RFA (UG3/UH3-Clinical Trials Not Allowed)

New Cohorts to Assess Environmental Exposures and Cancer Risk

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Purpose

- RFA will support new cancer etiology cohorts that use **innovative strategies and approaches** to
  - Address knowledge gaps between environmental exposures, genetics, and other molecular factors and cancer etiology across diverse populations
  - Ensure rigor and reproducibility of data and biospecimen collections

- RFA responsive to NCI NCAB Cohort Subcommittee Report (2019)
  - Need for new etiology cohorts to address research gaps on exposures

Goal

- Fund approximately five new cohorts:
  - Assess new and understudied exposures with innovative designs and measures
  - Focus on both short-term and longer-term research questions
  - Investigators required to collaborate– facilitated by Coordinating Center
  - **Common data elements and biospecimen collection**
  - Priority for innovative, significant, and actionable research

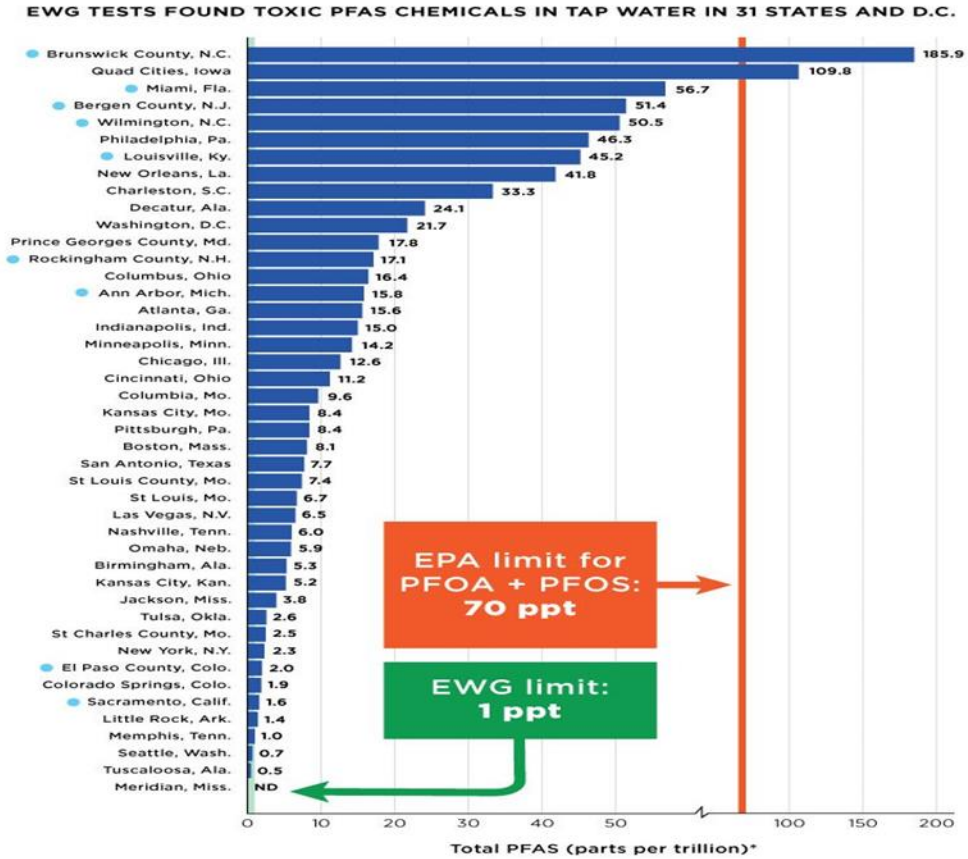
Need for New Etiology Cohorts

- Environmental exposures (e.g., new exposures, persistent chemicals, and chemical mixtures) understudied
- IARC and NTP have identified several “Group 1” or “Known Carcinogens” to humans, but many more environmental exposures lack adequate evidence to properly classify
- Identification of the key carcinogenic hallmarks of environmental exposures needed in prospective designs
- Challenge with existing cohorts include blood collected at the appropriate time point to assess new exposures; appropriate age; limited research on life-course exposures; diversity

Resources of existing cohorts (data and biospecimens) -- R01/R21/R03 applications

