RIPPLE EFFECT

Final Report

2019 ASSESSMENT OF THE PROVOCATIVE QUESTIONS (PQ) INITIATIVE

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*With minor hyperlink updates and investigator anonymization for 2024 web posting

2400 Research Boulevard, Suite 305, Rockville, MD 20850
Phone 1-800-277-5708 | Fax 240-745-3777 | evaluation@rippleeffect.com

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By Amanda Barczyk, PhD, MSW; Christine Lagana Riordan, PhD, MSW; Kristen Adams, MSPH; Michael Speiser, MA, MSc; and Esther Lau, MSPH from Ripple Effect.

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Overview and Purpose of the Evaluation

In 2011 the National Cancer Institute (NCI) established the Provocative Questions (PQ) Initiative. This program was created to support research projects designed to address specific problems and paradoxes in cancer research identified by the cancer research community as "Provocative Questions." NCI contracted with Ripple Effect to conduct a comprehensive and rigorous evaluation of the PQ initiative. The purpose of the evaluation is to provide an external, independent assessment of the PQ initiative, including scientific outputs and impacts. The assessment will be presented to NCI leadership and advisory boards and will be used when considering reissuance of the PQ program in the future.

Evaluation Design and Methodology

This evaluation relied on existing data and documentation and consultation with NCI staff to inform the study design and methods, which covered assessment of applicants, awardees, and outputs and PQ scientific outcomes. We convened an expert panel to review and evaluate publication outcomes of a subset of 10 randomly selected PQs. Methods also included quantitative analysis of NIH and other publicly available data, publication analyses and bibliometrics, and content analysis of program documentation (e.g., progress reports). Ripple Effect also created and used a comparison group of NCI Research Project Grants (RPG) to contextualize some of these metrics. The evaluation team conducted five informal interviews with six PQ Principal Investigators (PI) to create in-depth case studies or vignettes on topics of interest.

Summary of Findings

In the 2014 PQ RFA reissuance request, NCI suggested three evaluation criteria to measure the progress and outcomes of the PQ initiative: 1) Continued enthusiastic support from the community and NCI staff with the generation of well-received PQs, 2) Retiring of PQs when they have generated enough new research momentum and funding support, and 3) Producing strong PQ-targeted research from the grants funded under the PQ RFAs This evaluation was guided by these criteria, with a focus on areas that had not been fully addressed in previous evaluations.

Key findings are listed below, organized by the evaluation criteria. Additional details on each evaluation criteria, evaluation questions, assessment methods, and detailed findings, are provided in the body of the report.

Enthusiastic Support from Community and NCI Staff

- An external panel of experts in PQ research areas reviewed the output and impact of 10 randomly selected PQs. They determined that the PQs were well formulated and timely and had made a significant contribution to multiple areas of cancer research.
- Overall, panelists strongly endorsed the continuation of the PQ Program given its important impact on the field of cancer research.
- The external panel made the following recommendations for future enhancement to the PQ program: 1) focus on cross-disciplinary science, 2) ensure grant outcomes address the PQ and hold PIs accountable to focusing on the goal of the PQ, 3) continue assessing the success of the PQs in multiple ways, and 4) expand the collection of community input.

- The 2016 evaluation[1] found that interviewees, including NCI program staff, perceived the PQ development process to be democratic, inclusive, and produce relevant questions. Interviewees also believed the PQ initiative produces PQ questions that are perplexing and involve understudied areas.

Retiring of PQs

- Panelists relayed that the workshop approach to question development is productive and they appreciate that PQs can be refined over time to make sure that the PQ initiative is asking relevant questions, as well as continuing or retiring them as needed.
- Panelists suggested earlier and broader advertising of the PQs such as posting questions six months prior to the issuance of the PQ to allow time for a symposium, provide time for researchers to prepare for submission, and work to reach a broader community of researchers.
- As in the 2016 PQ evaluation, this study found the number of PQs retired varied for each RFA issuance, with 40-75% of PQs retired between each RFA over the duration of the program.

Producing Strong PQ-Associated Research

- Panelists stated that significant progress was made in the PQ research areas that likely would not have occurred without the PQ Program.
- PQ grants and an NCI RPG Comparison Group grants produced roughly the same number of mean publications per grant (8.09 versus 8.50 respectively) with similar citation metrics:
  - Across the groups, 84% (n=1,779) of PQ publications had citations and 85% (n=2,002) of NCI RPG Comparison Group publications had citations.
  - publications had a mean Relative Citation Ratio (RCR) of 2.40, meaning that the average PQ publications are more than twice as impactful as the average NIH-funded publication from the same field in the same time period. NCI RPG Comparison Group publications had a similar mean RCR (2.47).
- There were roughly the same number of PQ Early Stage Investigators (ESI) (n=67, 15%) as there were RPG Comparison Group ESIs (n=65, 16%). New Investigators (NI) are those investigators who have not received substantial, independent funding from NIH previously. There was a similar amount of PQ NIs (n=59, 13%) as there were RPG Comparison Group NIs (n=57, 14%).
- PQ PIs were more likely to be awarded subsequent NIH funding, as PQ PIs were awarded 241 grants and NCI RPG Comparison Group PIs were awarded 159 grants from January 2014 - August 2019.
- In five informal interviews with PQ awardees that received subsequent NIH grant funding, awardees directly connected their PQ work to a variety of subsequent awards including NCI R01s, NCI R21s, an R35 Outstanding Investigator Grant, a Transformational R01, SBIR funding, STTR funding, a DoD Breakthrough Award, and Cancer Moonshot funding. *Please note that names of investigators have been redacted for public posting.*
- A total of 143 presentations of PQ research, from 60 unique PQ grants, were presented at over 100 unique scientific meetings including conferences, symposiums, and workshops between FY 2012 and FY 2019.

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[1] National Cancer Institute Center for Strategic Scientific Initiatives (January 2016). The Provocative Questions Initiative Program Evaluation. National Institutes of Health. https://www.cancer.gov/about-nci/organization/cssi/resources/evaluation-reports

Future Considerations

Throughout the process of completing the assessment, some themes emerged that might be useful to consider for possible future iterations of the PQ program.

- NCI should strongly consider continuing support of the PQ Program, as it fills a unique cancer research need for the community.
- Continue to use stakeholder workshops to assist in choosing the PQs as these processes were well regarded and the PQs considered timely among scientific experts.
- Consider increased focus on cross-disciplinary science in future iterations of the PQ initiative to continue to push cancer researchers to collaborate with other disciplines.
- Consider adding additional oversight mechanisms to improve the likelihood that PQ PIs will remain focused on the intended goal of the PQ, even if this may mean null findings in some cases.
- NCI may also want to explore novel ways to collect community input on PQ research during and after the PQs are awarded to continue to increase awareness of the mechanism and collect impact on the field (e.g., symposium).
- Consider advertising the PQs earlier and more broadly with methods such as posting questions six months prior to the issuance of the PQ to allow time for a symposium, provide time for researchers to prepare for submission, and work to reach a broader community of researchers.
- NCI should identify multiple ways to define success among PQ research projects, aside from publications, which may differ between topic areas and based on novelty of the research, years since award, and initial project risk. Convening focus groups of previous PQ awardees with a range of outcomes may help to solidify additional ways to measure success for awards intended to be higher risk.
- Future evaluations of the PQ initiative should include publication analyses (with a comparison group) and expert panel review, as these were the most informative portions of the current evaluation.
- Although more resource intensive, future evaluations should also consider PI interviews to discuss the impact of PQ funding on their research trajectories and scientific areas, as well as in-depth review of progress reports, publications, and other outputs to better measure how PQ research has moved the science forward in targeted areas.

Introduction

Mission

In 2011 the National Cancer Institute (NCI) established the Provocative Questions (PQ) Initiative. This program was created to support research projects designed to address specific problems and paradoxes in cancer research identified by the cancer research community as "Provocative Questions" (PQs). The PQs were created to challenge cancer researchers to think about and elucidate specific problems in key areas of cancer research that are deemed important but have not received sufficient attention in general cancer research. The initiative addresses a breadth of cancer research topics across three overarching categories: (1) older, inadequately explored or neglected observations; (2) recent paradoxical findings; and (3) problems formerly thought to be intractable but may now be explorable due to recent scientific advances.[2] PQ grants are primarily awarded as R01s and R21s.[3]

PQ research builds on specific advances in understanding of cancer and cancer control, while addressing broad issues in the biology of cancer that have proven difficult to resolve, and specifies ways to overcome obstacles to answering the question.[4] The initiative is intended to encourage imaginative and bold approaches.[5]

Organization and Structure

The initial Funding Opportunity Announcement (FOA) that established the Provocative Questions Initiative was issued in 2011. PQ funding opportunities were subsequently published in fiscal years 2012, 2013, 2015/2016, and 2017/2018, and 2019. This assessment will focus on funding opportunities from fiscal years 2011 – 2018, as the evaluation team finished retrieving the data for this study prior to the end of the FY2019.

Each funding opportunity was comprised of a distinct set of 12 – 24 questions. In total, these 39 RFAs include 58 PQs (see Appendix A). Several PQs were repeated across multiple years. Since the initiative's inception in 2011, 362 NIH Research Project Grants (R01) and NIH Exploratory/Developmental Research Grants (R21) have been awarded to address the PQs.

The PQ areas for each funding opportunity are created with input from the cancer research community through workshops with a large range of stakeholders. These questions are intended to focus on specific research gaps, particularly those areas that may be considered high-risk or may not be funded under more traditional mechanisms.

Table 1 shows the PQ issuance, number of grants, and funding for all PQ R01 and R21 awards in this time frame.

[2] https://www.cancer.gov/about-nci/organization/cssi/research/past-programs

[3] NCI also funds supplement applications for adding PQ-relevant research to active NCI grants with at least two years remaining.

