NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCEINCES
Division of Extramural Research and Training

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Concept Clearance
**An Integrated, Multi-Institute Plan to Facilitate Gene-Environment Interaction Studies**

An NIEHS lead, trans-NIH effort in capacity building
Developed by a working group of the NIH Genes, Environment and Health Initiative
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**Rationale and Objectives**:
It has been estimated that 70-90% of human disease results from interactions between genetic and environmental factors; however, identifying the critical associations causing and exacerbating disease has proven to be a challenging research problem. Traditional approaches to disease investigation have focused largely on a single causative factor in disease etiology or in some cases straightforward interactions between a very small number of candidate factors. The NIH Genes, Environment and Health Initiative (GEI) was funded in 2007 to create a technological foundation for comprehensive, large-scale gene-environment interaction studies designed from the outset to test a large number of variables contributing to individual disease evolution. Despite significant progress towards that technological foundation, there are additional gaps that must be addressed in order to implement the intended large-scale studies. These include the continued development of tools for characterization of the personal environment, the development of statistical approaches for mapping gene-environment interactions and the design of mechanistic studies to explore the functional basis of candidate interactions. Nonetheless, while there is much developmental work remaining to be done the success of the initial program has laid the requisite foundation to enable small-scale, focused proof-of-principle studies on gene-environment interaction. The multi-year, multi-Institute plan outlined here will address these gaps and progressively build a series of studies conducting population based studies on Gene-Environment interaction in human disease with increasing power and depth.

**Overview of GEI-Phase I:**
The four year (2007-2011) GEI effort was overseen by two programs independently developing capacity on both the genomic variation and environmental characterization fronts. The effort was supported by the office of the Secretary of the Department of Health and Human Services and the NIH Director with $40M annually committed from these centralized sources; in addition individual ICs, including NIEHS, have contributed funds from their own appropriations to support this effort.

The GEI Genetics Program focused on establishing a capacity in genome-wide analysis of variation with the centerpiece being the support of multiple Genome Wide Association Studies (GWAS) to map the associations between genetic variants with disease or phenotypic endpoints on a whole genome scale. Other Genetics Program efforts included the replication and fine mapping of candidate variants from GWAS studies, the development of statistical methods for gene-gene and gene-environment interaction studies, the functional analysis of genetic variants and the translation of the findings into personalized medicine.

The GEI Exposure Biology Program focused on the development of tools for characterizing the personal environment. These include both the development of wearable sensors for assessing the exposure to environmental chemicals, diet, physical activity and psychosocial stress and also the identification of candidate markers of the initial biological response to those factors. A primary goal of this effort has been to change the view of exposure from a focus on single analytes to a complex view of the personal environment including both the chemical milieu and lifestyle factors along with the characterization of the individual response to that personal environment.

**Ongoing GEI derived activities being conducted in FY11 and 12:**
As the projects supported by GEI draw to an end in FY11 several short term activities are underway to maintain momentum and continue the development of the foundation for gene-environment interaction studies; these include:

- NIEHS led two multi-IC RFAs (RFA-ES-10-007 and -008) for the validation of tools for characterization of the personal environment and biological response. The applications for this program are being considered in the May 2011 council round.
- NHGRI released a supplement program (NOT-HG-11-009) to PhenX ([www.phenxtoolkit.org](www.phenxtoolkit.org)) to expand the granularity and utilization of this resource providing standardized methods for measurements in complex diseases, phenotypic traits and environmental exposures. This program will expand the PhenX resource beyond questionnaires and lists of clinical measures as potential short or longer term activities.
- NIEHS is leading a PAR (PAR-11-032) with several participating NIH Institutes on analytical methods for GxE studies. This PAR focuses on identifying the effectiveness of various types of novel G x E methods that might increase power to detect G x E (variations of case-only or trio designs, looking at extreme phenotypes in families, etc.). Applications were received on February 3, 2011 and will be discussed at the October 2011 NAEHSC meeting.
- NCI is leading a PAR on spatial uncertainty in interpreting geocoded data. This program will focus on identifying the sources of spatial uncertainty in human health, disease and exposure data and will develop statistical methods and visualization tools to enhance communication. It will be publicly released in the summer of 2011.

