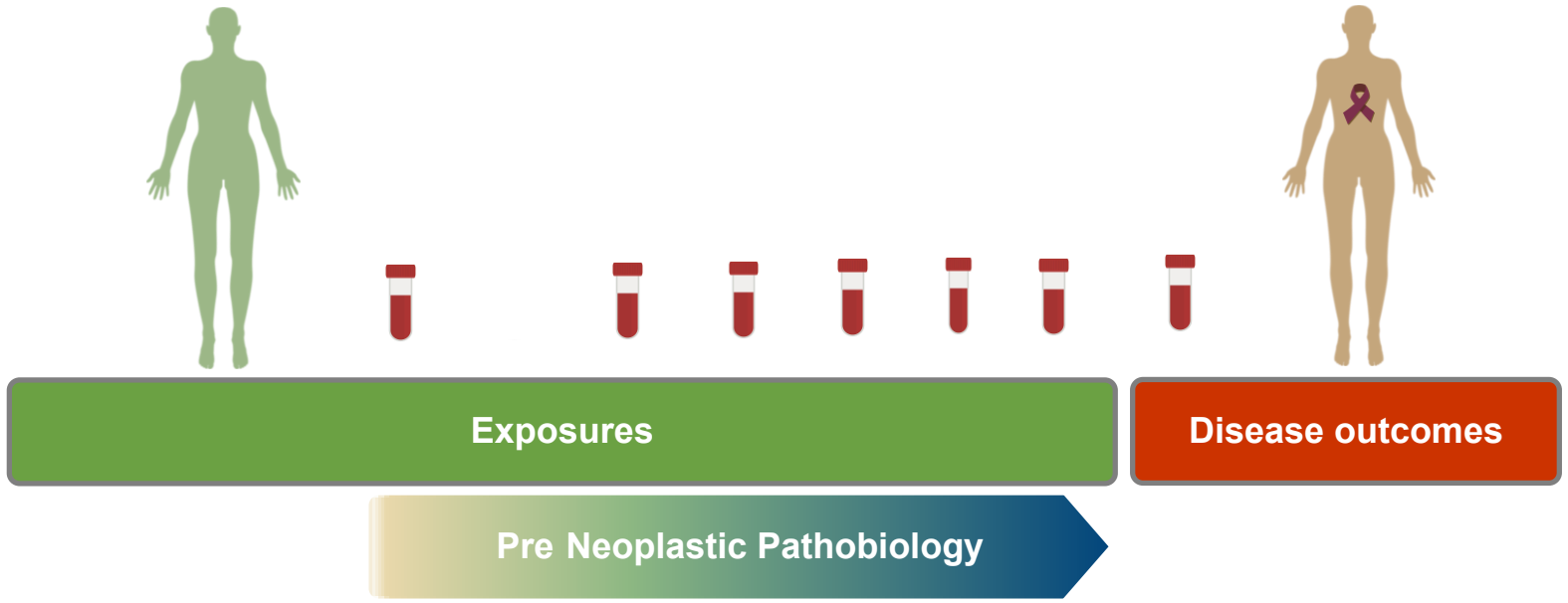
PROMETHEUS
PROject for Military Exposures and Toxin History Evaluation in US servicemembers



Research Programs

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

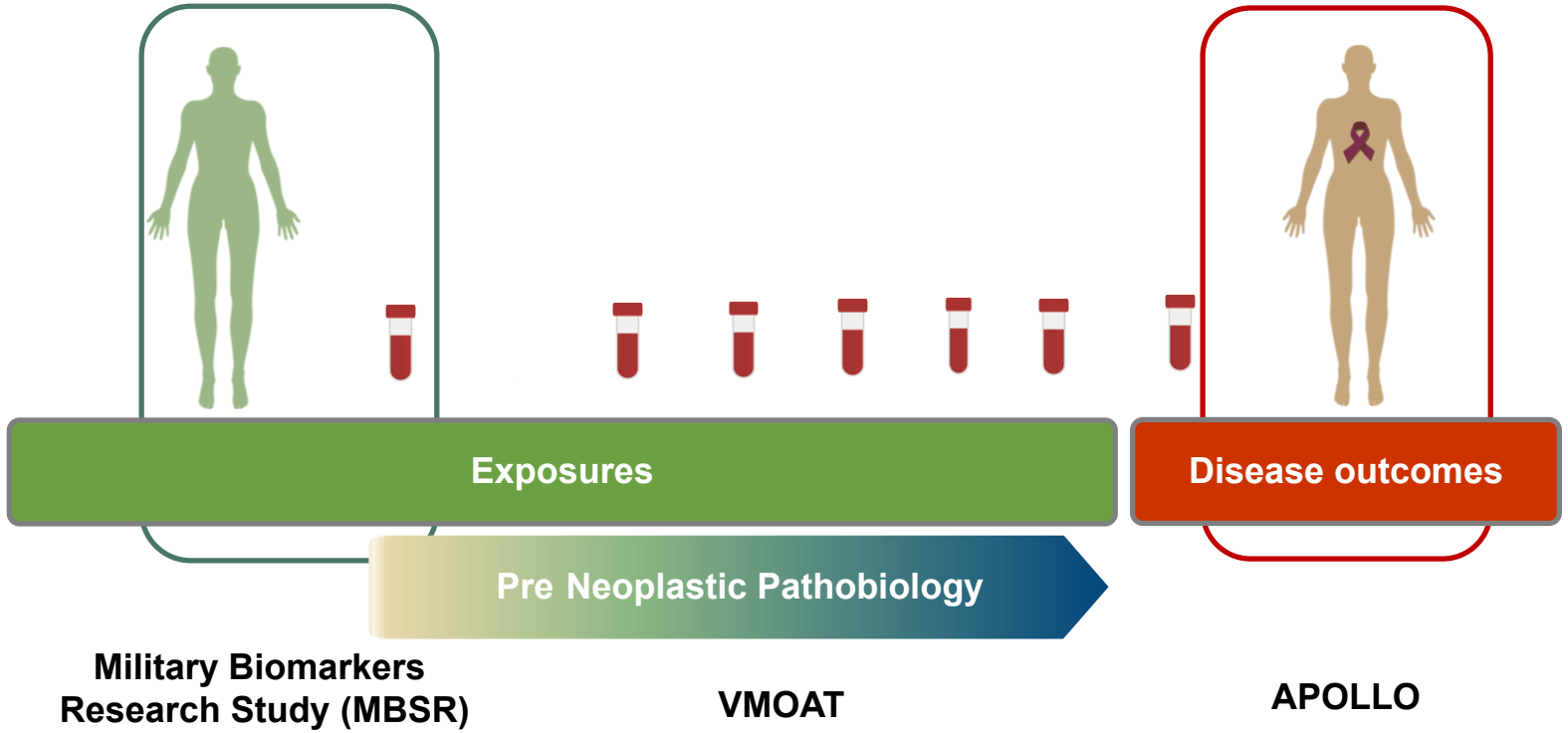
- Pan Cancer
- Focused on deployment-related exposures
- Includes cases that were Active Duty or Veterans at time of diagnosis



