# Opportunities for Gene and Environment Research in Cancer: An Updated Review of NCI's Extramural Grant Portfolio

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## ABSTRACT

**Background:** The study of gene–environment (GxE) interactions is a research priority for the NCI. Previously, our group analyzed NCI's extramural grant portfolio from fiscal years (FY) 2007 to 2009 to determine the state of the science in GxE research. This study builds upon our previous effort and examines changes in the landscape of GxE cancer research funded by NCI.

**Methods:** The NCI grant portfolio was examined from FY 2010 to 2018 using the iSearch application. A time–trend analysis was conducted to explore changes over the study interval.

**Results:** A total of 107 grants met the search criteria and were abstracted. The most common cancer types studied were breast (19.6%) and colorectal (18.7%). Most grants focused on GxE using specific candidate genes (69.2%) compared with agnostic approaches using genome-wide (26.2%) or whole-exome/whole-genome next-generation sequencing (NGS) approaches (19.6%); some grants used more than one approach to assess genetic variation. More funded grants incorporated NGS technologies in FY 2016–2018 compared with prior FYs. Environmental exposures most commonly examined were energy balance (46.7%) and drugs/treatment (40.2%). Over the time interval, we observed a decrease in energy balance applications with a concurrent increase in drug/treatment applications.

**Conclusions:** Research in GxE interactions has continued to concentrate on common cancers, while there have been some shifts in focus of genetic and environmental exposures. Opportunities exist to study less common cancers, apply new technologies, and increase racial/ethnic diversity.

**Impact:** This analysis of NCI's extramural grant portfolio updates previous efforts and provides a review of NCI grant support for GxE research.

## Introduction

Both genetic and environmental factors are known to contribute to cancer etiology (1–5), and risk of cancer is likely due to the interplay between genes and the environment. The study of gene–environment (GxE) interactions, or investigating how genetic variants modify the effect of lifestyle and the environment, is important as it can provide insight into biological processes and mechanisms of cancer etiology, identify individuals who may be more susceptible to cancer, and inform treatment decisions (6, 7). Although considerable work in GxE has been conducted to date, which has been summarized in recent review articles (8–10), the landscape of GxE research continues to be transformed by increasingly complex data types and larger datasets (11–13). Investigators are leveraging advances in next-generation sequencing (NGS; ref. 14) and other -omics data technologies (e.g., metabolomics, transcriptomics, and epigenetics; refs. 15–17) as sources of information to inform studies of genetic susceptibility to cancer. Similarly, researchers are incorporating innovative approaches to assess environmental exposures. Some examples include data from personal monitoring sensors, geographic information systems, or biomarker measurements using omics-based technologies to comprehensively assess an individual's exposure to environmental factors (18). In addition, new statistical methods are being developed to address the analytic challenges of integrating the diverse data types (19). The emergence of these approaches provides new opportunities (11, 20) for researchers to explore more fully the role of GxE in cancer etiology.

The NCI has made the study of GxE research a priority by committing resources to support multiple initiatives. The Institute has issued several funding opportunities announcements (FOA) and sponsored multiple workshops (11, 21, 22) over the past decade underscoring its commitment to this area of research. Because NCI recognizes the importance of GxE research in cancer, we previously conducted an analysis of its extramural grant portfolio from fiscal years (FY) 2007 to 2009 (23). In that portfolio analysis, we noted a number of possible opportunities for further investments in GxE research; they included: developing alternative approaches to exposure assessment, broadening the spectrum of cancer types investigated, developing new analytic and computational methods, and conducting GxE research using an agnostic approach, such as a gene–environment-wide interaction study (GEWIS).

To examine the current state of GxE research at NCI and explore potential changes in the portfolio over time, we conducted an analysis of the NCI extramural grant portfolio from FYs 2010 to 2018. This report characterizes the funded GxE applications and identifies the research gaps that remain.