**Proposed Short-term Activities:**
This concept includes several proposed activities to continue the evolution of the efforts initiated under the NIH Genes, Environment and Health Initiative. The long range goal is to enable future, large-scale studies of gene-environment interaction. Meeting this goal requires the continued development of tools for exposure assessment, the establishment of 'proof of principle' studies on Gene-Environment interaction studies and research to investigate the mechanistic and functional basis for gene-environment interactions. The specific concepts for these activities include:

- Continued Development of Tools for Characterization of the Personal Environment:
  - o Validation of Tools and Candidate Biomarkers for Exposure Biology: Given the response and results of the Validation RFAs as well as the recommendations from the Panel discussions at the Exposure Biology Program Grantees Meeting in April 2011 it is clear that there is a need to continue the effort to validate tools such as those developed in the GEI. This program will largely be a re-release of those initiatives but will allow for a longer project duration to allow for greater assessment of the added scientific value of the tools in an epidemiological setting. This appeared to be a common weakness across the applications.

- o Integration of wearable tools for characterization of the personal environment:  A critical aspect of exposure biology is the ability to assess multiple variables comprising the personal environment simultaneously.  While the GEI Exposure Biology Program supported the development of tools for assessing chemical exposures, dietary intake, physical activity, psychosocial stress and the use of addictive substances and encouraged integration across these variables very few tools exist today that allow simultaneous assessment of multiple factors in the environment in a single, minimally obtrusive device.  This program would support R01 and SBIR grants to develop, integrate and validate systems characterizing multiple aspects of the personal environment.
  - o Field Deployable tools for multi-analyte biomonitoring of environmental exposures: While the GEI has successfully developed a suite of tools for measuring exposure to airborne pollutants at the point of contact many environmental exposures have other, or mixed, route of exposure and very little information can be gained from a real-time point of contact exposure on longitudinal exposures. This program will mirror the tool development activities of GEI Phase I to develop a new set of tools based on in vitro diagnostic or lab-on-a-chip technologies to assay the levels of environmental factors (environmental agents, metabolites, macronutrients, or biomarkers) in readily accessible biological samples (blood, urine, saliva), including banked samples.  An emphasis will be placed on the ability to specifically detect multiple analytes in small volumes of biological fluids.  This could be conceived as a phased implementation with later support for an initial screen of exposures that might link with disease (mini-"EWAS") and subsequent application in larger genotyped case-control study for extensive G x E interaction detection. This program would support R01 or R21/R33, and SBIR grants.

- Proof-of Principle studies in Gene-Environment Interactions with three subcomponents:
  - o *Overlaying genomic information to human population studies having exposure characterization.*  This is an R01 program to add genetics analyses onto population studies with existing, well-characterized environmental exposure data with the purpose of identifying novel G x E interactions.  A portfolio analysis of parent projects suitable to this program across NIH is underway and it appears that there are relatively few projects with adequate numbers of sufficient scale (~3,000 cases and controls) with direct measures of environmental exposure.  Some possibilities of cohorts with suitable exposure characterization could include occupational cohorts or birth defects cohorts.  The CDC-NIH National Birth Defects Prevention Study would be a good example for a study having extensive environmental data but no genetics.  This study and other birth defect registries may have particularly extensive environmental information, including pre-natal (maternal) exposures.  In addition the Department of Defense has several studies that include a range of information of environmental factors and some information on genetics as well with extremely large repositories of banked biological samples for further analysis (the Millennium Cohort for instance has over 40 million banked samples from military personnel pre- and post- deployment as well as samples for their spouses).   This initiative could also take advantage of meta-analyses of ongoing, smaller studies with appropriately harmonized environmental data as well.
  - o *Applying new environmental measurement tools to existing human GWAS or other genetic population studies.*  This multi-IC program would make use of existing genetic or GWAS population studies or cohorts (Nurses Health, Framingham, etc.) to add additional measures of exposure (measure "E" better or for first time).  The addition of

prospective measures of the environment such as those developed by GEI phase I would require continuing contact with participants and likely needs to be staged to follow after the completion of the Validation effort; however, use of available gold standard measures without the precision of the GEI tools can also provide valuable proof of principle for the approach.

- *Secondary Analyses on GWAS studies for discovery of G x E interaction.* This small grant program would support a re-analysis of existing GWAS findings to look off main gene effects for epistatic and gene-environment interaction on existing data.

- Functional Analyses of Candidate Gene-Environment Interactions:
    - Conduct mechanistic/functional research on candidate Gene-Environment Interactions using model organisms or other in vitro systems. This could use either a small set of candidate gene-exposure interactions from GWAS or GxE studies or high -throughput screens in a hypothesis free manner. Realistically this may require an intermediate effort to fine map many of the GWAS hits given they are regulatory "hits" in gene desert regions.