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

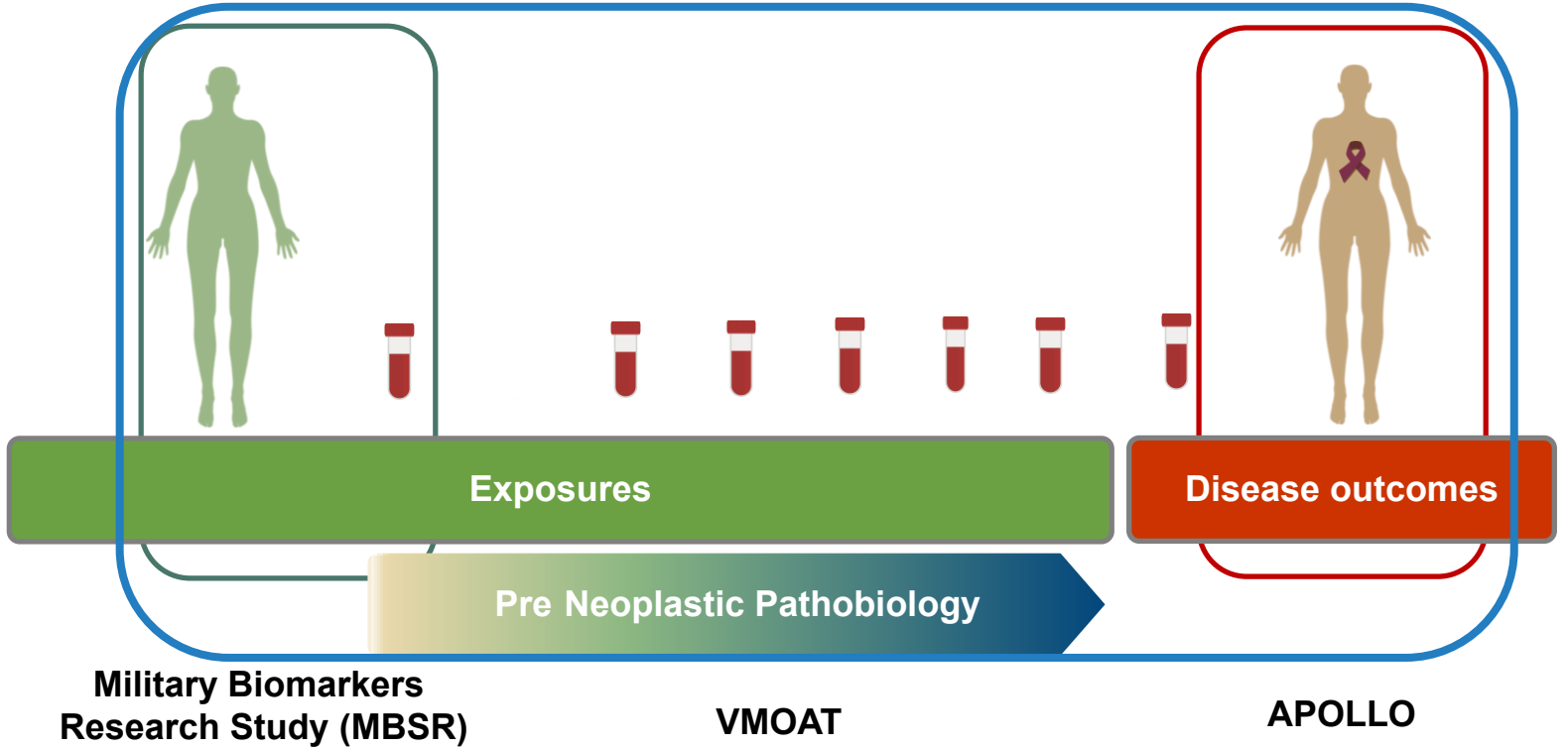
- Pan Cancer
- Focused on deployment-related exposures
- Includes cases that were Active Duty or Veterans at time of diagnosis