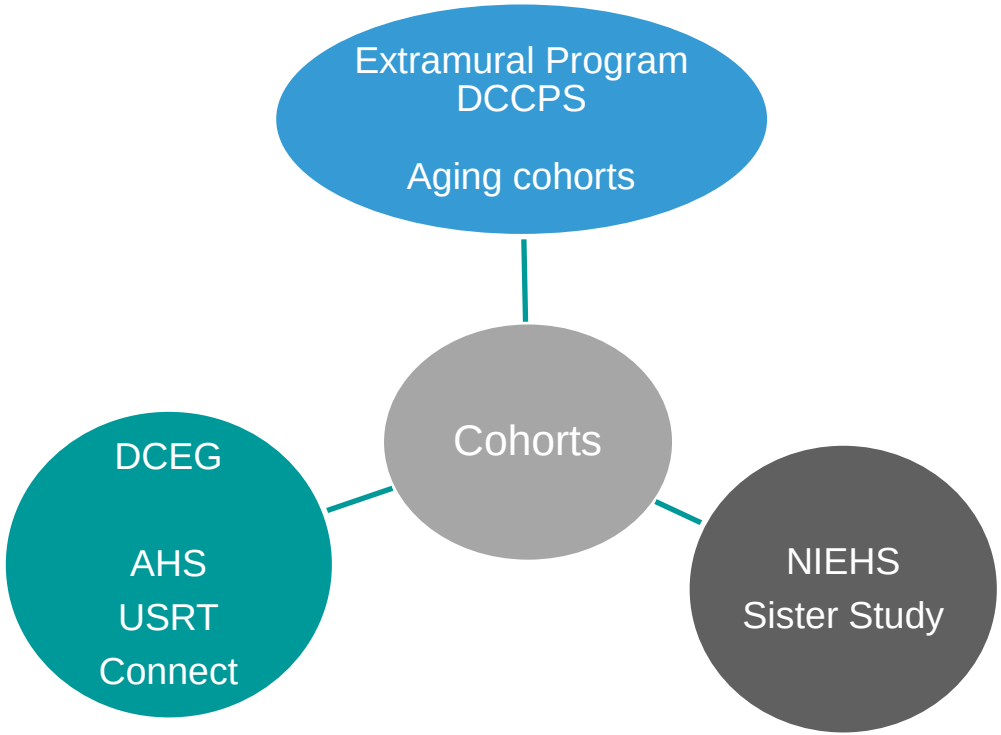
Example of New Exposure

- Emerging classes of chemicals are persistent in the environment and accumulate in humans [e.g., per- and polyfluorinated alkyl substances (PFAS) and endocrine disrupting chemicals (EDC)]
- Novel or understudied exposures
- Answers are needed regarding their potential to increase risk for cancer



Evans S et al. PFAS Contamination of Drinking Water Far More Prevalent Than Previously Reported. The Environmental Working Group, Jan. 22, 2020.

Cancer Etiology Cohorts



Relevance to NIH *All of Us*

- Not focused on cancer or environmental exposures
- Collected biological samples could be relevant
- Open resource available for research investigations

AHS – Agricultural Health Study (started 1993) – occupational cohort
USRT - U.S. Radiologic Technologists (following technologists since 1983) – occupational cohort
Connect - Comprehensive Oncology Network Evaluating Tumors – conducted within a set of integrated health care systems
Sister Study (started 2004) – study of women whose sister had breast cancer

Short-Term Research Examples

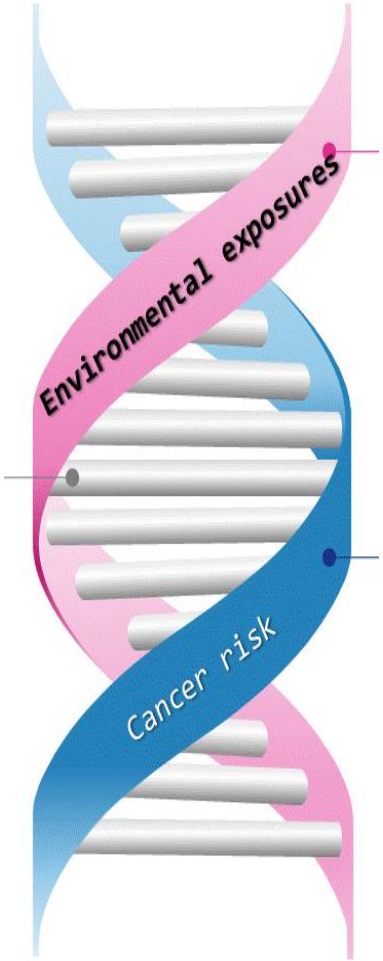
- Use IARC framework to assess biological mechanisms to support classification of environmental exposures
- Other bioassays
- Building cohort
- Use incident cases for case-control/case-cohort studies in the initial years

Biological Mechanisms (Carcinogenic characteristics)	Measures
Metabolic activation	DNA and Protein Adducts
Is genotoxic	DNA damage; Gene mutations, Cytogenic changes
Induces chronic inflammation	Elevated WBC; altered cytokine/chemokine production
Is immunosuppressive	Decreased immunosurveillance; immune dysfunction
Alters cell proliferation	Cell proliferation; Angiogenesis

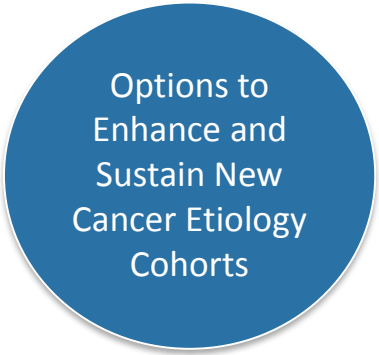
Smith et al. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Env Health Persp 124(6):713-21, 2016

Longer-Term Research Questions

- What chemical, physical, lifestyle and genetic factors interact to affect cancer risk in understudied populations?
- How are timing of environmental exposures, multiple exposures, and chronic low-dose exposures associated with cancer development?