**Long Range Goal – Comprehensive Assessment of Gene-Environment Interaction in Epidemiological Studies:**
We envision the developmental activities outlined here being implemented by the NIH over the next two to three years and supporting a research effort lasting approximately five years. The long-range goal of this concept is to continue the goal established with the GEI…to support meaningful, population based studies to understand how global variation in the personal environment and genetic composition affect disease development at the individual level. Following the successful completion of the short term activities outlined above we will have both the tools and the proof of principle needed to adequately conduct such large-scale population based studies.

**Short- and Long-term Impacts:**
The completion of the proposed efforts will position NIH for a comprehensive effort to conduct large-scale GxE studies designed from the outset to have adequate characterization of the personal environment and to have sufficient power to enable associations of interactions with phenotypic endpoints. More specifically, it will address several of the primary gaps in our ability to conduct such studies:
- The ability to simultaneously and without increased participant burden assess multiple aspects of the personal environment including multiple chemical exposures at the point of contact as well as lifestyle factors such as dietary intake, physical activity and psychosocial stress.
- The need for improved measures of environmental exposure, moving beyond external point of contact to internal dose.
- The proof-of-principle that a comprehensive analysis of genetic variation and environmental exposure is feasible and provides insight into disease etiology and progression, and
- The investigation of the mechanistic underpinnings of the interaction between genetic and environmental information.

Individually these elements will aid NIEHS in fulfilling our mission of understanding the impact of environmental factors on human health. In the longer term, they may also enable the development of strategies to intervene to improve health either through improved prevention or therapy.

**Initiatives, Timeline and Budget:**

*Currently ongoing activities:*

| Initiative | Lead IC | Total Annual Budget (Thousands) | Timing | Mechanism | Other ICs | Status |
|---|---|---|---|---|---|---|
| RFA-ES-10-007: Validation and Field Testing of New Tools for Characterizing the Personal Environment | NIEHS | $2,500 | 2011 | R01 | NCI, NIAA, NIDA, OBSSR | Applications under consideration May 11 Council |
| RFA-ES-10-008: Validation and Field Testing of Novel Biomarkers of Response to Environmental Stressors | NIEHS | $2,500 | 2011 | R01 | NCI, NIAA, NIDA, OBSSR | Applications under consideration May 11 Council |
| NOT-HG-11-009: Administrative Supplements for the Addition of Standard Measures to Population-based Genomic Research: The PhenX Toolkit | NHGRI | $700 | 2011 | Administrative supplements | OBSSR | March 2011 receipt date |
| PAR-11-032: Methods and Approaches for Detection of Gene-Environment Interactions in Human Disease | NIEHS | No Set Aside | 2011 | R21 | NCI, NHLBI, NHGRI, NIBIB, NIDCR, NIDA, NLM | Applications Received (October 11 Council) |
| Spatial Uncertainty: Data, Modeling, and Communication | NCI | No Set Aside | 2012 | R03, R21, R01 | NIEHS, NICHD | Release date summer 2011 |

*Proposed activities for Concept Clearance:*

| Initiative | Lead IC | Total Annual Budget (Thousands) | Timing | Mechanism | Other ICs | Status |
|---|---|---|---|---|---|---|
| Integration of Sensors for monitoring Components of the Personal Environment | NIEHS | $2,500 | 2012 | R01, SBIR | NCI, NHLBI, NIDA, NIAAA, OBSSR | Concept Clearance |
| Lab on Chip Biomonitoring Technologies | NIEHS | $5,000 | 2012 | R01 or R21/R33, SBIR | NIBIB | Concept Clearance |
| Overlaying genomic information to human population studies having exposure characterization | NIEHS | $4,000 | 2012 | R01 | NCI, NHLBI, NIDDK, OBSSR | Concept Clearance |
| Applying new environmental measurement tools to existing human GWAS or other genetic population studies | NHLBI | $3,500 | 2013 | R01 | NIEHS, NCI, OBSSR, NIDDK | Concept Clearance |
| Secondary Analyses on GWAS studies for discovery of G x E interaction | NCI | $2,200 | 2013 | R03 or R21 | NIEHS | Concept Clearance |
| Functional Analyses of Candidate Gene-Environment Interactions | NIDA | $5,500 | 2013 | R01 | NIEHS | Concept Clearance |