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## Materials and Methods

To identify NCI-funded GxE research grants for inclusion in the portfolio analysis, the NIH's iSearch application was queried for newly awarded competing grants that supported research aims during FYs 2010 through 2018. Grants that were identified for possible inclusion were those that were primary research projects only (i.e., excluding center grants, supplements, and R25, T32, R13, U24, and U10 mechanisms; $n =$ 10,485). Grants from the NCI division of cancer biology were excluded ($n$ = 4,270). From these applications ($n = 6,215$), grants that contained both a genetic and an environmental search term and had a cancer outcome in the specific aims were selected for inclusion. A complete list of the genetic and environmental search terms can be found in Supplementary Table S1. A total of 429 research grants were initially identified using these search criteria. Four individuals (A.A. Ghazarian, G.Y. Lai, L.E. Mechanic, and N.I. Simonds) each evaluated a quarter of the grant's specific aims to determine whether it should be considered a GxE interaction application and was examining cancer outcomes. Only studies done among human populations were considered. Ten percent of the grants that were identified for possible inclusion ($n = 43$) were reviewed by all four reviewers together to ensure consistency on how the inclusion and exclusion criteria were being applied with a concordance between individual reviewers of 84%. Discordant results were discussed, and consensus results were recorded.

A total of 107 grants (**Fig. 1**) were identified as relevant according to the inclusion criteria and specific genetic and environmental information was abstracted from these grants. More specifically, the following genetic terms were captured: candidate gene study, genome-wide association study (GWAS), epigenetic, targeted sequencing, and/or whole-exome/genome sequencing, as well as whether germline and/or somatic variation was being studied. Note that for a grant to be considered GWAS, analyses of GxE interactions were required to be agnostic (i.e., GEWIS). More specifically, even if a grant application used data from GWAS, it was not included in this category if assessment of GxE focused on specific candidate genes or regions that were identified previously. Grants were also characterized according to the following environmental term categories: infection and inflammation, drugs/treatment, exogenous hormones, reproductive factors, chemical environment, physical environment, lifestyle, energy balance, metabolomics, microbiome, social environment, and/or general (Supplementary Table S2). Even though metabolomics and microbiome measures may also be considered intermediate endpoints, they were included as environmental exposures because these measures can reflect possible exposures to environmental factors (24, 25). Environmental and genomic categories were not mutually exclusive as grant applications may examine multiple measures. Specific environmental terms, such as smoking, obesity, and physical activity, were also captured by reviewers. Grants were characterized as methods if they included statistical or analytic methods development. In addition, reviewers determined whether the grant application examined racial/ethnic differences. Finally, data on study design, cancer outcome(s) of interest (defined as cancer diagnosis or cancer survival), and cancer type were abstracted.

Among the relevant grants, 10% were reviewed by all four reviewers, the remaining were reviewed in pairs to ensure that data abstraction was done consistently for quality control. Concordance between reviewer pairs ranged between 77% and 90% for each batch of grants reviewed. Any discordant results were discussed by all four reviewers and consensus results were recorded. In addition, other consistency checks were conducted on data, such as comparison of all specific environmental terms within environmental exposure categories and review of all specific genetic terms.