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

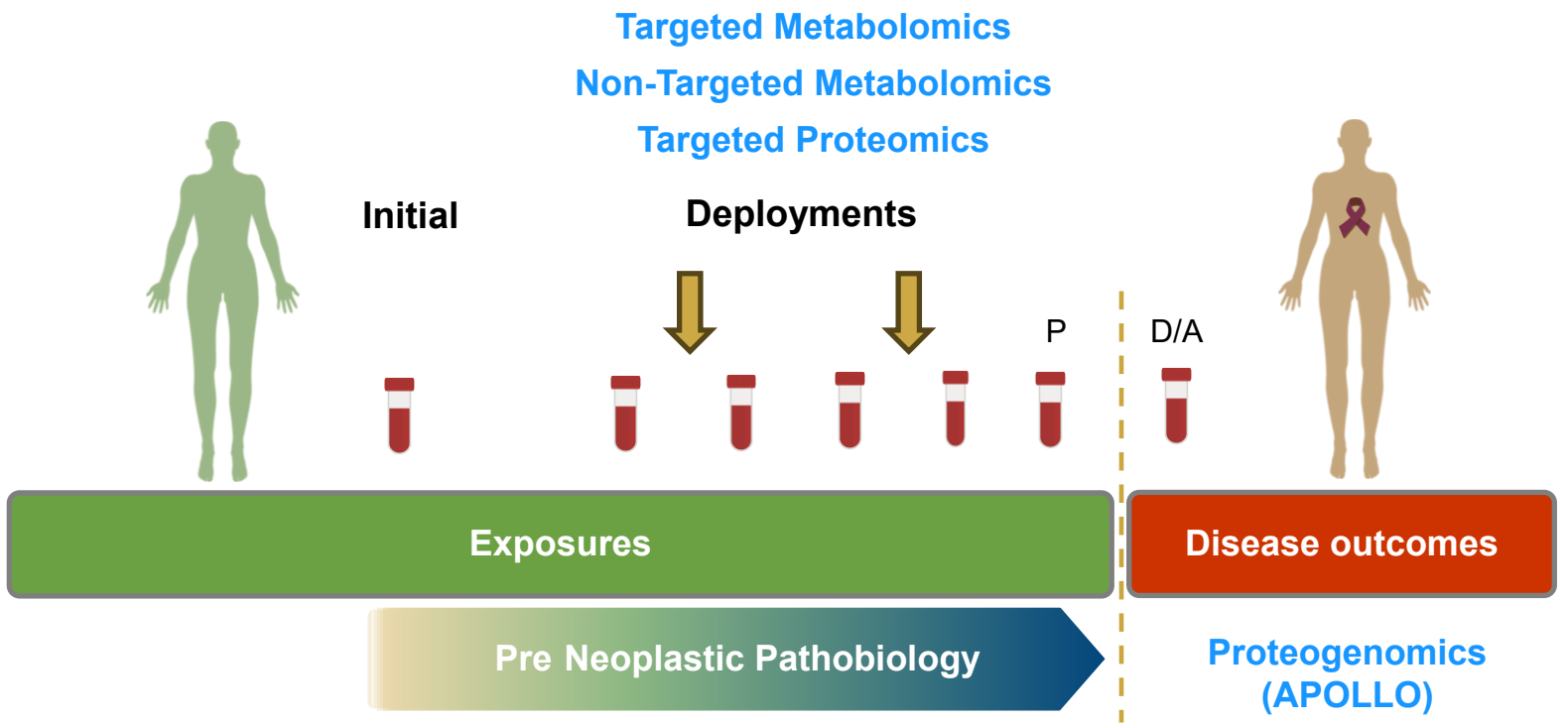
Use of DoDSR Sera and Toxin Exposure Data in APOLLO-enrolled Patients to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes

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



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



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

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

Exposures

Disease outcomes

Pre Neoplastic Pathobiology

Conference Report

Colorectal Cancer

Early-onset colorectal cancer research: gaps and opportunities

Laura Brockway-Lunardi[1], Stefanie Nelson[2], Arun R Pandiri[3], James V Tricoli[4], Asad Umar[5], Anil Wali[6] & Phillip J Daschner*[,7]

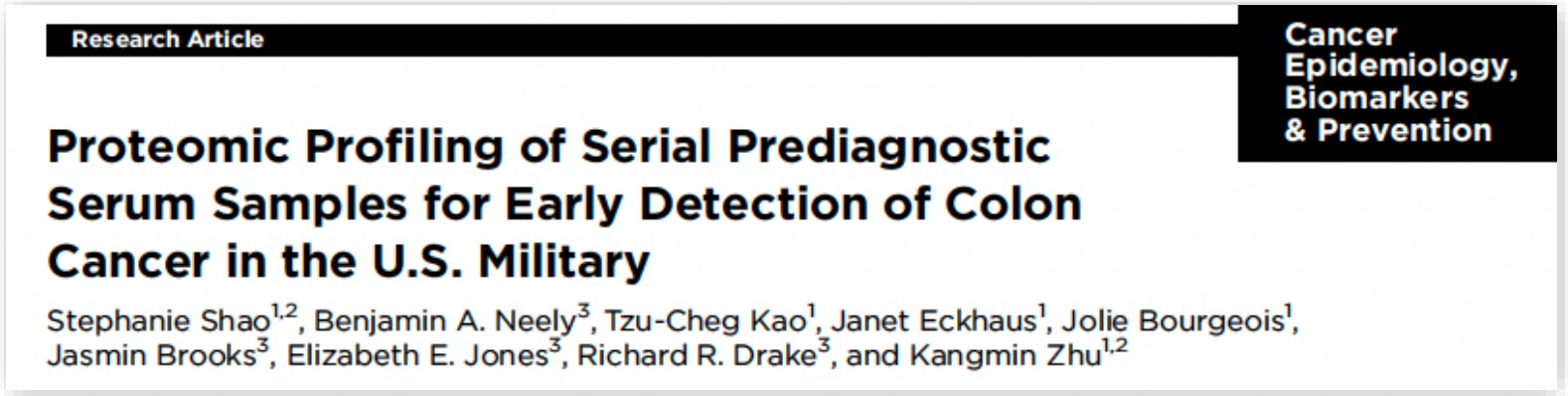
Greatest interest in the contribution of environmental exposures

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 non*APC* 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.