[4] https://www.cancer.gov/about-nci/organization/cssi/research/past-programs

[5] https://cancerres.aacrjournals.org/content/74/19_Supplement/3500

Table 1. Funding for PQ Initiative R01 & R21 awards (in Millions of Dollars)

Issuance	Awards	Funding (in millions)
2011	56	$73.9 million
2012	94	$125.3 million
2013	38	$44.4 million
2015/2016	95	$151.2 million
2017/2018	79	$144.2 million
Total	362	$539.0 million

Previous Evaluations of the PQ Initiative

The current evaluation took all previous evaluations of the PQ initiative into account in the design of the evaluation, including an evaluation of 2011 – 2012 PQ RFAs and an evaluation of 2011 – 2013 RFAs.

Evaluation of 2011 – 2012 PQ RFAs[6]

In 2014, Thomson Reuters assisted NCI in evaluating the early progress of the PQ initiative and produced the 2014 Evaluation of Provocative Questions Initiative Report. This evaluation focused on early publications and research outcomes for the PQ portfolio from the 2011 – 2012 RFAs. Additionally, it considered whether the PQ research has led to an increase in publications in PQ topic areas across the research community, whether the initiative is attracting new ideas in the PQ areas, and whether it has been effective in attracting and retaining investigators without prior NIH or NCI submissions.

The evaluation found that the PQ grants performed as well as comparison groups (composed of seven similar initiatives) in terms of research outcomes and there was a small increase (5.2 – 6.5%) in the proportion of cancer-related research that focused on PQ question areas post-PQ launch, as measured by publication and grant activity. It also found that approximately 30% of PQ applications did not meet adequate "relevance to PQ criteria" assessing the match between the research and the PQ topic. Additionally, this evaluation suggested the initiative attracted high-quality researchers that continue to obtain additional NIH funding. Despite the early evidence of research productivity, the authors noted that more time must elapse before conducting quantitative bibliometric analyses.

Recommendations as a result of this evaluation included interviewing applicants in future evaluations and that program staff should consider making scientific responsiveness determinations prior to peer review to increase the relevance of the reviewed pool. As a result of this evaluation, starting with the 2015/2016 RFAs, NCI included an intent statement for each PQ that specified the research area and was the basis of a programmatic assessment for scientific responsiveness to ensure applications addressed the PQ topic before advancing to peer review.

[6] National Cancer Institute Center for Strategic Scientific Initiatives (May 2014). *2014 Evaluation of the Provocative Questions Initiative (2011 AND 2012 PQ RFAS)*. National Institutes of Health. https://www.cancer.gov/about-nci/organization/cssi/resources/evaluation-reports

Evaluation of 2011 – 2013 PQ RFAs[7]

In 2016 Clarivate Analytics assisted NCI in an evaluation of 2011 – 2013 PQ RFAs to determine the effectiveness of PQ initiative processes, the size of increase in PQ research areas following each PQ, and the degree to which the PQ initiative supported novel science in the targeted areas. These results are available in The Provocative Questions Initiative Program Evaluation Report. As recommended in the 2014 evaluation, methods included interviews with key stakeholder groups (e.g., PQ Executive Committee members (NCI staff), Program Directors, Reviewers, PQ Workshop participants), and a survey of applicants (awarded and not awarded), and quantitative analysis of proposal applications, funded publications, and PQ-related literature.

This evaluation found that, overall, the PQ initiative processes were perceived to be effective. Workshops were viewed by stakeholders as a democratic, effective, and inclusive mechanism for developing and selecting PQ questions. It also found that the majority of PQs (91%) targeted research areas that had not previously been well represented in the scientific literature. This evaluation determined that there was an increase in the cancer research literature in two-thirds of the PQ topic areas after they were included in the program and that the number of authors publishing in each area increased, as well. Finally, it found that the average number of publications for each PQ award was four publications with two of these focused on the direct topic of the PQ award. Most awardees (85%) believed new research findings resulted from their PQ award and 65% indicated they had identified new methods or model sets.

Select recommendations from this evaluation included:

- Continue to improve program processes to lessen burden on program officers
- Continue to track publication trends related to the PQ initiative
- Review the role, experience, and type of researchers best suited to pursue PQ projects and strategies to target them
- Investigate methods for targeting researchers outside of NCI to apply for PQ awards
- Consider realistic expectations for research outcomes for each PQ
- Identify research areas that have a high percentage of PQ-related publications
- Conduct a follow-up evaluation in approximately five years

As a result of this evaluation, NCI took the following actions: narrowed the list of PQs in each funding opportunity from 20-24 to a more focused list of 12 for the 2015/2016 and 2017/2018 RFAs and restructured the program management to create NCI teams with relevant expertise for each question to manage applications and support the long-term success of the research area.

Purpose of the Evaluation

Beginning in 2019, NCI contracted with Ripple Effect to conduct a comprehensive and rigorous evaluation of the PQ initiative. The purpose of the evaluation is to provide an external, independent assessment of the PQ initiative, including scientific outputs and impacts. The assessment will be presented to NCI leadership and advisory boards and will be used when considering reissuance of the PQ program in the future.

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[7] National Cancer Institute Center for Strategic Scientific Initiatives (January 2016). *The Provocative Questions Initiative Program Evaluation*. National Institutes of Health. https://www.cancer.gov/about-nci/organization/cssi/resources/evaluation-reports

The current evaluation builds on the two previous evaluations by focusing on evaluation areas that had not been thoroughly studied because they required additional time to elapse. For instance, this evaluation focuses heavily on tracking publication and bibliometric trends for PQ awards versus a comparison group now that enough PQ publications have accumulated. Conversely, it did not assess NCI program staff perceptions of or support for the PQ program, because that had been thoroughly assessed in previous evaluations studies. Throughout the Key Evaluation Findings section, we make connections to previous studies by highlighting some previous findings, where appropriate.

Evaluation Criteria and Questions

In the 2014 PQ RFA reissuance request, NCI suggested three evaluation criteria to measure the progress and outcomes of the PQ initiative. These criteria included:

- RFA Criteria 1: Continued enthusiastic support from the community and NCI staff with the generation of well-received PQs
- RFA Criteria 2: Retiring of PQs when they have generated enough new research momentum and funding support
- RFA Criteria 3: Producing strong PQ-targeted research from the grants funded under the PQ RFAs

This evaluation was guided by these criteria, with a focus on areas that had not been fully addressed in previous evaluations. The three main evaluation criteria and their corresponding assessment methods and evaluation questions are listed below. We have also referenced related evaluation questions from previous PQ evaluation studies (2014 evaluation[8], 2014 portfolio analysis/interviews[9], and 2016 evaluation[10]).

1. **CRITERIA 1: ENTHUSIASTIC SUPPORT FROM COMMUNITY AND NCI STAFF**
    - *Assessments and Corresponding Evaluation Questions*
        - Expert Panel Assessment of Scientific Impact
            - What level of support does the PQ initiative receive from the research community?
            - How does the community view the quality of PQ questions?
        - Previous Evaluation Studies
            - What level of support does the PQ initiative receive from NCI Program staff? (2014 portfolio analysis/interviews and 2016 evaluation)

2. **CRITERIA 2: RETIRING OF PQs**
    - *Assessments and Corresponding Evaluation Questions*
        - Expert Panel Assessment of Scientific Impact

[8] National Cancer Institute Center for Strategic Scientific Initiatives (May 2014). *2014 Evaluation of the Provocative Questions Initiative (2011 AND 2012 PQ RFAS)*. National Institutes of Health. https://www.cancer.gov/about-nci/organization/cssi/resources/evaluation-reports

[9] National Cancer Institute Center for Strategic Scientific Initiatives (2014). Provocative Questions RFA Reissuance Request. Provided by NCI.

[10] National Cancer Institute Center for Strategic Scientific Initiatives (January 2016). The Provocative Questions Initiative Program Evaluation. National Institutes of Health. https://www.cancer.gov/about-nci/organization/cssi/resources/evaluation-reports

    - What is the perception of PQ questions over time?
  - Current and Previous Evaluation Studies
    - What is the rate of retirement for PQs? (2014 portfolio analysis/interviews and 2016 evaluation)

3. **CRITERIA 3: PRODUCING STRONG PQ-ASSOCIATED RESEARCH**
   - *Assessments and Corresponding Evaluation Questions*
     - Expert Panel Assessment of Scientific Impact
       - How does the data on outcomes suggest significant research progress in the PQ research areas?
     - Assessment of Outputs, Applicants, and Awardees
       - What is the total volume and relative citation index of publications produced by PQ awardees with relevance to the PQ topic? How does this compare to productivity of NCI RPG awardees?
       - What is the breakdown of applicants and awardees across early stage, new, and established investigators? How does this compare to applicants and awardees from the NCI research project grant (RPG) pool?
     - Assessment of PQ Influence on Science
       - How many PQ awardees have been awarded follow-on funding?
       - What is the total number of patent and clinical trials produced by PQ awardees?
       - Since the launch of the initiative in 2011, how have PQ themes been included in scientific meetings and sessions?
     - Previous Evaluation Studies
       - Has there been an increase in the volume of research publications and grants within the targeted PQ research areas that corresponds with the launch of the initiative? (2014 evaluation)
       - Has the PQ initiative supported high quality and novel science in the supported areas? (2016 evaluation)

Evaluation Design and Methodology

Ripple Effect relied on existing data and documentation and consultation with NCI staff to inform the study design and methods. We used primarily secondary data sources to assess applicants, awardees, and outputs and PQ scientific outcomes. Methods included quantitative analysis of NIH and other publicly available data, publication analyses and bibliometrics, and content analysis of program documentation (e.g., progress reports). We created and used a comparison group of NCI Research Project Grants (RPG) to contextualize some of these metrics. We also conducted five interviews with six PQ Principal Investigators (PI) to create in-depth case studies or vignettes on topics of interest. There are highlighted throughout the report with full vignettes available in Appendix B. Finally, we convened an expert panel to qualitatively evaluate the publication and bibliometric outcomes of a subset of randomly selected PQs.

The use of multiple data sources allowed us to examine PQ outcomes using multiple quantitative metrics. Using multiple metrics allows for data triangulation, or the validation of findings from more than a single source, to enhance confidence in the study results. A full description of all evaluation methods is available in Appendix C.