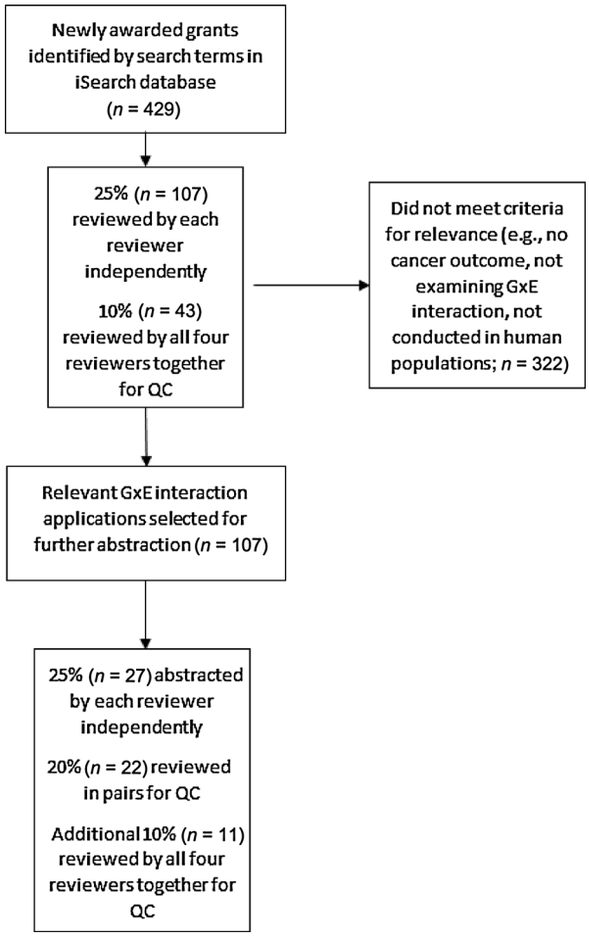


**Figure 1.**
Flow diagram of search strategy and review process of the NCI's extramural grant portfolio on GxE interaction research, FYs 2010–2018. Flow diagram of portfolio analysis search strategy and review process. QC, quality control.

A time–trend analysis was conducted to explore whether any changes in research focus occurred over the 9-year study interval. The trend of overall number of NCI-awarded research grants was examined by calculating a Pearson correlation in Microsoft Excel. Relevant grants were grouped into 3-year groups by FY (2010–2012, 2013–2015, and 2016–2018) and temporal trends were explored by genomic categories (GWAS, candidate genes, and whole-exome/whole-genome sequencing) and environmental categories (drugs/treatment, lifestyle, and energy balance). Other categories had limited sample size for exploring these trends and thus, were not evaluated. Because candidate gene and whole-exome/whole-genome approaches may be used to determine both germline and somatic variation, the trend analysis was examined overall and restricted to germline studies. Finally, we evaluated whether changes in the number of GxE methods grant applications were observed over time.

## Results

A total of 107 grants were considered relevant according to the selection criteria. The different cancer types examined in the research grants that included studies of GxE interaction research are presented

in **Fig. 2**. The most common cancer type examined was breast (19.6%), followed by colorectal (18.7%), blood cancers (14.0%), melanoma and other skin (9.3%), lung (7.5%), and prostate (7.5%). Less common cancer types in the portfolio (<5%) included: ovarian (4.7%), pancreatic (4.7%), brain/neurologic (3.7%), esophageal (3.7%), liver (3.7%), renal (3.7%), head/neck (2.8%), bladder (1.9%), gastric (1.9%), Kaposi sarcoma (1.9%), and cervical (0.9%). Approximately 10.3% of grants examined more than one cancer type and each cancer type was counted independently (i.e., such grants were included more than once). There were also grants (13.1%) that examined cancer in general, which we classified as "cancer, multiple types." Eleven of the grants classified as "cancer, multiple types" were developing statistical or analytic methods that may be used for different cancer types. Several of the methods grants specified an individual cancer type (if evaluating a method using a specific dataset), but indicated methods were broadly applicable to other cancers. The other applications in this category were examining GxE in relation to risk of second cancers where any cancer type was included or were assessing prevention across cancer types.

Other key variables abstracted from the relevant grants are presented in **Table 1**. The majority of grants were studies of associations with cancer diagnosis (65.4%) compared with cancer survival (26.2%). The most common study designs used were case–control studies (53.3%) and cohort studies (31.8%). Only 6.5% of grants examined GxE in a randomized control trial. We found 15.9% of the relevant grants involved research exploring differences in racial/ethnic groups and 27.1% were methods-related applications.

The majority of the 107 relevant grants (74.8%) examined germline variation, 14.9% examined only somatic alterations, and 7.5% of grants explored both types of variation (**Table 1**). Most of the germline-only grants ($n = 80$) examined GxE interactions with specific candidate genes (77.5%) compared with agnostic genome-wide GxE analysis approaches using GWAS (30%) or whole-exome/whole-genome sequencing data (11.3%). In contrast, 37.5% of the somatic-only grants assessed GxE interactions with specific candidate genes. In addition, somatic-only grants and those applications that evaluated both germline and somatic variations frequently explored GxE agnostically using whole-exome/whole-genome sequencing (50% each). Combined (germline, somatic, or germline and somatic grants), most grants focused on GxE using specific candidate genes (69.2%) compared with agnostic approaches using genome-wide (26.2%) or whole-exome/whole-genome NGS approaches (19.6%). The majority (60%) of the targeted sequencing grants were measuring somatic variation and one application was exploring both germline and somatic changes. Finally, approximately 9.3% of grants investigated an epigenetic marker. The majority of grants exploring analytic methods focused on germline variation (89.7% of 29 methods grants).