Slide courtesy of Arun Pandiri

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]

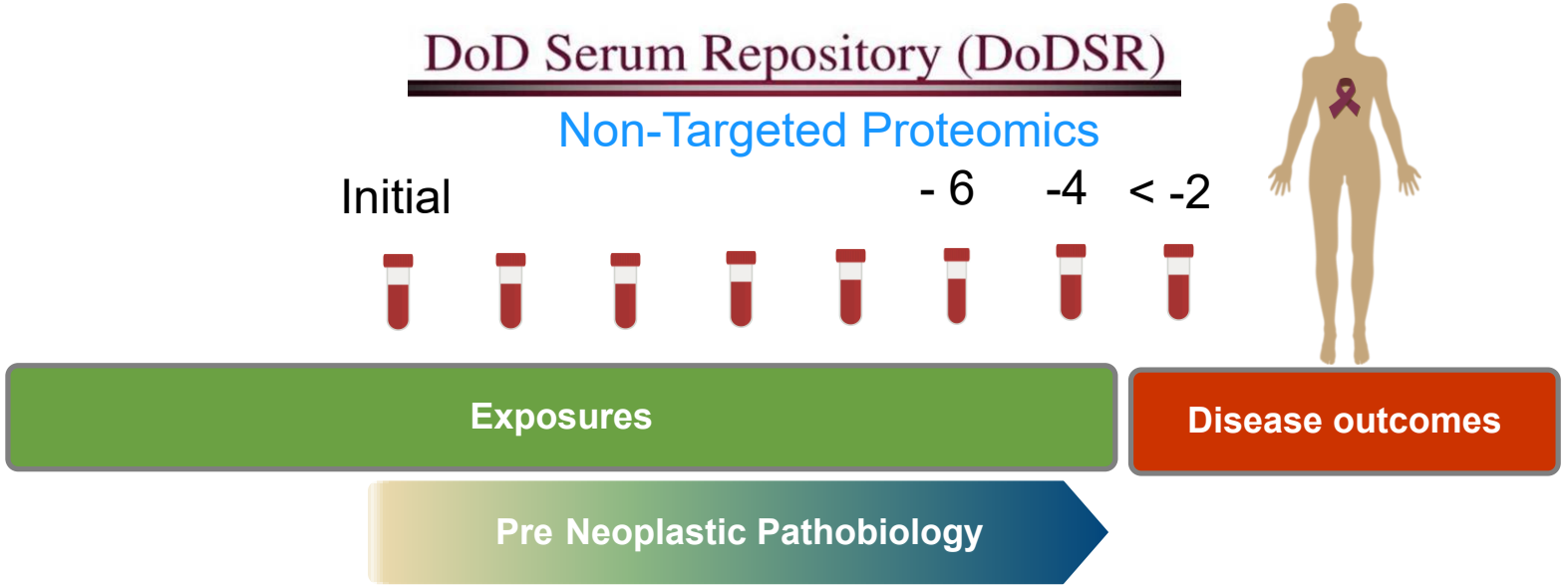
› Cancer Epidemiol Biomarkers Prev. 2017 May;26(5):711-718.
doi: 10.1158/1055-9965.EPI-16-0732. Epub 2016 Dec 21.

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.

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 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

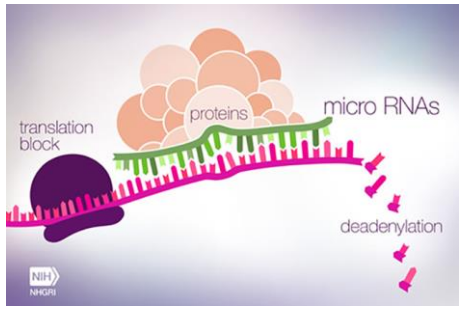


PROMETHEUS
PROject for Military Exposures and Toxin History Evaluation in US servicemembers

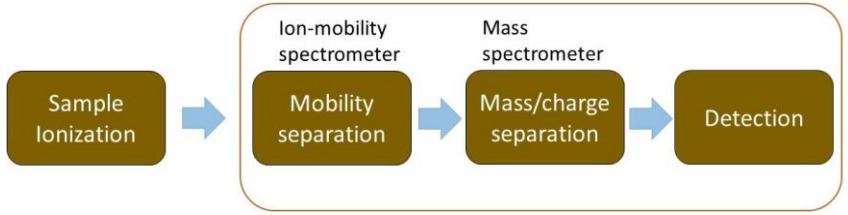
Use of DoDSR Sera and Toxin Exposure Data in to Identify Potential Biomarkers of Cancer Risk, Biology, and Outcomes for Early Onset Colorectal Cancer

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)



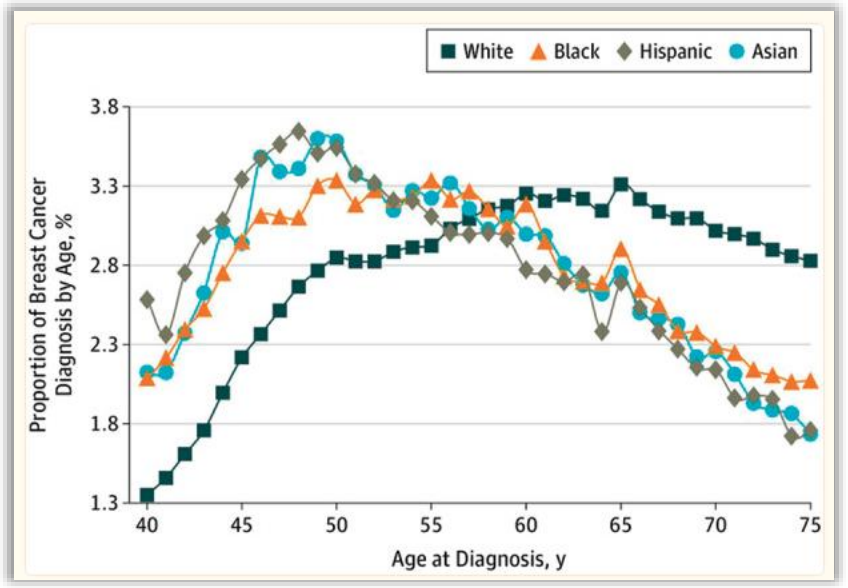
Ion mobility spectrometry-mass spectrometry

Erin Baker

Ivan Rusyn

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)