Key Evaluation Findings

Key findings from the PQ Evaluation are presented below and are organized by the evaluation domains and corresponding evaluation questions.

Criteria 1: Enthusiastic Support from Community and NCI Staff

Expert Panel Assessment of Scientific Impact

What level of support does the PQ initiative receive from the research community? How does the community view the quality of PQ questions?

The evaluation team convened an external panel of scientists with expertise in each of the 10 randomly selected PQ topics based on professional knowledge and a review of the literature in each scientific area. Ripple Effect and NCI collaborated to select a total of eight experts to review the first five PQs on Panel Day 1 and eight experts to review the remaining five PQs on Panel Day 2. The panels were held virtually via Zoom meeting and were moderated by a trained scientific moderator provided by Ripple Effect.

Detailed information about the External Panel created for this evaluation can be obtained in the appendices. Appendix C contains information about Expert Panel Selection. Appendix D is a list of all panel members. Appendix E provides a sample excerpt from the panel data book. Finally, Appendix F displays the discussion guide used during the panel sessions.

Six themes emerged from an analysis of the feedback provided by the PQ Expert Panel. We have organized these themes into two overarching categories with corresponding sub-categories:

1. Significant Progress in Cancer Research, Particularly in Understudied Areas
    a. The Provocative Questions are well formulated and timely
    b. The Provocative Questions made a significant contribution to multiple areas of cancer research
    c. The Provocative Question Program should be continued
2. Recommended Enhancements for the PQ Program
    a. Focus on cross-disciplinary science
    b. Ensure grant outcomes address the Provocative Question and hold PIs accountable to focusing on the goal of the PQ
    c. Continue assessing the success of the Provocative Question in various ways
    d. Expand the collection of community input

The themes, explanations of the themes, and sample quotes from the Expert Panel are further described below.

Significant Progress in Cancer Research, Particularly in Understudied Areas

The Provocative Questions are well formulated and timely

Overall, the panelists felt the PQs were well formulated. Predominately, the panelists felt the questions were timely and the program itself was valuable to aiding cancer research progress in important areas. Below are a few examples of panelists describing their satisfaction with the questions.

- From a clinical standpoint the questions were spot on.

- I think in a disease like cancer, we want to think about things which are the most impactful. I think this is a great mechanism to make sure the US is looking at the most necessary problems in the most competitive way possible. It feels like a lot of PQs hit right in the front of the wave and bring together the cancer community to figure out where we should be going. I think the creation of the PQs helps determine what the community views as the most important things to happen in cancer research.

The Provocative Questions made a significant contribution to multiple areas of cancer research

Panelists were asked about the broader impact the PQs made on the field, if any, and whether the trajectory of the field was altered. Overall, panelists felt the PQs made a significant contribution to the field and without them, research in cancer treatment may not have advanced as much as it has during the duration of the PQs. Table 2 includes specific examples of contributions to cancer research provided by panelists.

Table 2 shows some examples of significant cancer research progress among PQ awardees.

Table 2. Examples of Significant Research Progress in the Field of Cancer Research

Topic	Research Progress
Cancer Cachexia	• The role of sarcopenia, strength, and fat mass versus muscle mass in non-metastatic breast cancer survival and obesity • Identifying muscle mass, but not BMI alone, was a predictor of mortality in women with non-metastatic breast cancer
Mitochondria and Cancer	• Migration of mitochondria researchers beginning to contribute to cancer research • PQ has helped cancer begin to learn from mitochondria field • Foresee a future cancer research emphasis on mitochondrial heterogeneity
Obesity, Metabolism, and Cancer	• PQs likely had an influence on the growing foundation of the link between obesity and cancer • Strong focus on mechanisms and reversibility of obesity to reduce risk, given the link to 13 types of cancer • Exploration of at molecular pathways linking obesity and renal cell carcinoma discovering particular SNP in an ITP receptor that affected renal cell carcinoma in relation to diet • Determined that mitochondrial DNA copy number can be altered with physical activity • Recent increase in studies on metformin, likely a result of this PQ, are useful and important to understand cancer incidence • Given the links between obesity and cancer, the significant contributions made to the metabolism field, especially mechanistic data, were important • Helping metabolism to make a comeback in cancer biology by examining imaging modalities to look at metabolic profiles.
Cancer and Optical Imaging	• Large preclinical value with multi-photon endoscopy • Optical metabolic imaging to measure redox potential and the use of fluorescence lifetime to characterize concentration of NADH • Impressive progress in early cancer detection, such as the ability to target the biopsy site and combine it with MRI to bring the needle in to the right hot spot • Interesting work in automatic detection of residual tumor after surgical removal

PQ Spotlight: PQ Research Leads to Development of the First Total Body PET Scanner

Dr. X and a colleague were looking for funding for their idea to build a total body PET scanner, which was seen as risky and expensive. When the PQ call was released, Dr. X felt it was written for his research. He received sufficient funding to form a consortium to begin technology development. He feels the PQ gave his work the credibility and momentum it needed to begin. Dr. X's PQ research has created a new research field and allowed his team set up a molecular imaging center to foster national and international collaboration. To commercialize the scanner, the team collaborated with United Imaging Healthcare. See Appendix B for full vignette.

The Provocative Questions Program should be continued

Overall, panelists strongly endorsed the continuation of the PQ Program given its important impact on the field of cancer research. Below are a few examples of panelists describing their desire to continue to PQ Program.

- I think it's a great program to bring people's attention to specific areas of research so from that point of view, there's no question that it should continue.
- I also agree that these [PQs] have value, especially when the questions are being revised to keep up with the forefront of the field.

Recommended Enhancements to the PQ Program

While panelists supported the continuation of PQs given the impact on cancer research, some enhancements were recommended. These enhancements are described in detail below.

Focus on cross-disciplinary science

One suggested enhancement for further expanding the impact of PQ grants was to put emphasis on exploring cross-disciplinary science. Panelists expressed that including scientists from different disciplines could bring new talent to the field and further expand upon contributions to the field. It could allow investigators to push the boundaries of their work by working with other disciplines and obtain the best of both worlds. This could also bring new talent to the field by engaging researchers from outside the field of cancer research.

Ensure grant outcomes clearly address the Provocative Question and hold PIs accountable to focusing on the goal of the PQ

Participants observed that grantees did not always directly address the original PQ in their publications and instead veered into other avenues of research. Despite some of this research producing promising results, if a goal of the PQs were to trigger focused research, this did not consistently occur. The panel recommended that NCI find new methods for holding PIs accountable for pursuing the focus of the PQ, or clearly documenting any changes or deviations. Panelists suggested tracking the progress of the research more closely through progress reports to determine if researchers were veering off course from the goal of the question. It is important to note that the majority of the PQs assessed by the panel were funded before the scientific responsiveness requirement was established and newer awards are more likely to address the PQ research area.

Continue assessing the success of the Provocative Questions in multiple ways

The panel reviewed a random sample of PQs, with some at the beginning of funding and some at the end. Within specific PQs, particularly those with the most recent funding, panelists discussed how to operationalize in-progress success. Panelists noted that some awardees seemed less productive in terms of publication outcomes but debated whether enough time had passed to show true productivity. Some panelists also highlighted that null findings are significant, yet these findings are often not published giving more reason to not solely base success on publications. These discussions emphasized the need for NCI to continue assessing the success of PQ awardees in various ways to ensure that publications and citation metrics were not the sole basis, given that some less productive awardees had also advanced cancer research with their PQ work. While the research productivity of some awardees and PQ topic areas was lower than anticipated, panelists suggested that some of the questions were just beginning to be explored and may need more time and attention to demonstrate robust impacts.

Expand the collection of community input

While NCI does a great deal to collect community input on the development and trajectory of the PQs, panelists highlighted the need to build upon and expand the current methods for integrating the community. Community input was recommended to be obtained before, during, and after the PQ to assist with brainstorming new directions of meaningful research, promote the program, and capture the impact of the work conducted. One panelist proposed the idea of holding five minute "lightening talks" focused on a researcher's topic area to facilitate brainstorming across the field. Panelists also suggested obtaining input from societies with a focus on cancer research, such as The Federation of American Societies for Experimental Biology. Lastly, posting questions six months prior to the issuance of the PQ was suggested to allow time for a symposium, provide time for researchers to prepare for submission, and work to reach a broader community of researchers.

Previous Evaluation Findings on PQ Support from NCI Staff

What level of support does the PQ initiative receive from NCI Program staff?

This evaluation question was not explored for this evaluation because it was addressed in the 2016 evaluation,[11] which found that interviewees, including NCI program staff, perceived the PQ development process to be democratic, inclusive, and produce relevant questions. Interviewees also stated that the PQ initiative does what it was intended by producing PQ questions that are perplexing and involve understudied areas. At that time, some NCI Branch Chiefs and Program Directors cited early PQ successes and promising approaches but cautioned that additional time was needed to judge the success of PQ science. NCI's Office of the Director also conducted individual and group interviews with program staff in 2014 and indicated high enthusiasm for continuing the PQ initiative.[12]

[11] National Cancer Institute Center for Strategic Scientific Initiatives (January 2016). The Provocative Questions Initiative Program Evaluation. National Institutes of Health. https://www.cancer.gov/about-nci/organization/cssi/resources/evaluation-reports

[12] National Cancer Institute Center for Strategic Scientific Initiatives (2014). Provocative Questions RFA Reissuance Request. Provided by NCI.

Criteria 2: Retiring of PQs

External Panel Assessment of Scientific Impact

What is the perception of PQ questions over time?

Panelists described the PQ questions as thoughtful and appropriately adjusted over time on the 10 PQs they reviewed, including some with various iterations of questions over multiple years. Panelists relayed that the workshop approach to question development seems productive and they like that PQs can be refined over time to make sure that the PQ initiative is asking relevant questions, as well as continuing or retiring them as needed. One panelist stated:

- One thing NCI has done well is learn through the process and mutate as they go along to make sure that they are asking the best questions, and reformulating them as they go, to make sure the community is aware of what they're going off of.