Environmental exposure data were also abstracted for all relevant grants using the terms described in the Materials and Methods section. The environmental terms that were evaluated in our portfolio analysis of GxE interaction research are presented in **Fig. 3**. The most common environmental exposures that were examined in the GxE research grants included energy balance (46.7%), followed by drugs/treatment (40.2%), and lifestyle factors (37.4%). Other environmental exposures that were studied included exogenous hormones (11.2%), infection/inflammation (9.3%), reproductive factors (7.5%), chemical environment (5.6%), social environment (5.6%), metabolomics (3.7%), physical environment (2.8%), and microbiome (0.9%). The majority of the methods applications (48.3% of 29 methods applications) also examined lifestyle and/or variables associated with energy balance (41.3% of 29). Ten of the methods applications examined exposures in general or did not list a specific exposure as the focus of methods development. The two most common specific exposures for all relevant applications observed within each environmental exposure category are shown in **Table 2**. Specific environmental exposures that were most frequently studied included diet ($n = 33$), smoking ($n = 29$), alcohol use ($n = 18$), chemotherapeutic drugs ($n = 22$), and physical activity ($n = 14$).

To evaluate whether changes in research focus were observed over the 9-year period, we conducted a time–trend analysis. The number of

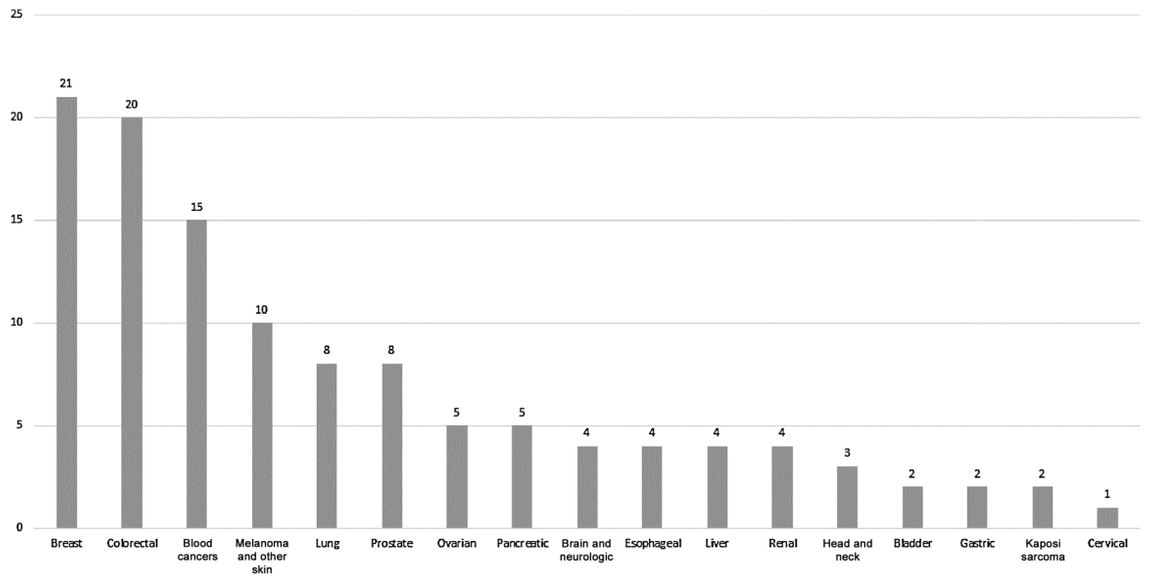


**Figure 2.**

Distribution of the cancer types examined among the 107 relevant GxE interaction grants funded by the NCI, FYs 2010–2018. Number of cancer types and categories captured in portfolio analysis. The bars are labeled with the total number of grants that investigated each cancer type. The total number of grants is 107; however, some grants investigated more than one cancer type and were counted more than once in the total for this specific figure.