Sustainability



- Cohort Infrastructure Support PAR
- SEER Virtual Pooled Registry Cancer Linkage System
- Human Health Exposure Analysis Resource (HHEAR)
- Innovative Molecular Analysis Technologies (IMAT)
- R01 Grants

NCI Portfolio Analysis

- NCI currently provides infrastructure-only support for 16 etiology cohorts (2 are in phased close-out; 2 are not US-based; 3 started as RCTs)

Age – majority 75 years and older

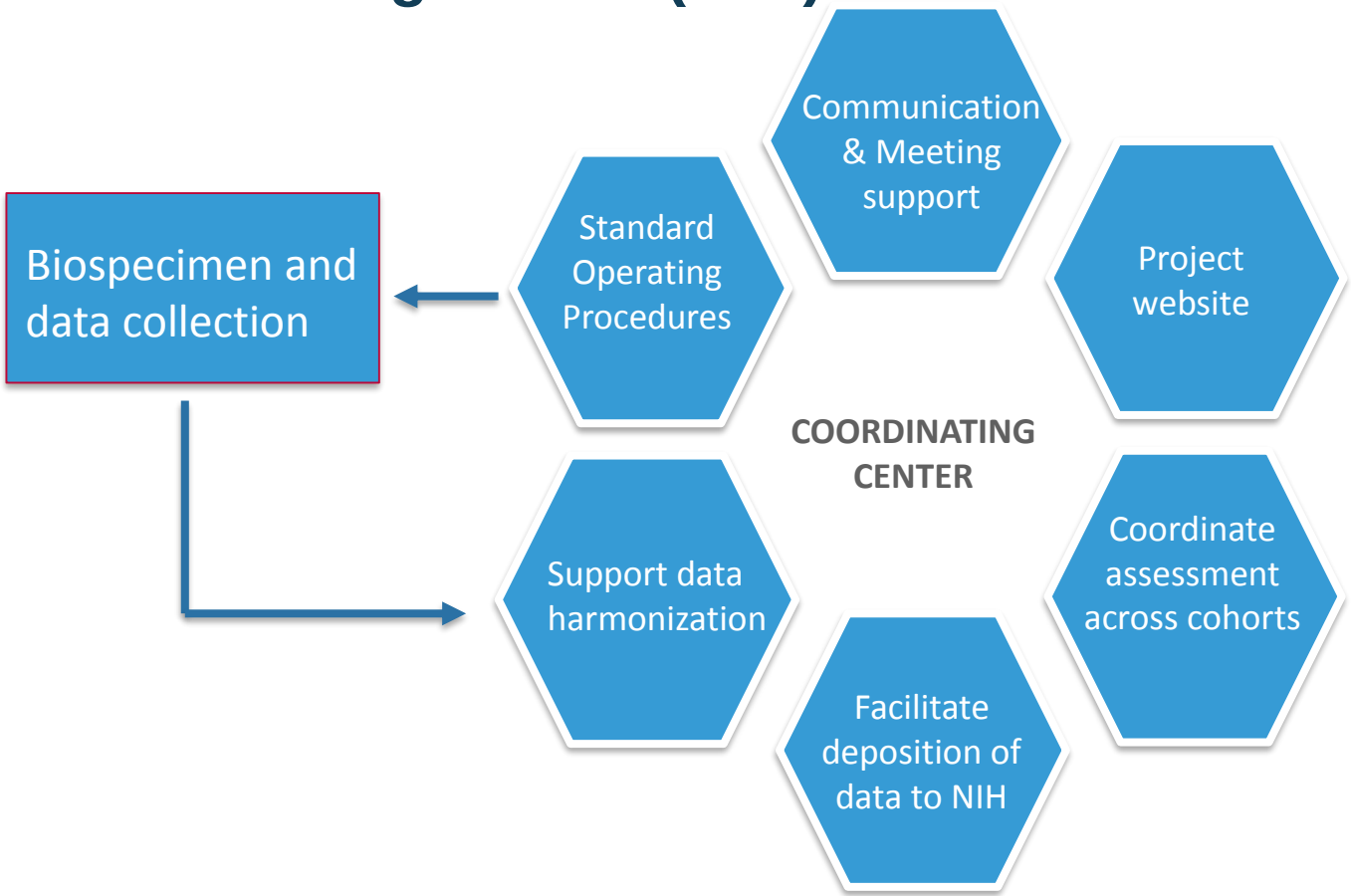
Attrition – due to deaths approx. 62%

Racial/Ethnic – majority Whites (75%); African Americans (16%)