Current and Previous Calculations on Retirement of PQs

What is the rate of retirement for PQs?

In the 2016 evaluation survey, 99% of awardees and 96% of applicants agreed that the "process of updating, renewing, and retiring PQs is an important feature of the PQ initiative." As in the 2016 PQ evaluation, this study found the number of PQs retired varied for each RFA issuance, with 40-75% of PQs retired between each RFA over the duration of the program.

Criteria 3: Producing Strong PQ-Associated Research

External Panel Assessment of Scientific Impact

How does the data on outcomes suggest significant research progress in the PQ research areas?

Overall, when presented data on PQ outcomes during the expert panel, panelists agreed that significant progress was made in the PQ research areas that would likely not have occurred without the PQ initiative. For instance, panelists discussed that the PQs get people thinking, talking, and may be leading researchers to veer into areas they may not have otherwise. When focusing on outcomes and how research moves the field, panelists also noted that there is continual new research from the PQs and a lot of the grants would not advance without the PQ.

PQ Spotlight: PQ Research Fosters Collaboration and Innovative Thinking

While Dr. Y focuses on the clinical side of oncology, Dr. Z applies principles from evolutionary biology to cancer. Despite the different angles of their research, they found that there was much synergy in their interests. Since the PQ award, Dr. Z and Dr. Y have received a DoD Breakthrough Award and an NCI grant to develop the Breast Pre-cancer Atlas – a repository for information about breast tumors available to the community, both of which built on their PQ work. This subsequent funding has allowed them to continue their work on the evolution of pre-cancers. Dr. Y credits the PQ for supporting out-of-the-box thinking to benefit cancer research and would love to see an additional focus on interdisciplinary collaboration through PQ research. Dr. Z believes that the PQ is essential to speeding up novel cancer research approaches and allowing researchers to use alternate methods. The PQ started in 2014 and they have been working together ever since. See Appendix B for full vignette.

Assessment of Applicants, Awardees, and Outputs

What is the total volume of publications and citation metrics produced by PQ awardees with relevance to the PQ topic? How does this compare to productivity of NCI RPG awardees?

Table 3 shows that PQ grants and the RPG Comparison group grants produced roughly the same number of publications per grant, when measured by mean and median. Compared to the PQ grants, NCI RPG Comparison Group grants had a slightly higher mean publications per grant (8.09 versus 8.50 respectively), but a lower median (5 versus 4 respectively). Of the 321 PQ grants included in the analyses (only assessing from 2012-2018), 15% (n=49) did not have associated publications. Similarly, of the 321 RPG Comparison Group grants from 2012-2018, 12% (n=40) did not have associated publications.

Table 3. Descriptive Data for Publications Per Grant

Metric	PQ Grants (n 321)	NCI Research Project Grant (RPG) Comparison Group Grants (n 321)
Mean	8.09	8.50
Median	5	4
Range	1 – 58	1-72

Table 4 provides the citation-based impact metrics for the PQ publications and the NCI RPG Comparison Group publications. Please see Bibliometrics for detailed information on citation metrics including RCR, hot papers, and citation lag. Across the 321 analyzed PQ grants, there was a total of 2,128 unique publications identified and 84% (n=1,779) of these publications had citations. In contrast, across the 321 grant NCI Research Project Grant (RPG) Comparison Group, there was a higher total of 2,369 unique publications identified and a similar proportion (85%, n=2,002) of these publications had citations. Finally, NCI RPG Comparison Group publications had the same median number of citations as the PQ publications but a slightly higher mean number of total citations, likely due to the higher maximum number of citations per publication.

Table 4. Total Citations and Citations per Publication per Group

Metric	PQ Publications (n 2,094)	NCI Research Project Grant (RPG) Comparison Group Publications (n 2,356)
Mean	20.17	20.90
Median	6.00	6.00
Range	0 – 1934	0-3007

Note: Citation data was not available for roughly 2% (n=34) of PQ publications and 0.6% (n=13) of NCI RPG Comparison Group publications

Of the PQ publications and NCI RPG Comparison Group publications, 5% were highly cited papers (n=105 and n=113 respectively) and 0.1% were hot papers (n=3 and n=2 respectively) in each group.

Table 5 shows the RCR for all PQ publications and all NCI RPG Comparison Group publications with RCR data. PQ publications had a mean RCR of 2.40, meaning that the average PQ publications are more than twice as impactful as the average NIH-funded publication from the same field in the same time period. NCI RPG Comparison Group publications had a slightly higher mean (2.47) and median (1.29) RCR than PQ publications (2.40 and 1.20 respectively). RPG Comparison Group publications also had a higher

maximum RCR for a publication (229) when compared to the highest maximum RCR for an PQ publication (96).

The RCR is not available for 26% (n=551) of PQ publications and 27% (n=644) NCI RPG Comparison Group publications given that recent publications (2018 and 2019) have not had sufficient time to accrue citations. Approximately 3% of PQ and NCI RPG Comparison Group publications (n=70 and n=74 respectively) had an RCR of zero indicating that the publications have not been cited.

Table 5. Relative Citation Ration (RCR) per Group

Metric	PQ Publications (n = 1,577)	NCI Research Project Grant (RPG) Comparison Group Publications (n 1,725)
Mean	2.40	2.47
Median	1.20	1.29
Range	0 – 96	0-229

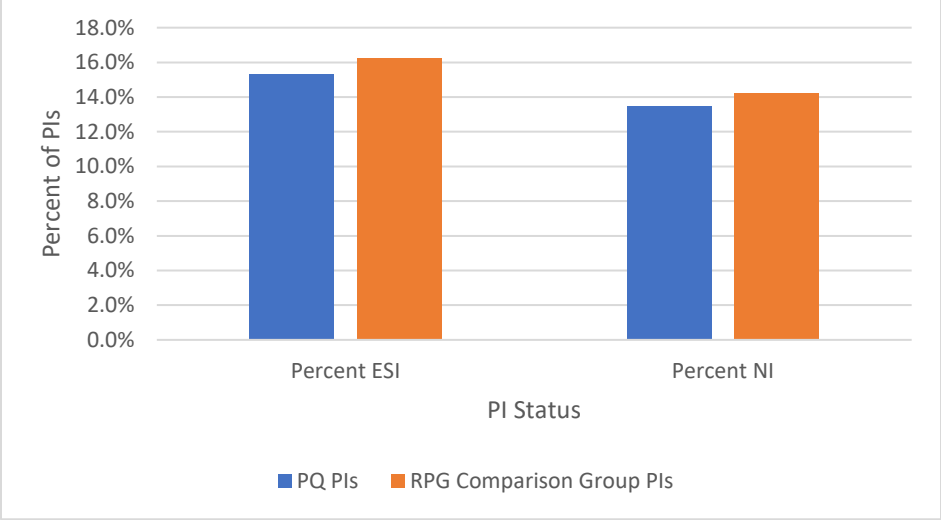
Note: An RCR of zero indicates that the publication has not been cited.

An analysis of citation lags for PQ publications and NCI RPG Comparison Group publications, or the number of months between publication and the first citation, showed that PQ publications and NCI RPG publications had similar citations timelines with comparable median (6 months for both) and mean (7.69 months and 8.22 months, respectively) citation lags.

What is the breakdown of applicants and awardees across early stage and new investigators? How does this compare to applicants and awardees from the NCI research project grant (RPG) pool?

Figure 1 provides the ESI and NI status of all awarded PQ PIs (n=438) and RPG Comparison Group PIs (n=401) for each grant application and shows similar findings between the groups. Please see Comparison Group Selection for information on how the comparison group of NCI RPG grants were selected and matched on funding year, grant type, and grant funding. There were roughly the same number of PQ ESIs (n=67, 15%) as there were RPG Comparison Group ESIs (n=65, 16%). There was also a similar amount of PQ NIs (n=59, 13%) as there were RPG Comparison Group NIs (n=57, 14%).

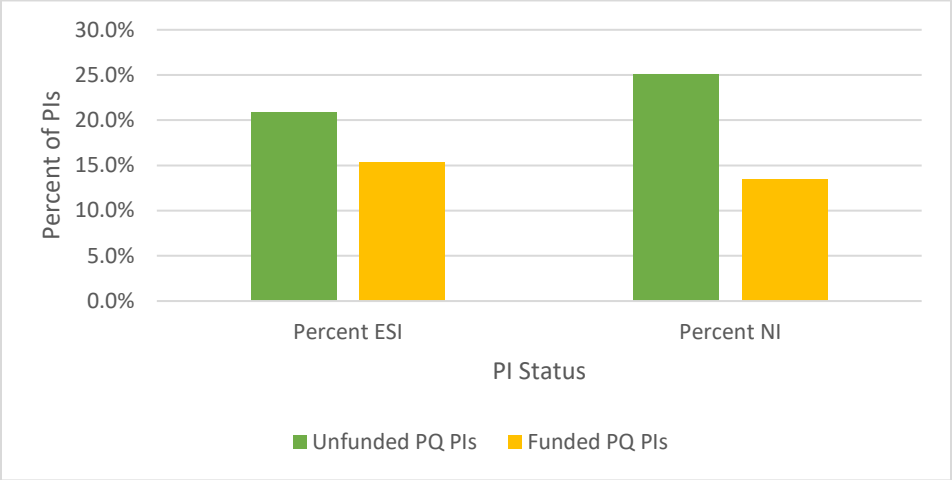
Figure 1. ESIs and NIs Status for Awarded Grants



Note: A total of two PIs submitted a grant in the same FY and met the NI criteria for both applications that were awarded.

We also assessed the PI status among PQ awardees compared to those who applied for PQ funding but did not receive it. First, Figure 2 provides the ESI and NI status of all unfunded PQ PIs for each grant (n=2,107). Approximately 21% (n=439) of unfunded PIs met ESI criteria and 25% (n=528) met NI criteria.