**Table 1.** Distribution of select grant characteristics among the 107 relevant GxE interaction grants funded by the NCI, FYs 2010–2018.

| Grant characteristics[a] | Number of grants | Percentage of grants |
|---|---|---|
| FY | | |
| 2010 | 16 | 15.0% |
| 2011 | 10 | 9.3% |
| 2012 | 11 | 10.3% |
| 2013 | 12 | 11.2% |
| 2014 | 13 | 12.1% |
| 2015 | 12 | 11.2% |
| 2016 | 13 | 12.1% |
| 2017 | 10 | 9.3% |
| 2018 | 10 | 9.3% |
| Outcome | | |
| Cancer diagnosis | 70 | 65.4% |
| Cancer survival | 28 | 26.2% |
| Cancer diagnosis and survival | 9 | 8.4% |
| Study design | | |
| Case–control | 57 | 53.3% |
| Cohort | 34 | 31.8% |
| Randomized control trial | 7 | 6.5% |
| Multiple[b] | 6 | 5.6% |
| Case-only | 1 | 0.9% |
| Not specified | 2 | 1.9% |
| Health disparity | | |
| No | 90 | 84.1% |
| Yes | 17 | 15.9% |
| Methods | | |
| No | 78 | 72.9% |
| Yes | 29 | 27.1% |
| Genetics category[c] | | |
| Germline | 80 | 74.8% |
| Somatic | 16 | 14.9% |
| Germline and somatic | 8 | 7.5% |
| Epigenetic | 10 | 9.3% |
| Genetics category (germline-only grants) | | |
| Candidate | 62 | 77.5% |
| GWAS | 24 | 30.0% |
| Whole exome/whole genome | 9 | 11.3% |
| Targeted sequencing | 3 | 3.8% |
| Epigenetics | 3 | 3.8% |
| Genetics category (somatic-only grants) | | |
| Candidate | 6 | 37.5% |
| GWAS | 0 | 0% |
| Whole exome/whole genome | 8 | 50.0% |
| Targeted sequencing | 6 | 37.5% |
| Epigenetics | 2 | 12.5% |
| Genetics category (germline and somatic grants) | | |
| Candidate | 5 | 62.5% |
| GWAS | 4 | 50.0% |
| Whole exome/whole genome | 4 | 50.0% |
| Targeted sequencing | 1 | 12.5% |
| Epigenetics | 3 | 37.5% |

[a]Grant characteristics were coded as described in the "Materials and Methods."
[b]Grants that included more than one study design were considered "multiple."
[c]Genetics categories and definitions are provided in Supplementary Table S2.

newly awarded competing NCI grants remained stable over the time period (median, 1,160; $r = 0.11$). The distribution of relevant grants by each FY was also relatively consistent, with the greatest number in FY 2010 (15%). When restricted to studies of germline variation, we observed a decrease in the number of candidate gene applications. Although GxE applications using a GWAS approach remained constant throughout the same time period, the proportion of the funded applications using an agnostic approach (i.e., GWAS or NGS) increased (**Table 3**). Similar observations were noted when including all applications ($n = 28$, 27, and 18 candidate gene applications and two, six, and 13 whole-exome/whole-genome sequencing grants during the three time periods). Among the environmental exposures examined for trends, we observed less of an emphasis on energy balance applications over the 9-year time interval, while an increase in the number of applications examining drugs/treatments was found. In contrast, no changes were observed in funded methods-related applications over the time interval (**Table 3**).

## Discussion

The development and outcome of many cancers are understood to be a product of genetic and environmental factors. Thus, NCI considers understanding the interaction between genetic variation and the environment as an important area of research. We conducted an analysis of the NCI extramural research grant portfolio of GxE interaction research from FY 2010 through 2018 to examine the distribution of cancer types, environmental exposures studied, and the approaches used to assess genetic variation. Not surprisingly, most of the funded grants in GxE research focused on breast, colorectal, and lung cancers, which are all common cancer types with a well-known environmental component (26–28). Approximately 70% of the grants evaluated in this study had a candidate gene target in the GxE analysis. The most commonly studied environmental factor categories included factors contributing to energy balance, drugs/treatment, and lifestyle. Although these findings are similar to those observed in our previous portfolio analysis based on projects active for FYs 2007 through 2009 (23), we noted some differences that reflect the incorporation of new methodologies and approaches (e.g., NGS and new analytic methods), as well as a shift in research focus (e.g., precision oncology and different distribution of cancer types).