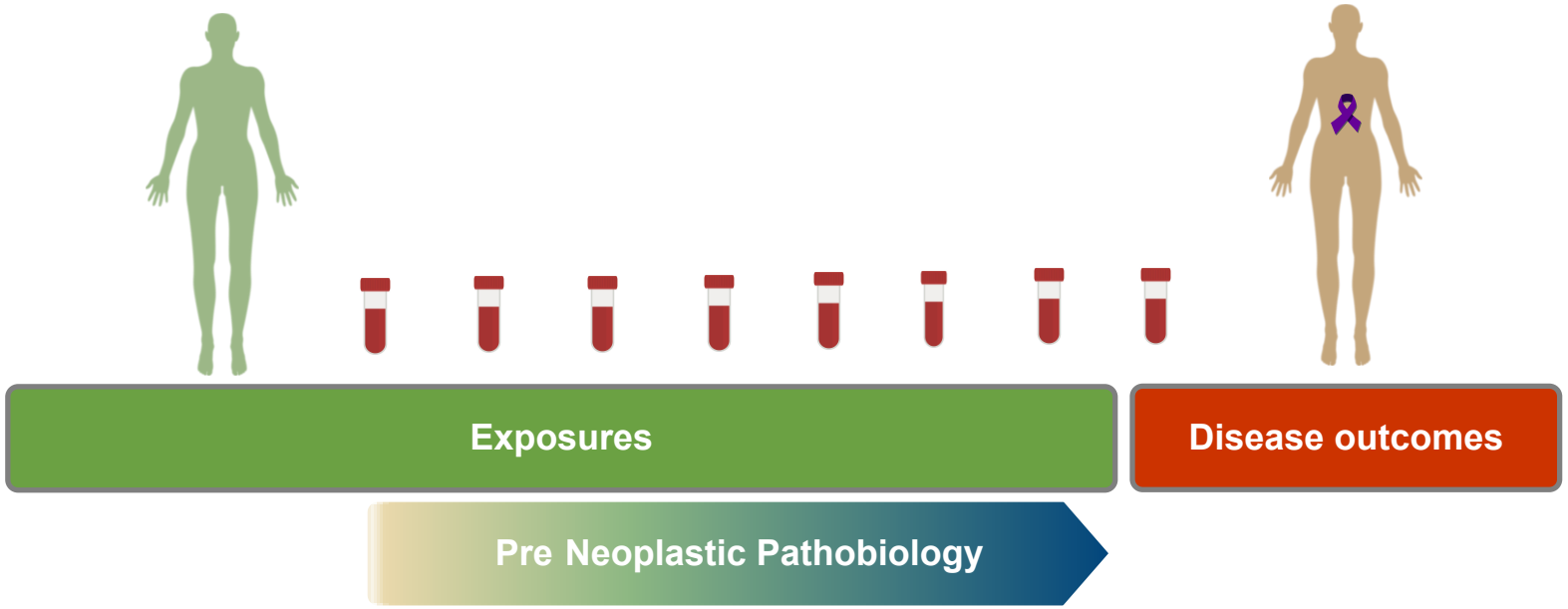


Chelmow. Early-Onset Breast Cancer Executive Summary. Obstet Gynecol 2020

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

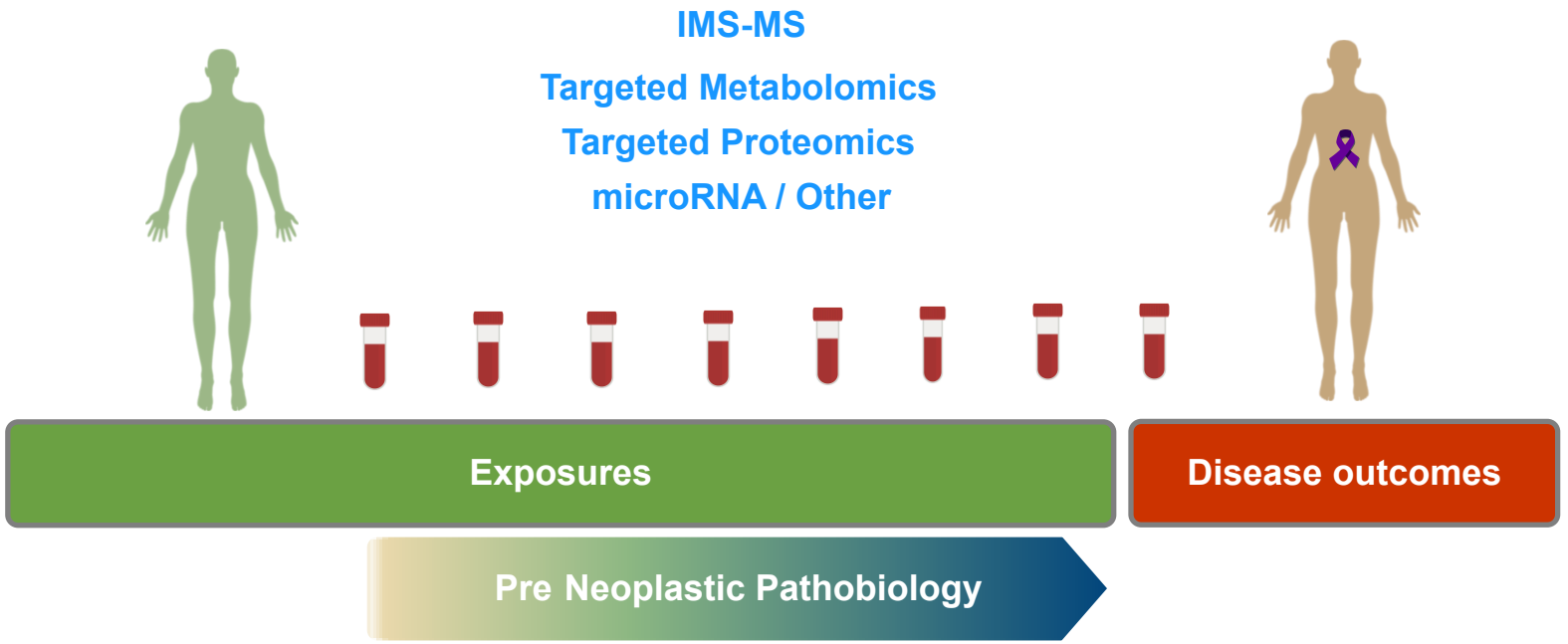
- Include only those on Active Duty at time of diagnosis
- Deployment-agnostic
- Requesting all available samples (~10-12 / per individual)