New Exposures – cannot be adequately addressed

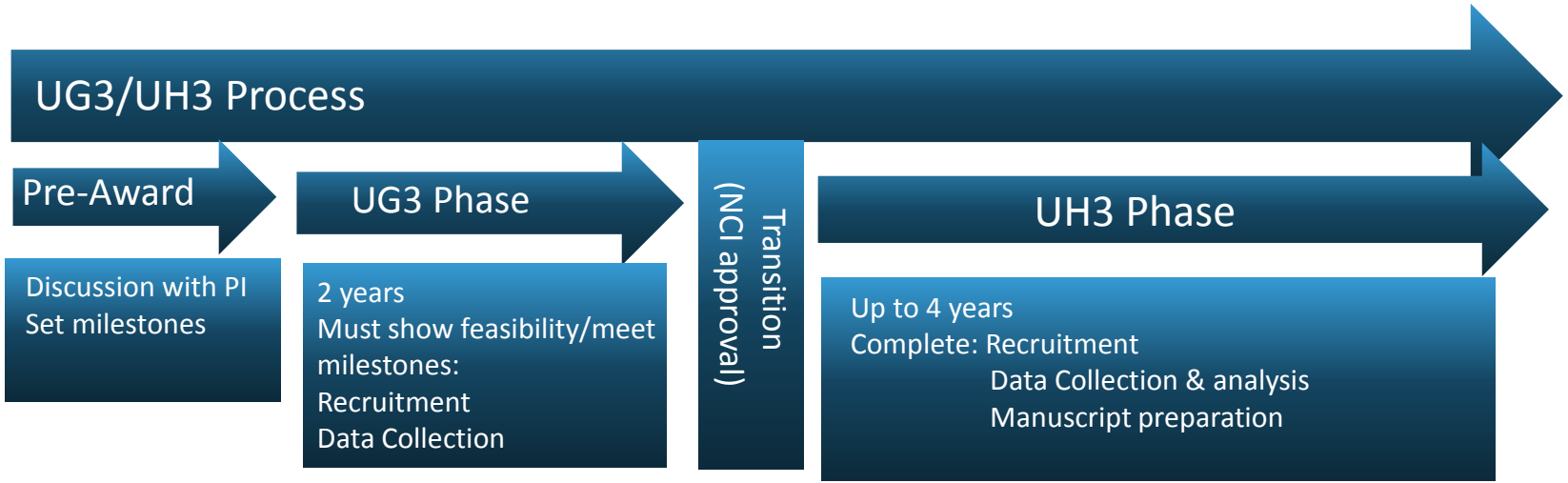
- **NCI active grants portfolio show scarcity of funding research focused on environmental exposures**

Coordinating Center (U01)



UG3/UH3 Research Mechanism

- UG3 phase PI sets milestones for recruitment and data collection (requires approval from Program and NCI leadership)
- UH3 phase focused on completing research



Evaluation Criteria

- Innovation - priority **to innovative and novel** projects and **study designs** using **technological and molecular innovation t**o address identified research gaps related to environmental exposures
- **Inclusivity**: Representation of understudied and diverse populations
- Strong scientific justification for research questions to be addressed, approach, and population; Willingness to **collect core data and biospecimens**
- UG3/UH3 milestones must be appropriate
- Data sharing – compliance with NIH policies
- Proposals for the CC will be evaluated on the evidence of having provided administrative and logistic support for cohorts

RFA Justification and Budget

- Set aside funds
- Specialized review - scientific expertise with diverse reviewers

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	All Years
Total Costs (5 cohorts)	6.5M	6.5M	12.5M	12.5M	12.5M	12.5M	63M

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	All Years
Total Costs: CC	0.8M	0.8M	0.8M	0.8M	0.8M	0.8M	4.8M

Reviewer Comments and Responses (Seewaldt, Robison, and Bondy)

- **Emphasize innovative strategies** – RFA will be modified to emphasize innovation in scientific questions, design, and assessments
- **Rigor and reproducibility** – RFA will emphasize rigor and reproducibility in biospecimen and data collection and require core collections
- **Rationale for new cohorts** – New exposures; appropriate population-relevant to research questions; diversity
- **Clarify population-based** – appropriately defined and relevant to research questions; International allowed with relevance to US populations
- **Coordinating Center** – PI will be part of the collaborative steering committee

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