The results of this portfolio analysis mirrored the advances in high-throughput genomic technologies. Grantees incorporated NGS technologies, such as whole-genome or whole-exome sequencing, to capture genetic data in their studies; moreover, this shift over time in the technologies being used was more pronounced in grant applications that were funded in FYs 2016 through 2018 compared with prior FYs. In addition, compared with the previous portfolio analysis, a greater number of grantees proposed studying GxE interactions in GWAS (26% vs. 8%). This area was suggested in our previous report (23) as a possible area of opportunity to investigate these associations. Not only have studies using this approach been recently published (29, 30), but grant applications focused on developing such analytic methods to study GxE on a genome-wide scale were observed in this grant portfolio. We also observed some changes as to which environmental exposures were more frequently included in the aims of the abstracted grants. For example, there was more interest in studying interactions with drugs and treatments than in the portfolio analysis of active grants funded in FYs 2007–2009 (40% vs. 29%), likely reflecting the excitement around precision oncology (31, 32). Within this environmental exposure category, chemotherapeutic agents were the most frequently studied class of drugs. Despite this interest, there were only a small number of randomized controlled trial studies ($n = 7$). For this portfolio analysis, we also expanded our evaluation to other factors related to the environment, namely, the microbiome, metabolomics, and social environment (socioeconomic status and neighborhood characteristics), that have garnered growing interest in cancer

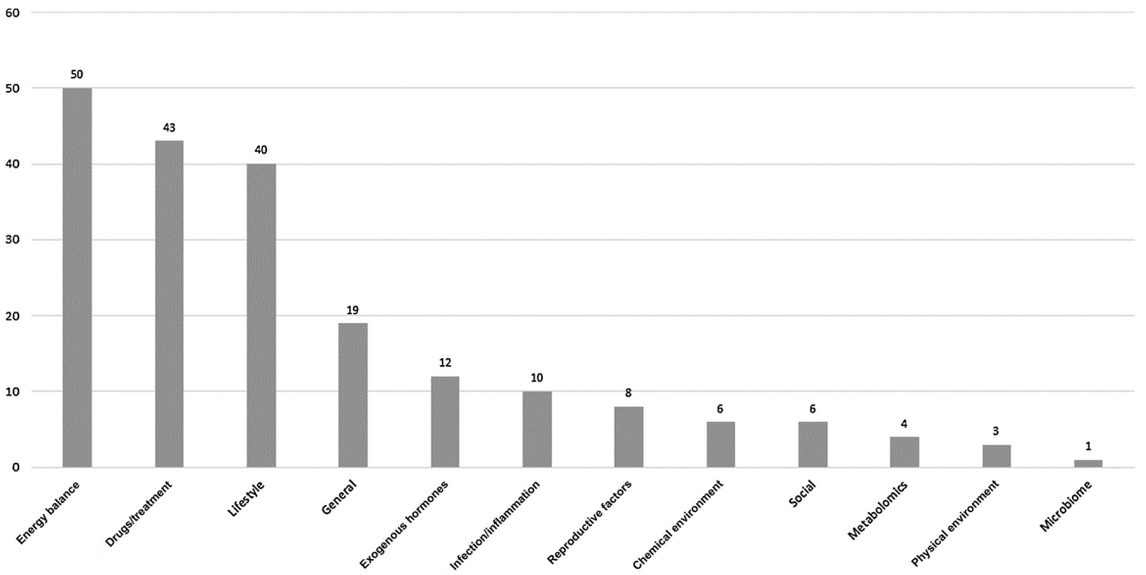


**Figure 3.**

Distribution among the most common environmental exposure categories examined among the 107 relevant GxE interaction grants funded by the NCI, FYs 2010–2018. Number of environmental exposures captured in portfolio analysis. Environmental exposure categories used in this portfolio analysis are listed, and the bars are labeled with the total number of grants that investigated each environmental exposure category. The total number of grants is 107; however, some grants investigated more than one environmental exposure and were counted more than once in the total for this specific figure.

epidemiology studies (33–37). Compared with other environmental exposures, we did not observe many grants that included these factors. While these aspects are not considered to be traditional components of the environment in GxE studies, these factors do represent a broad and complex interplay of various external exposures with that of the host, and the observation of these grants may reflect the growing awareness and interest in these fields.