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

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



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

Prospective Exposure Studies using OneDraw

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

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 Exposure 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

USU Uniformed Services University

NIH National Institute of Environmental Health Sciences

Chan Soon-Shiong Institute of Molecular Medicine at Windber

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

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)

Pacific Northwest National Laboratory

Ellison Institute

USU Uniformed Services University

NIH National Institute of Environmental Health Sciences

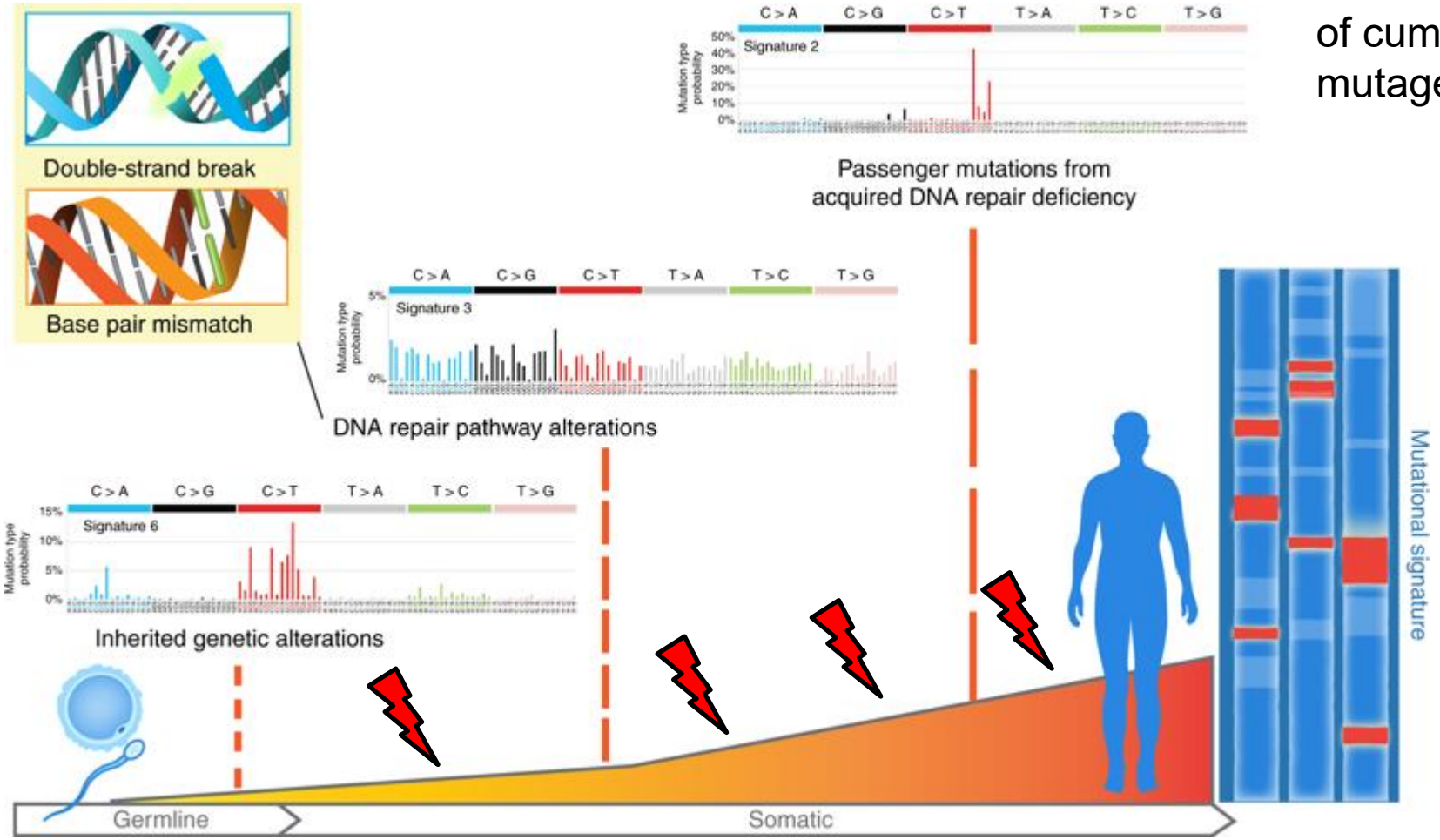
Chan Soon-Shiong Institute of Molecular Medicine at Windber

VA U.S. Department of Veterans Affairs

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

Introduction

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

http://cancer.sanger.ac.uk

Translational relevance of rodent cancers

Linking cancer mutation signatures to exposures

CANCER MOONSHOT

Collaboration with VA/CDC(ATSDR)

Camp Lejeune Tumors → WES → Mutation signatures

TCE, PCE, VC, BZ

Camp Pendleton Tumors → WES → Mutation signatures

Controls

Compare

Collaboration with JPC

Agent Orange tumor registry → WES → Mutation signatures

TRANSLATION

Mutation signatures of Rodent tumors

Ahr, CAR/PXR, PPARa carcinogens

- Bettina Grasl-Kraupp (MUV)
- DTT/NIEHS studies

IARC group I and 2A Carcinogens

- Dave Adams (Sanger)
- Daniele Mandrioli (Ramazzini)
- DTT/NIEHS studies

A. Pandiri

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

National Institute of Environmental Health Sciences
Division of Translational Toxicology