Figure 2. ESIs and NIs PI Status for Unfunded and Funded Applications



PQ Spotlight: PQ Jump Starts Funded Work for Early Stage Investigator

Dr. A's PQ research focused on early breast tumor metastasis to the brain and the tumor microenvironment. At the time of PQ award, he was in the early years of his assistant professorship. Although he had a good understanding of how to perform the work he was interested in, he did not yet have preliminary work as an early stage investigator. He felt that the focus on vision rather than preliminary results in the PQ review process was particularly helpful for him as an early stage investigator and was essential to launching his lab and research program. He also believes that the PQ program is essential for stimulating innovation for questions that are ignored in his field, or which are technically challenging. The preliminary results from Dr. A's PQ research led to a subsequent R01 grant to study the brain microenvironment and metastasis. See Appendix B for full vignette.

Assessment of PQ Influence on Science

How many PQ awardees have been awarded follow-on funding?

Overall, the PQ PIs were awarded more follow-on funding than the RPG comparison group PIs. The PQ PIs were awarded a total of 241 grants and the RPG PIs were awarded a total of 159 grants. Table 6 shows the number of subsequent awards broken down by grant mechanism. For PQ PIs and RPG Comparison Group PIs, R01s (44.4%, n=107 versus 47.2%, n=75 respectively) were the most awarded subsequent funding mechanism. U awards (15.4%, n=37 and 8.2%, n=13 respectively), R21s (15.8%, n=38 and 17.6%, n=28 respectively), and all other R awards (15.8%, n=38 and 9.4%, n=15 respectively) were the most awarded subsequent funding mechanisms after R01s for PQ PIs and RPG Comparison Group PIs. Also of note, PQ PIs had a higher proportion of subsequent R35 awards compared to RPG Comparison Group PIs (5.0%, n=12 versus 0.6%, n=1).

Table 6. Subsequent PQ and RPG Comparison Groups PI Grant Funding

Mechanism	Subsequent PQ Grant Funding	Subsequent RPG Comparison Group Grant Funding
R01	44.4% (n = 107)	47.2% (n = 75)
R21	15.8% (n = 38)	17.6% (n = 28)
R35	5.0% (n=12)	0.6% (n=1)
P Awards	2.9% (n = 7)	4.4% (n = 7)
U Awards	15.4% (n = 37)	8.2% (n = 13)
Small Business Awards	3.7% (n = 9)	8.2% (n = 13)
All Other R Awards	10.8% (n = 26)	8.8% (n = 14)
All Other Awards	2.1% (n = 5)	5.0% (n = 8)
Total	**100% (n=241)**	**100% (n=159)**

Note: Small business awards include R41, R43, R44; All other includes K24, S10, and T32

Table 7 compares the mean (2.99 years versus 2.85 years respectively), median (3 years for both groups), and range (2 – 6 years for both groups) between the fiscal year and the year the application was received for the first subsequent NIH grant awarded to each of the PIs who were awarded a subsequent grant. As shown, the mean, median, and range are similar for both groups.

Table 7. Time Between First PQ and RPG Comparison Group Grant Awarded and Fiscal Year

Metric	PQ Grants Time Between First Grant Awarded and PQ Fiscal Year (In Years)	RPG Comparison Group Time Between First Grant Awarded and RPG Fiscal Year (In Years)
Mean	2.99	2.85
Median	3	3
Range	2 - 6	2 - 6

PQ Spotlights

As described in the Methods section, the evaluation team conducted five informal telephone interviews with a six PQ PIs or Co-PIs to gain in-depth information about their perceptions and experiences related to PQ initiative. Potential participants were extracted from evaluation outcomes with a focus on those PIs who had gone on to receive subsequent NIH funding or those who appeared to engage in new collaborations through the PQ initiative. The results from these interviews are presented throughout the report in brief PQ Spotlights and can be viewed in their entirety in Appendix B.

Dr. B's PQ research focused on understanding the "brain circuitry" underlying health behaviors that increase risk of cancer in response to a PQ addressing "can we change the brain to change behavior?" Dr. B's group completed a clinical trial which studied the impact of commercially available cognitive exercise training against a computerized control condition. The results of the study showed that commercially available cognitive exercise trainings had no differential effect than the control group for most of the measures included. These results were published in the Journal of Neuroscience and received more press than Dr. B had received on any previous papers. Although the study did not find new cancer prevention methods, it did have a public health impact by requiring companies to modify unsubstantiated claims about their products, leading to changes in the marketing of those products. Recently Dr. B received a R35 Outstanding Investigator Grant (7-year award) as a direct result of her PQ work. See Appendix B for full vignette.

What is the total number of patent and clinical trials produced by PQ awardees?

Thus far, there are 20 clinical trials associated with PQ grant numbers for 13 unique PQs, and most are in the Phase 1 or 2, noted in the clinicaltrials.gov database. There are also are nine patents associated with six unique PQs, which are listed in Table 8, along with the title of the patent and the assignee. In addition, there are approximately 200 pending applications associated with PQ awards noted in the USPTO database

Table 8. Patents by PQ

Provocative Questions (Most Recent)	USPTO Serial Number	Assignee	Patent Title
Given the recent discovery of the link between a polyomavirus and Merkel cell cancer, what other cancers are caused by novel infectious agents and what are the mechanisms of tumor induction?	10203329	Johns Hopkins University	Biofilm formation to define risk for colon cancer
Since current methods to predict the efficacy or toxicity of new drug candidates in humans are often inaccurate, can we develop new methods to test potential therapeutic agents that yield better predictions of response?	9757727 10317395	Massachusetts Institute of Technology Cornell University	Hydrodynamic trap array Ex vivo engineered immune organoids for controlled germinal center reactions
Are there new technologies to inhibit traditionally "undruggable" target molecules, such as transcription factors, that are required for the oncogenic phenotype?	10266823	Southern Research Institute; University of North Carolina, Chapel Hill	Small molecules that enhance the activity of oligonucleotides

Provocative Questions (Most Recent)	USPTO Serial Number	Assignee	Patent Title
How can the physical properties of tumors, such as a cell's electrical, optical, or mechanical properties, be used to provide earlier or more reliable cancer detection, diagnosis, prognosis, or monitoring of drug response or tumor recurrence?	9983399	Commonwealth System of Higher Education; University of Pittsburgh	Depth-resolved spatial-domain low-coherence quantitative phase microscopy for unstained tissue and cells
Can tumors be detected when they are two to three orders of magnitude smaller than those currently detected with in vivo imaging modalities?	10241178 9508256	Case Western Reserve University Case Western Reserve University	System and method for magnetic resonance fingerprinting at high field strengths Magnetic resonance imaging (MRI) with dual agent characterization
What mechanisms initiate or sustain cancer cachexia, and can we target them to extend lifespan and quality of life for cancer patients?	10036018 10191033	N/A Broad Institute of MIT and Harvard, Dana-Farber Cancer Institute	Compositions and methods for treating cachexia Biomarkers for detecting pre-cachexia or cachexia and methods of treatment thereof

Since the launch of the initiative in 2011, how have PQ themes been included in scientific meetings and sessions?

PQ progress reports listed a total of 143 presentations of PQ research at over 100 unique scientific meetings including conferences, symposiums, and workshops between FY 2012 and FY 2019. These presentations included research from 60 unique PQ grants out of a total of 321 PQ grants awarded from FY 2012 to FY 2018. Table 9 shows the scientific meetings with more than two PQ presentations, and the specific number of presentations made at each scientific meeting. The scientific organization that had the largest number of presentations was the American Association of Cancer Research (n=11).

Table 9. Scientific Meetings and Presentations of PQ Research with More than One Presentation

Scientific Meeting/Organization	Number of Presentations
American Association of Cancer Research	11
Gordon Conference	10
International Cachexia Conference	4
Keystone Conference	4
Society of Photo-optical Instrumental Engineers Conference (SPIE)	4
National Institutes of Health (NIH) Workshop/Symposium	4

Table 10 shows all PQs with at least six presentations at scientific meetings, as well as the number of unique scientific meetings given that in some instances more than one presentation was made at the

same scientific meeting. The PQ, "What molecular or cellular events establish tumor dormancy after treatment and what leads to recurrence?" had the highest number of presentations (n=16) while the PQ, "How does obesity contribute to cancer risk?" had the second highest number of presentations (n=11). For additional comparison, we have included the total number of PQ grants awarded from FY 2012 to FY 2018. There does not appear to be a correlation between the number of PQ grants awarded and the number of presentations given at scientific meetings.

Table 10. PQs and Scientific Meetings with Six or More Presentations

Provocative Questions (Most Recent)	PQ Grants Awarded	Number of Presentations Given at Scientific Meetings	Number of Unique Scientific Meetings
What molecular or cellular events establish tumor dormancy after treatment and what leads to recurrence?	5	16	13
How does obesity contribute to cancer risk?	17	11	9
What are the molecular and/or cellular mechanisms that underlie the development of cancer therapy-induced severe adverse sequelae?	20	10	10
Are there new technologies to inhibit traditionally "undruggable" target molecules, such as transcription factors, that are required for the oncogenic phenotype?	6	8	7
What in vivo imaging methods can be developed to determine and record the identity, quantity, and location of each of the different cell types that contribute to the heterogeneity of a tumor and its microenvironment?	9	8	6
Can we develop tools to directly change the expression or function of multiple chosen genes simultaneously and use these tools to study the range of changes important for human cancer?	3	7	7
Since current methods to predict the efficacy or toxicity of new drug candidates in humans are often inaccurate, can we develop new methods to test potential therapeutic agents that yield better predictions of response?	11	7	5
Can tumors be detected when they are two to three orders of magnitude smaller than those currently detected with in vivo imaging modalities?	8	6	5
How does the selective pressure imposed by the use of different types and doses of targeted therapies modify the evolution of drug resistance?	8	6	6
What mechanisms initiate or sustain cancer cachexia, and can we target them to extend lifespan and quality of life for cancer patients?	10	6	3

Previous Evaluation Findings on Strong PQ-Associated Research

Findings from this evaluation support similar findings from the 2014 evaluation[13] that showed two particular questions had shown early signs of productivity in publications, based on publication volume, though it was too early for further bibliometric analysis at that time. The original text of these highly productive PQs are:

- Given the appearance of resistance in response to cell killing therapies, can we extend survival by using approaches that keep tumors static?
- What mechanisms initiate cachexia in cancer patients, and can we target them to extend lifespan and quality of life for cancer patients?