As noted above, investments made to study GxE interactions were mostly focused on common cancers; however, the distribution was different from the results of the prior portfolio analysis (23). Colorectal cancer was more frequently studied compared with the prior analysis (16% vs. 9%). This shift in research focus could be because the reported findings for colorectal cancer appear to show evidence for GxE interactions, particularly for diet and lifestyle factors that are more readily modifiable (38, 39). Also, recent reports of increased colorectal cancer incidence rates observed among younger patients (i.e., those under 50 years of age; refs. 40, 41) has drawn considerable interest among researchers as the etiology accounting for this phenomenon remains unclear, but the rapid increase in incidence is suggestive of an environmental etiology. However, while these circumstances may explain, in part, the percentage shift and focus of GxE research on colorectal cancer, the actual number of grants is still relatively small and could be due to chance.

**Table 2.** Most commonly observed environmental exposures in the NCI's extramural grant portfolio on GxE interaction research, FYs 2010–2018.

| Environmental exposure category | Specific exposure |
|---|---|
| Energy balance | Diet ($n = 33$), physical activity ($n = 14$) |
| Drugs/treatment | Chemotherapeutic drugs ($n = 22$), NSAIDs ($n = 10$) |
| Lifestyle | Smoking ($n = 29$), alcohol use ($n = 18$) |
| Exogenous hormones | Hormone replacement therapy ($n = 8$), oral contraceptive use ($n = 2$) |
| Infection/inflammation | Human papillomavirus ($n = 3$), hepatitis infection ($n = 2$) |
| Reproductive factors | Parity ($n = 4$), age at menarche ($n = 4$) |
| Chemical environment | Heavy metals ($n = 3$), occupational chemical exposures ($n = 2$) |
| Social environment | Socioeconomic status ($n = 2$), neighborhood characteristics ($n = 2$) |
| Metabolomics | Metabolites not otherwise specified ($n = 3$) |
| Physical environment | Sun exposure ($n = 2$), ionizing radiation ($n = 1$) |
| Microbiome | Microbiome not otherwise specified ($n = 1$) |

Abbreviation: *n*, number of grants.

Only 15% of the grant applications reviewed focused on examining racial/ethnic differences in GxE. The relatively small number of grants exploring health disparities in GxE research is consistent with the documented lack of diversity in cohort studies (42) and genomics research (43, 44). Increasing diversity in research studies could potentially increase the success of GxE research (4). Unfortunately, considerable effort, including policy changes and interventions, is required to help address the persistent underrepresentation of racial/ethnic and other understudied populations in research studies (42, 45, 46). More importantly, as genomic data are being used to inform precision medicine, research gaps may potentially exacerbate current health disparities (47).

In our previous analysis of the NCI extramural research grant portfolio, we found that very few studies were funded to develop new analytic and computational methods related to GxE research. In response to this finding, NCI participated in two FOAs (48, 49) led by the National Institute of Environmental Health Sciences to encourage submissions of applications focusing on the development and application of novel GxE methods, with an emphasis on

**Table 3.** Distribution of GxE interaction grants funded by the NCI from FY 2010 to 2018 classified into 3-year groups, by category.

| Category | Number of grants | Percentage of grants |
|---|---|---|
| Genetics[a] | | |
| Candidate | | |
| 2010–2012 | 28 | 41.8% |
| 2013–2015 | 24 | 35.8% |
| 2016–2018 | 15 | 22.3% |
| GWAS | | |
| 2010–2012 | 9 | 32.1% |
| 2013–2015 | 10 | 35.7% |
| 2016–2018 | 9 | 32.1% |
| Whole exome/whole genome | | |
| 2010–2012 | 2 | 15.4% |
| 2013–2015 | 5 | 38.5% |
| 2016–2018 | 6 | 46.1% |
| Environmental exposure[b] | | |
| Energy balance | | |
| 2010–2012 | 22 | 44.0% |
| 2013–2015 | 18 | 36.0% |
| 2016–2018 | 10 | 20.0% |
| Lifestyle | | |
| 2010–2012 | 13 | 32.5% |
| 2013–2015 | 15 | 37.5% |
| 2016–2018 | 12 | 30.0% |
| Drugs/treatment | | |
| 2010–2012 | 11 | 25.6% |
| 2013–2015 | 14 | 32.6% |
| 2016–2018 | 18 | 41.8% |
| Methods | | |
| 2010–2012 | 10 | 34.5% |
| 2013–2015 | 9 | 31.0% |
| 2016–2018 | 10 | 34.5% |