MCCRP Uniformed Services University

PROMETHEUS RETREAT

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

MCCRP
Uniformed Services University

PROMETHEUS RETREAT

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

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

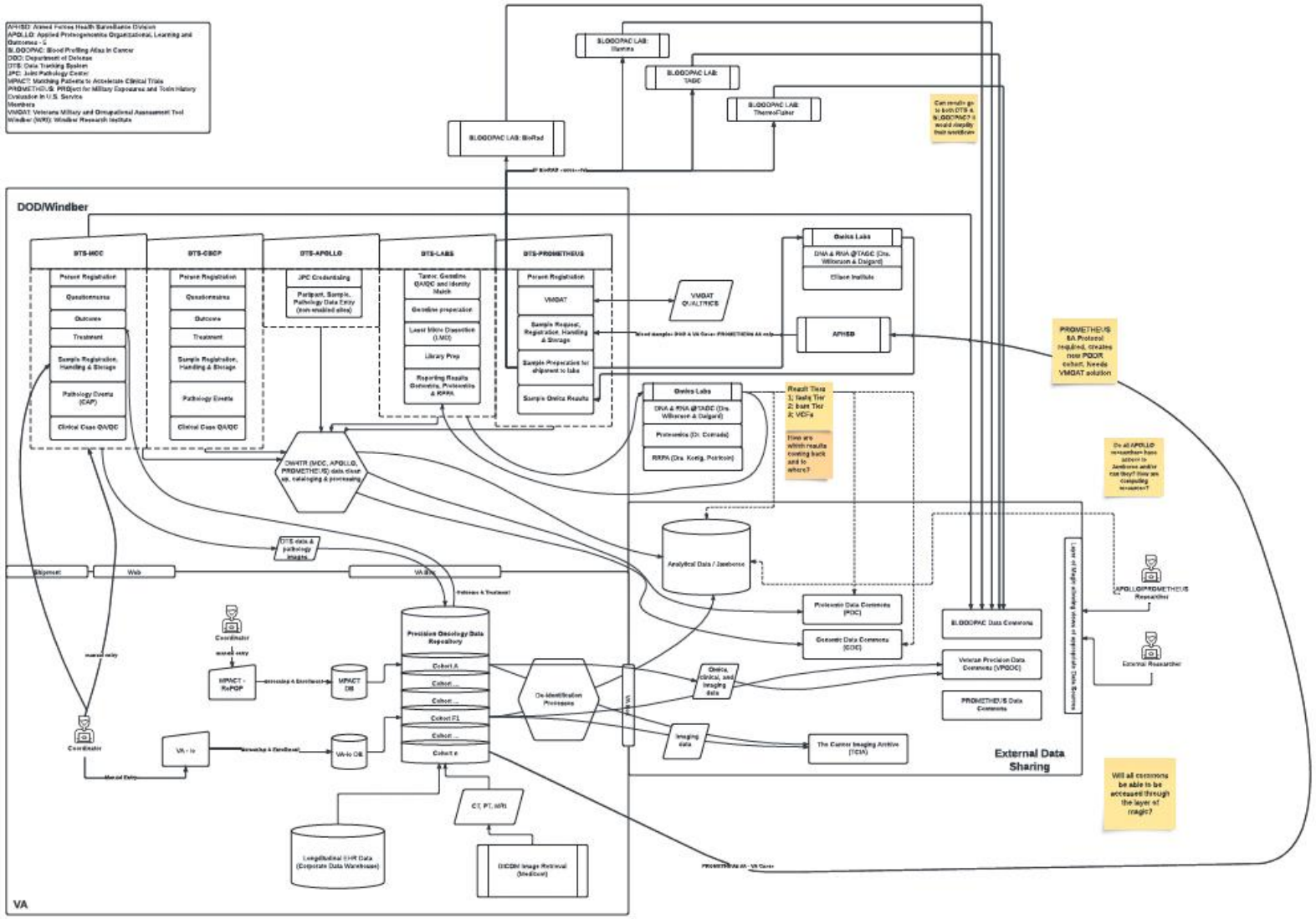
EWG PFAS Map
https://www.ewg.org/interactive-maps/2020-military-pfas-sites/map/

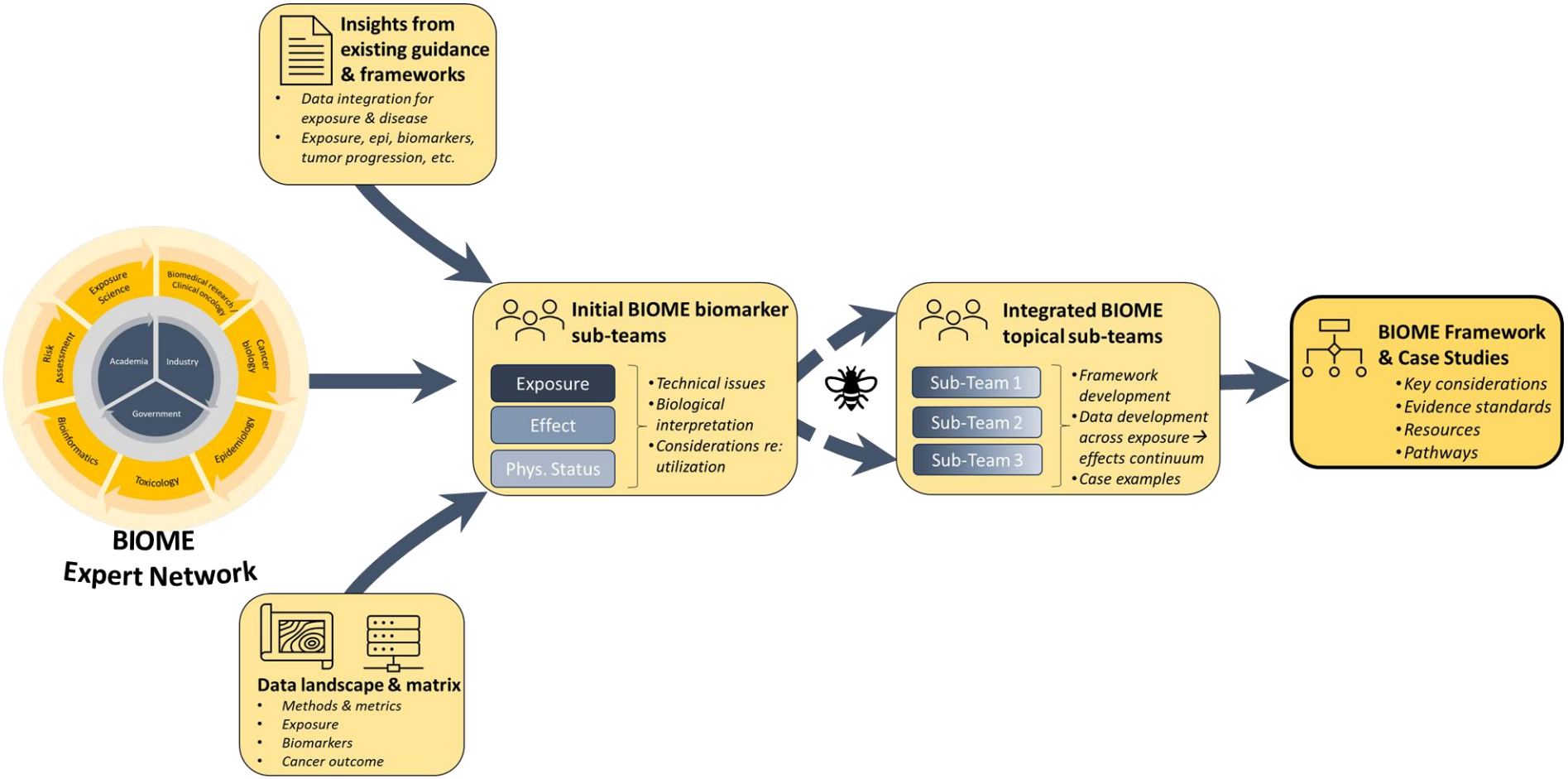
Lee JY, Shi T, Petyuk VA, Schepmoes AA, Fillmore TL, Wang YT, Cardoni W, Coppit G, Srivastava S, Goodman JF, Shriver CD, Liu T, Rodland KD. Detection of Head and Neck Cancer Based on Longitudinal Changes in Serum Protein Abundance. Cancer Epidemiol Biomarkers Prev. 2020 Aug;29(8):1665-1672. doi: 10.1158/1055-9965.EPI-20-0192.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