In addition, this evaluation found there had been small increases in the volume of research related to PQ question areas comparing the pre- and post-PQ years using key word literature searches. Specifically, a 5.2% in the proportion of cancer-related publications and a 6.5% increase in the proportion of relevant grant applications (excluding PQ applications).

Findings from this evaluation also support initial findings from the 2016 evaluation,[14] which found that the normalized citation impact of papers funded by the PQ program was twice as high as other papers in the PQ research areas. The 2016 evaluation also found via surveys that 85% of PQ awardees had new research findings that directly resulted from PQ work and 65% had developed new methods or model sets from their PQ work.

Summary and Discussion of the Findings

In the 2014 PQ RFA reissuance request, NCI suggested three evaluation criteria to measure the progress and outcomes of the PQ initiative: 1) Continued enthusiastic support from the community and NCI staff with the generation of well-received PQs, 2) Retiring of PQs when they have generated enough new research momentum and funding support, and 3) Producing strong PQ-targeted research from the grants funded under the PQ RFAs This evaluation was guided by these criteria, with a focus on areas that had not been fully addressed in previous evaluations.

Key findings are listed below, organized by the evaluation criteria. Additional details on each evaluation criteria, evaluation questions, assessment methods, and detailed findings, are provided in the body of the report.

Enthusiastic Support from Community and NCI Staff

- An external panel of experts in PQ research areas reviewed the output and impact of 10 randomly selected PQs. They determined that the PQs were well formulated and timely and had made a significant contribution to multiple areas of cancer research.
- Overall, panelists strongly endorsed the continuation of the PQ Program given its important impact on the field of cancer research.

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[13] National Cancer Institute Center for Strategic Scientific Initiatives (May 2014). *2014 Evaluation of the Provocative Questions Initiative (2011 AND 2012 PQ RFAS)*. National Institutes of Health. https://www.cancer.gov/about-nci/organization/cssi/resources/evaluation-reports

[14] National Cancer Institute Center for Strategic Scientific Initiatives (January 2016). The Provocative Questions Initiative Program Evaluation. National Institutes of Health. https://www.cancer.gov/about-nci/organization/cssi/resources/evaluation-reports

- The external panel made the following recommendations for future enhancement to the PQ program: 1) focus on cross-disciplinary science, 2) ensure grant outcomes address the PQ and hold PIs accountable to focusing on the goal of the PQ, 3) continue assessing the success of the PQs in multiple ways, and 4) expand the collection of community input.
- The 2016 evaluation[15] found that interviewees, including NCI program staff, perceived the PQ development process to be democratic, inclusive, and produce relevant questions. Interviewees also believed the PQ initiative produces PQ questions that are perplexing and involve understudied areas.

Retiring of PQs

- Panelists relayed that the workshop approach to question development is productive and they appreciate that PQs can be refined over time to make sure that the PQ initiative is asking relevant questions, as well as continuing or retiring them as needed.
- Panelists suggested earlier and broader advertising of the PQs such as posting questions six months prior to the issuance of the PQ to allow time for a symposium, provide time for researchers to prepare for submission, and work to reach a broader community of researchers.
- As in the 2016 PQ evaluation, this study found the number of PQs retired varied for each RFA issuance, with 40-75% of PQs retired between each RFA over the duration of the program.

Producing Strong PQ-Associated Research

- Panelists stated that significant progress was made in the PQ research areas that likely would not have occurred without the PQ Program.
- PQ grants and an NCI RPG Comparison Group grants produced roughly the same number of mean publications per grant (8.09 versus 8.50 respectively) with similar citation metrics:
  - Across the groups, 84% (n=1,779) of PQ publications had citations and 85% (n=2,002) of NCI RPG Comparison Group publications had citations.
  - publications had a mean Relative Citation Ratio (RCR) of 2.40, meaning that the average PQ publications are more than twice as impactful as the average NIH-funded publication from the same field in the same time period. NCI RPG Comparison Group publications had a similar mean RCR (2.47).
- There were roughly the same number of PQ Early Stage Investigators (ESI) (n=67, 15%) as there were RPG Comparison Group ESIs (n=65, 16%). New Investigators (NI) are those investigators who have not received substantial, independent funding from NIH previously. There was a similar amount of PQ NIs (n=59, 13%) as there were RPG Comparison Group NIs (n=57, 14%).
- PQ PIs were more likely to be awarded subsequent NIH funding, as PQ PIs were awarded 241 grants and NCI RPG Comparison Group PIs were awarded 159 grants from January 2014 - August 2019.
- In five informal interviews with PQ awardees that received subsequent NIH grant funding, awardees directly connected their PQ work to a variety of subsequent awards including NCI R01s, NCI R21s, an R35 Outstanding Investigator Grant, a Transformational R01, SBIR funding, STTR funding, a DoD Breakthrough Award, and Cancer Moonshot funding.

[15] National Cancer Institute Center for Strategic Scientific Initiatives (January 2016). The Provocative Questions Initiative Program Evaluation. National Institutes of Health. https://www.cancer.gov/about-nci/organization/cssi/resources/evaluation-reports

- A total of 143 presentations of PQ research, from 60 unique PQ grants, were presented at over 100 unique scientific meetings including conferences, symposiums, and workshops between FY 2012 and FY 2019.

Future Considerations

Throughout the process of completing the assessment, some themes emerged that might be useful to consider for possible future iterations of the PQ program.

- NCI should strongly consider continuing support of the PQ Program, as it fills a unique cancer research need for the community.
- Continue to use stakeholder workshops to assist in choosing the PQs as these processes were well regarded and the PQs considered timely among scientific experts.
- Consider increased focus on cross-disciplinary science in future iterations of the PQ initiative to continue to push cancer researchers to collaborate with other disciplines.
- Consider adding additional oversight mechanisms to improve the likelihood that PQ PIs will remain focused on the intended goal of the PQ, even if this may mean null findings in some cases.
- NCI may also want to explore novel ways to collect community input on PQ research during and after the PQs are awarded to continue to increase awareness of the mechanism and collect impact on the field (e.g., symposium).
- Consider advertising the PQs earlier and more broadly with methods such as posting questions six months prior to the issuance of the PQ to allow time for a symposium, provide time for researchers to prepare for submission, and work to reach a broader community of researchers.
- NCI should identify multiple ways to define success among PQ research projects, aside from publications, which may differ between topic areas and based on novelty of the research, years since award, and initial project risk. Convening focus groups of previous PQ awardees with a range of outcomes may help to solidify additional ways to measure success for awards intended to be higher risk.
- Future evaluations of the PQ initiative should include publication analyses (with a comparison group) and expert panel review, as these were the most informative portions of the current evaluation. Additional considerations for future evaluations are in Appendix G.
- Although more resource intensive, future evaluations should also consider PI interviews to discuss the impact of PQ funding on their research trajectories and scientific areas, as well as in-depth review of progress reports, publications, and other outputs to better measure how PQ research has moved the science forward in targeted areas.

Limitations

As with any evaluation, there are several limitations that should be considered when interpreting these findings:

- Publications that cited PQ grant numbers or the NCI RPG Comparison group grant numbers were included in the outcomes for each group. Using this technique may have missed some publications if the author forgot to reference the grant number or may have oversampled publications if authors included the grant number on publications that were not directly supported by these funds.

- Bibliometrics measures, including RCR, citations, and citation lag were used as general proxy measures for publication quality. There are, however, some potential limitations that should be considered when interpreting these measures.
    - The number of times an article is cited is impacted by the article's age, with older articles more likely to be cited more frequently than newer articles.
    - The most recently published articles lack citation counts and RCR, as these bibliometrics take time to accumulate to be able to calculate.
- The analysis of subsequent grant funding for PQ PIs and RPG Comparison group PIs took time into account by ensuring subsequent funding occurred at least one year after receipt of the original grant. However, the evaluation team was unable to assess if the subsequent grants were a direct result of findings from the original grants.
- The sample of six interview participants for vignettes were purposively selected in consultation with NCI staff. Other PIs were not included in the sample and may have different perspectives and experiences.
- Panel findings are a representation of the perceptions and beliefs of participants. They are not generalizable and may not reflect the attitudes of all potential panelists.
- All data is limited by the quality and completeness of the sources from which it was abstracted. To ensure full capture of outcomes, we used multiple sources and data triangulation where possible.
- The metrics to assess PQ retirement have varied over PQ issuances, including: 1) due to limited progress, 2) after robust progress, 3) to make room for new and timely questions, and 4) after other funding opportunities were developed to support the PQ research area. With these changes over time, analysis of retired questions may not fully reflect progress in a PQ research area.

Appendix A – Provocative Questions for FY 2011 – 2018

Table 11. Provocative Questions FY 2011 – 2018

Table 11 displays all PQs within FY 2011 – 2018 RFAs. Questions that appear in more than one column indicate PQs that were reissued in a later RFA on the same topic, often with some changes to refocus the original question.

2011 RFAs	2012 RFAs	2013 RFAs	2015/2016 RFAs	2017/2018 RFAs
PQ1. How does obesity contribute to cancer risk?	PQA2. How does obesity contribute to cancer risk?			
PQ2. What environmental factors change the risk of various cancers when people move from one geographic region to another?				
PQ3. Are there ways to objectively ascertain exposure to cancer risk using modern measurement technologies?	PQA4. As modern measurement technologies improve, are there better ways to objectively ascertain exposure to cancer risk?			
PQ4. Why don't more people alter behaviors known to increase the risk of cancers?	PQA3. How do cognitive processes such as memory and executive function interact with emotional or habitual processes to influence lifestyle behaviors and decisions, and can we use this knowledge to design strategies to change behaviors that increase cancer risk?	PQA1: (Rewritten for 2013) How do decision-making processes influence habitual behaviors, and how can that knowledge be used to design strategies that lead to adoption and maintenance of behaviors that reduce cancer risk?		
PQ5. Given the evidence that some drugs commonly and chronically used for other indications, such as an anti-inflammatory drug, can protect against cancer incidence and mortality, can we determine the mechanism by which any of these drugs work?	PQA1. What is the molecular mechanism by which a drug (such as aspirin or metformin) that is chronically used for other indications protects against cancer incidence and mortality?			