[a]Limited to the 88 grants examining germline variation (germline-only and those assessing both germline and somatic variation).
[b]For the energy balance category, grants were exploring factors that contribute to energy balance (e.g., diet and exercise), but not necessarily specifically assessing the balance of intake/output of energy.

genome-wide data. We found that the number of grants funded to develop new analytic and computational methods remained stable over time from 2010 to 2018, although the specific focus of these grants has changed. Notably, compared with the previous analysis (2007–2009; ref. 23), there was a large increase in the number of grants which explored analytic methods (1.4% vs. 27.1%). These findings may suggest that the evolution of more high-throughput data has resulted in a corresponding evolution of analytic methods; yet, more methods development in this area is needed (19), including innovative analytic frameworks (e.g., machine learning; ref. 50) that can accommodate the increasingly larger volumes of data collected.

There were a few differences in the design of this analysis compared with the previous study (23). In this study, we included additional genetic (whole-exome/genome sequencing and targeted sequencing) and environmental terms (social environment, microbiome, and metabolomics) to reflect the evolution in how genetic variation and environmental exposures (14, 51, 52) are assessed. We also limited the genetic terms specifically to DNA-related measures in this analysis (the previous included RNA and proteomics). Finally, this portfolio analysis included only newly awarded grants compared with our previous analysis, which included a sample of all relevant active grants between FYs 2007 and 2009. Nevertheless, these differences in study design are unlikely to impact the interpretation of our study findings because of the length of time period explored.

However, there are limitations of this portfolio analysis. First, the analysis does not reflect all NCI-funded cancer researches devoted to GxE interaction (i.e., NCI intramural program and those evaluating cancer outcomes other than risk and survival, such as treatment toxicity). Another limitation is that, we relied primarily on the specific aims of the funded grants, which may not provide a complete picture of the scope of actual research being conducted. Furthermore, we were unable to assess how much of actual GxE research noted in the aims of the applications has been completed. Finally, due to small numbers, we were unable to statistically analyze temporal trends, and our observations are qualitative in nature. Nevertheless, we believe this analysis provides an overall picture of the scope of NCI support for GxE research over the past approximately 10 years.

The findings from our current portfolio analysis suggest that the focus of GxE cancer studies mirrors the evolution of the field. We observed a greater proportion of GxE research being conducted using agnostic approaches in GWAS compared with our previous analysis and a decrease in GxE focused on candidate genes, as well as increased incorporation of NGS technologies over the 9-year time period. We also found a greater emphasis on studying chemotherapeutic agents in this analysis. GxE in cancer research, however, continues to be concentrated in common cancer types and reflects racial/ethnic underrepresentation commonly observed in other research studies, suggesting possible opportunities in these areas. The increasing availability of new technologies for the characterization of genetic and environmental variation and application of these approaches to more diverse populations for studies of GxE in cancer has the potential to provide new insights into underlying mechanisms and health effects associated with the disease.

## Authors' Disclosures

N.I. Simonds was supported by Scientific Consulting Group during the conduct of the study. No disclosures were reported by the other authors.

## Disclaimer

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the NCI.

## Authors' Contributions

**A.A. Ghazarian:** Conceptualization, formal analysis, writing-original draft, writing-review and editing. **N.I. Simonds:** Conceptualization, formal analysis, writing-original draft, writing-review and editing. **G.Y. Lai:** Conceptualization, formal analysis, writing-original draft, writing-review and editing. **L.E. Mechanic:** Conceptualization, formal analysis, writing-original draft, writing-review and editing.

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