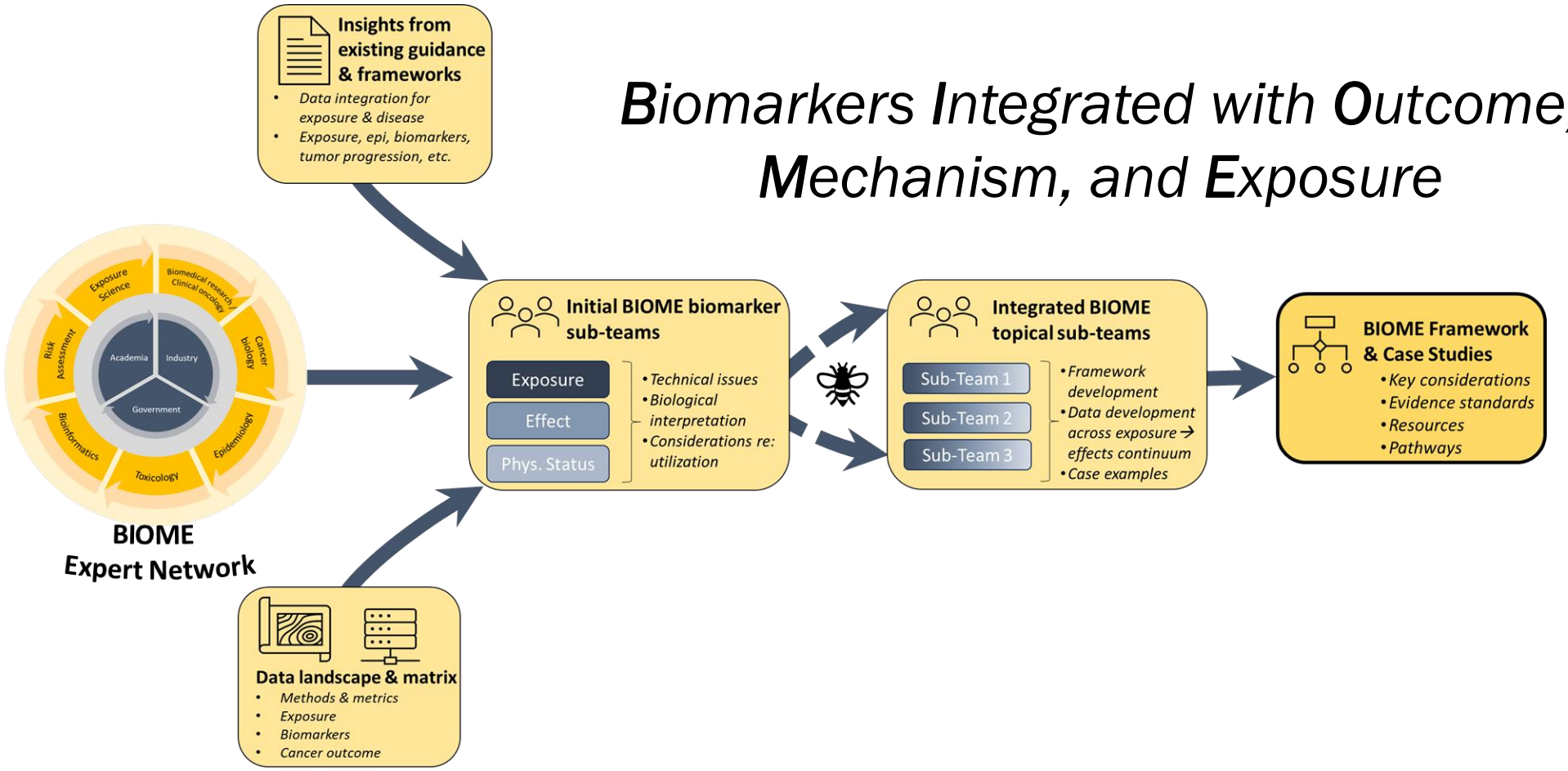
Data management





Health and Environmental Sciences Institute

Biomarkers Integrated with Outcome, Mechanism, and Exposure



Health and Environmental Sciences Institute

PROMETHEUS

M. Embry, HESI