2011 RFAs	2012 RFAs	2013 RFAs	2015/2016 RFAs	2017/2018 RFAs
PQ6. What are the molecular and cellular mechanisms by which patients with certain chronic diseases have increased or decreased risks for developing cancer, and can these connections be exploited to develop novel preventive or therapeutic strategies?				
PQ7. How does the life span of an organism affect the molecular mechanisms of cancer development and can we use our deepening knowledge of aging to enhance prevention or treatment of cancer?	PQB4. What mechanisms of aging, beyond the accumulation of mutations, promote or protect against cancer development?			
PQ8. Why do certain mutational events promote cancer phenotypes in some tissues and not in others?				
PQ9. As genomic sequencing methods continue to identify large numbers of novel cancer mutations, how can we identify the mutations in a given tumor that are most critical to the maintenance of its oncogenic phenotype?				
PQ10. As we improve methods to identify epigenetic changes that occur during tumor development, can we develop approaches to discriminate between “driver” and “passenger” epigenetic events?	PQB2. As we improve methods to identify epigenetic changes that occur during tumor development, can we develop approaches to discriminate between “driver” and “passenger” epigenetic events?			
PQ11. How do changes in RNA processing contribute to tumor development?				

2011 RFAs	2012 RFAs	2013 RFAs	2015/2016 RFAs	2017/2018 RFAs
PQ12. Given the recent discovery of the link between a polyomavirus and Merkel cell cancer, what other cancers are caused by novel infectious agents and what are the mechanisms of tumor induction?				
PQ13. Can tumors be detected when they are two to three orders of magnitude smaller than those currently detected with in vivo imaging modalities?	PQC5. Can tumors be detected when they are two to three orders of magnitude smaller than those currently detected with in vivo imaging modalities?			
PQ14. Are there definable properties of a non-malignant lesion that predict the likelihood of progression to invasive or metastatic disease?	PQC3. Are there definable properties of pre-malignant or other non-invasive lesions that predict the likelihood of progression to metastatic disease?	PQC1: (Rewritten for 2013) What properties of pre-cancerous lesions or their microenvironment predict the likelihood of progression to malignant disease?		
PQ15. Why do second, independent cancers occur at higher rates in patients who have survived a primary cancer than in a cancer-naïve population?	PQB1. Why do second, independent cancers occur at higher rates in patients who have survived a primary cancer than in a cancer-naïve population?	PQB1: (Retained from 2012) Why do second, independent cancers occur at higher rates in patients who have survived a primary cancer than in a cancer-naïve population?		
PQ16. How do we determine the clinical significance of finding cells from a primary tumor at another site?	PQC4. How do we determine the significance of finding cells from a primary tumor at another site and what methods can be developed to make this diagnosis clinically useful?			
PQ17. Since current methods to assess potential cancer treatments are cumbersome, expensive, and often inaccurate, can we develop other methods to rapidly test interventions for cancer treatment or prevention?	PQD5. Since current methods to predict the efficacy or toxicity of new drug candidates in humans are often inaccurate, can we develop new methods to test potential therapeutic agents that yield better predictions of response?			

2011 RFAs	2012 RFAs	2013 RFAs	2015/2016 RFAs	2017/2018 RFAs
PQ18. Are there new technologies to inhibit traditionally "undruggable" target molecules, such as transcription factors, that are required for the oncogenic phenotype?				
PQ19. Why are some disseminated cancers cured by chemotherapy alone?	PQD2. What molecular properties make some cancers curable with conventional chemotherapy?	PQD1: (Retained from 2012) What molecular properties make some cancers curable with conventional chemotherapy?		
PQ20. Given the recent successes in cancer immunotherapy, can biomarkers or signatures be identified that can serve as predictors or surrogates of therapeutic efficacy?				
PQ21. Given the appearance of resistance in response to cell killing therapies, can we extend survival by using approaches that keep tumors static?	PQD1. How does the selective pressure imposed by the use of different types and doses of targeted therapies modify the evolution of drug resistance?			
PQ22. Why do many cancer cells die when suddenly deprived of a protein encoded by an oncogene?				
PQ23. Can we determine why some tumors evolve to aggressive malignancy after years of indolence?	PQC1. Can we determine why some tumors evolve to aggressive malignancy after years of indolence?			
PQ24. Given the difficulty of studying metastasis, can we develop new approaches, such as engineered tissue grafts, to investigate the biology of tumor spread?	PQB6. Given the difficulty of studying metastasis, can we develop new approaches, such as engineered tissue grafts, to investigate the biology of tumor spread?			

2011 RFAs	2012 RFAs	2013 RFAs	2015/2016 RFAs	2017/2018 RFAs
	PQA5. How does the level, type, or duration of physical activity influence cancer risk and prognosis?	PQA2: (Retained from 2012) How does the level, type, or duration of physical activity influence cancer risk and prognosis?		
	PQA6. How does susceptibility of exposure to cancer risk factors change during development?	PQA3: (Rewritten for 2013) What biological mechanisms influence susceptibility to cancer risk factors at various stages of life?		
	PQB3. What molecular and cellular events determine whether the immune response to the earliest stages of malignant transformation leads to immune elimination or tumor promotion?	PQB2: (Rewritten for 2013) What molecular and cellular events in the tumor microenvironment (for example, the local immune response) determine if a tumor at the earliest stages of malignant transformation is eliminated, stimulated for further development, or made indolent?		
	PQB5. How does the order in which mutations or epigenetic changes occur alter cancer phenotypes or affect the efficacy of targeted therapies?			
	PQC2. How can the physical properties of tumors, such as a cell's electrical, optical, or mechanical properties, be used to provide earlier or more reliable cancer detection, diagnosis, prognosis, or monitoring of drug response or tumor recurrence?			
	PQC6. What molecular events establish tumor dormancy after treatment and what leads to recurrence?	PQC2: (Retained from 2012) What molecular or cellular events establish tumor dormancy after treatment and what leads to recurrence?		

2011 RFAs	2012 RFAs	2013 RFAs	2015/2016 RFAs	2017/2018 RFAs
	PQD3. What underlying causal events—e.g., genetic, epigenetic, biologic, behavioral, or environmental—allow certain individuals to survive beyond the expected limits of otherwise highly lethal cancers?			
	PQD4. What properties of cells in a pre-malignant or pre-invasive field—sometimes described as the result of a cancer field effect—can be used to design treatments for a tumor that has emerged from this field or to block the appearance of future tumors?	PQA4: (Rewritten for 2013) For tumors that arise from a pre-malignant field, what properties of cells in this field can be used to design strategies to inhibit the development of future tumors?	PQ1: For tumors that arise from a pre-malignant field, what properties of cells in this field can be used to design strategies to inhibit the development of future tumors?	
	PQD6. What mechanisms initiate cachexia in cancer patients, and can we target them to extend lifespan and quality of life for cancer patients?	PQB3: (Rewritten for 2013) What mechanisms initiate or sustain cancer cachexia, and can we target them to extend lifespan and quality of life for cancer patients?		
		PQB4: (New for 2013) What methods can be devised to characterize the functional state of individual cells within a solid tumor?		
		PQC3: (New for 2013) How do variations in tumor-associated immune responses among patients from distinct well-defined populations, such as various racial/ethnic or age groups, contribute to differences in cancer outcomes?	PQ3: How do variations in tumor-associated immune responses contribute to differences in cancer risk, incidence, or progression?	
		PQC4: (New for 2013) What in vivo imaging methods can be developed to portray the "cytotype" of a tumor — defined as the identity,	PQ7: What in vivo imaging methods can be developed to determine and record the identity, quantity, and location of each of the different cell	

2011 RFAs	2012 RFAs	2013 RFAs	2015/2016 RFAs	2017/2018 RFAs
		quantity, and location of each of the different cell types that makes up a tumor and its microenvironment?	types that contribute to the heterogeneity of a tumor and its microenvironment?	
		PQD2: (New for 2013) What features of standard-of-care therapies enhance or inhibit the efficacy of immunotherapy?	PQ11: What mechanisms of action of standard-of-care cytotoxic, radiologic, or targeted therapies affect the efficacy of immunotherapy?	
		PQD3: (New for 2013) Do tumors evolve common features that could act as new therapeutic targets when they metastasize to the same secondary site?		
		PQD4: (New for 2013) What are the mechanistic bases for differences in cancer drug metabolism and toxicity at various stages of life?		
		PQE1: (New for 2013) What strategies optimize adoption and sustainability of guideline concordant cancer treatments in community settings?		
		PQE2: (New for 2013) What care delivery models can be developed to transition cancer patients effectively from active therapy to end of life care?		
		PQE3: (New for 2013) What methods and approaches induce physicians and health systems to abandon ineffective interventions or discourage adoption of unproven interventions?	PQ12: What methods and approaches induce physicians and health systems to abandon ineffective interventions or discourage adoption of unproven interventions?	
		PQE4: (New for 2013) What are the best methods to identify and stratify subgroups of		

2011 RFAs	2012 RFAs	2013 RFAs	2015/2016 RFAs	2017/2018 RFAs
		patients with particular co-morbidities who will benefit from defined cancer therapies?		
			PQ2: What molecular mechanisms influence disease penetrance in individuals who inherit a cancer susceptibility gene?	PQ1: What molecular mechanisms influence disease penetrance in individuals who inherit a cancer susceptibility gene?
			PQ4: Why do some closely related tissues exhibit dramatically different cancer incidence?	
			PQ5: How does mitochondrial heterogeneity influence tumorigenesis or progression?	PQ5: How does mitochondrial heterogeneity influence tumorigenesis or progression?
			PQ6: What are the underlying molecular mechanisms that are responsible for the functional differences between benign proliferative diseases and premalignant states?	
			PQ8: What cancer models or other approaches can be developed to study clinically stable disease and the subsequent transition to progressive disease?	
			PQ9: What are the molecular and/or cellular mechanisms that underlie the development of cancer therapy-induced severe adverse sequelae?	PQ12: What are the molecular and/or cellular mechanisms that underlie the development of cancer therapy-induced severe adverse sequelae?
			PQ10: How do microbiota affect the response to cancer therapies?	PQ10: How do microbiota affect the response to cancer therapies?
				PQ2: How do variations in immune function caused by comorbidities or observed among different populations

2011 RFAs	2012 RFAs	2013 RFAs	2015/2016 RFAs	2017/2018 RFAs
				affect response to cancer therapy?
				PQ3: Do genetic interactions between germline variations and somatic mutations contribute to differences in tumor evolution or response to therapy?
				PQ4: Can we develop tools to directly change the expression or function of multiple chosen genes simultaneously and use these tools to study the range of changes important for human cancer?
				PQ6: How do circadian processes affect tumor development, progression, and response to therapy?
				PQ7: How do cancer-specific subcellular pathognomonic structures develop, what is their function, and can they be a source of novel therapeutic targets?
				PQ8: What are the predictive biomarkers for the onset of immune-related adverse events associated with checkpoint inhibition, and are they related to markers for efficacy?
				PQ9: Can we develop bifunctional small molecules that will couple oncoproteins or other cancer-causing molecules of interest to inactivating processes such as degradation and achieve tissue-specific loss of function?

2011 RFAs	2012 RFAs	2013 RFAs	2015/2016 RFAs	2017/2018 RFAs
				PQ11: Through what mechanisms do diet and nutritional interventions affect the response to cancer treatment?

Appendix B – PQ Vignettes

PQ Work Results in R35 Outstanding Investigator Grant

Research Focus

Dr. B's PQ research focused on understanding the "brain circuitry" underlying health behaviors that increase risk of cancer in response to a PQ addressing "can we change the brain to change behavior?" Dr. B's group completed a clinical trial which studied the impact of commercially available cognitive exercise training against a computerized control condition. They analyzed the impact of cognitive training on self-control, changes in brain function that are associated with self-control, and changes in behaviors. The hypothesis of the study is if the brain circuitry underlying self-control processes is strengthened, it will translate into increased self-control over cancer risk behaviors such as tobacco use, eating unhealthy foods, and sedentary behavior.

The results of the study showed that commercially available cognitive exercise trainings had no differential effect than the control group for most of the measures included. These results were published in the Journal of Neuroscience and received more press than Dr. B had received on any previous papers. Shortly after the paper was published, the companies that offer these types of cognitive exercise trainings released a statement modifying their claims. Subsequent papers were published from the study data investigating the brain processes of how people make choices that underlie cancer risk behaviors.

Although the study did not find new cancer prevention methods, it did have a public health impact by requiring companies to modify unsubstantiated claims about their products, leading to changes in the marketing of those products.

Subsequent Funding

Recently Dr. B received an NCI R35 Outstanding Investigator Grant (7-year award) as a direct result of her PQ work. This grant has allowed her lab to pursue other avenues for brain modulation, including electrical stimulation and helped to create a new area of neuromodulation research in the field of cancer risk behavior change. If Dr. B had not received the PQ, she would not have become interested in leveraging neuroscience to understand the behavioral aspects of cancer prevention.

Collaborations

Dr. B views the main impact of the PQ grant as stimulating collaborations between researchers who have not worked together previously answer the PQs. While reviewing articles in neuromodulation in preparation for her PQ research, Dr. B discovered the work of Dr. C on self-control and how people make choices. He had not published in the health or cancer context. Dr. B met with Dr. C and introduced him into the field of cancer research. They became co-PIs on a grant and have published many papers together since.

She has also seen collaborations form across the cancer center and at her university. As the Director of a Cancer Center, Dr. B has sent out notifications of the PQ RFAs to its members and others outside the center. The Dean of the School of Gerontology teamed up with another faculty member to conduct cancer prevention research to respond to PQ grants related to aging. Other researchers at her University also responded to the PQ to research fasting and cancer outcomes.

PQ Research Leads to Development of the First Total Body PET Scanner

Research Focus

Dr. X and his colleague Dr. D were looking for funding for their idea to build a total body PET scanner, which was seen as risky and expensive. When the PQ call was released, Dr. X felt it was written for his research. He received sufficient funding to form a consortium to begin technology development. He feels the PQ gave his work the credibility and momentum it needed to begin. As a result of the PQ award, Dr. X claims that the research has taken over his life, as his career is entirely focused on total body PET.

Subsequent Funding

Dr. X's team received subsequent funding from UC Davis, including the Chancellor's Innovation Award. Dr. X's work was later funded by a Transformational R01 to build the scanner, which would not have happened without the credibility given to his team's work from prior PQ funding. The team received an R01 from NCI to compare their scanners to regular scanners in conventional imaging situations. They also received various R01s in other fields outside of cancer research such as arthritis and HIV and grants from the company that built the scanner for the purposes of additional research.

Impact

The funding from the PQ and subsequent R01 allowed his group to create a step change in molecular imaging and boost the physical sensitivity of molecular imaging by a factor of 40 which has never been achieved before. It is the first scanner that can image the entire body in 3 dimensions at the same time. The scanner reduces radiation doses patients are exposed to, which may have implications for imaging in cancer prevention studies and immune-based treatment as scans can be done more frequently. They are also now able to make videos of drugs circulating in the body effectively in real time, which has implications outside of cancer research and across the spectrum of human health and disease.

Dr. X claims that the best part of the PQ program is its willingness to fund unconventional ideas, which he says made the difference for his work, and which he hopes to see continue.

Collaborations

During his PQ research, Dr. X's team set up the Explorer Consortium, named after the scanner. The consortium consisted of approximately 15 people, including representatives from most of the major companies in PET imaging, implementation physicists, and high-powered molecular imaging scientists at academic institutions.

Dr. X's PQ research has created both a new research field and a new industry. After the total body PET scanner was built, Dr. X's team set up a molecular imaging center which allows researchers around the country and internationally to collaborate. To commercialize the scanner, they collaborated with United Imaging Healthcare. Siemens has also built a similar version.

PQ Work Changes the Focus of Investigator's Subsequent Research

Research Focus

Dr. E's PQ research focused on how cancer cells respond to fluid shear stress. Dr. E's lab took two approaches to the work: 1) to understand the biology of cancer cells' response to fluid shear stress and its impact on metastatic disease and 2) the utility as a biomarker as cancer cells may be distinguished by their resistance to fluid shear stress. There was almost no prior work in this area.

At the time of PQ award, the PQ research was a small fraction of Dr. E's work as he was studying other topics such as cell matrix interactions. Since then, it has become the main focus of his lab's research and was the foundation of a start-up company he later founded. The PQ grant was the first significant funding he received for this work.

Dr. E says that this research is "like peeling away the layers of an onion." He initially expected this topic to be a simple problem, but it has revealed many other aspects. Currently, his lab is investigating an unexpected finding where exposure to fluid shear stress may make cells more capable of metastasis. Dr. E's lab has been able to begin to understand the underlying mechanisms of fluid shear stress resistance through subsequent funding.

Subsequent Funding

Dr. E received two subsequent grants from NCI and other agencies including a SBIR grant focused on using their technology as a preparative separation method for single cell sequencing applications, and an NCI STTR grant using their technology to improve urine-based cytology in bladder cancer. Both grants were successful as they were able to achieve phase 1 milestones, and Dr. E's lab was selected to participate in a Precision Medicine World Conference (PMWC) meeting which allowed them to broaden their connections for this work.

Dr. E feels that one of the main objectives of the PQ program was to fund new ideas which might be difficult to fund under the traditional system, illustrated by the PQ grant he received. However, Dr. E sees his lab as currently in a funding gap as his research may no longer be viewed as "provocative" enough for a PQ, but still too risky for mainstream funding systems. Dr. E hopes that the PQ program will have an impact on the whole grant system to place more value on innovation.

Collaborations and Impact

Other groups have validated Dr. E's initial findings on fluid shear stress, extended his model into other areas, or built different models for other forms of fluid shear stress. The PQ also enabled Dr. E to collaborate with biomedical engineers who he otherwise may not have collaborated with and pushed him into biomedical engineering which was not an area he was involved in before.

PQ Research Fosters Collaboration and Innovative Thinking

Collaborations

Although Dr. Z and Dr. Y had previously met at a university and through their involvement in the Physical Sciences Oncology Network (PS-ON), they had never collaborated on a research project. When Dr. Y saw the PQ announcement in 2013, she thought it might be the perfect opportunity to initiate a collaboration with Dr. Z and reached out to him. As a previous PQ grant awardee, Dr. Z was familiar with the PQ initiative and credited the support for helping launch his research into the use of adaptive therapy in cancer, taking ideas from pest management.

The investigators began talking about how they could combine their research specialties in evolutionary biology in cancer research and clinical oncology research in unique ways. The PS-ON had started their thinking about cross-disciplinary work and applying tools from a variety of disciplines such as physics, ecology, and sociology to cancer research. However, without the PQ, they believe there would not have been a natural place for their collaboration.

Their PQ work focused on evolutionary analysis of pre-cancer in the breast, and they believe there is still much to be done in understanding the ecology of tumor cells. The investigators co-authored a paper outlining the development of a classification system for ecology of tumors, which has led to significant additional work in characterizing pre-cancers and developing a classification system for evolution of cell biology.

While Dr. Y focuses on the clinical side of oncology, Dr. Z focuses on applying principles from evolutionary biology to cancer. Despite the different angles of their research, they found that there was much synergy in their interests and the collaboration went very well. The PQ started in 2014 and they have been working together ever since, including on multiple post-PQ projects.

Subsequent Funding

Since the PQ award, Dr. Z and Dr. Y have received a DoD Breakthrough Award, and an NCI grant to develop the Breast Pre-cancer Atlas – a repository for information about breast tumors available to the community, both of which built on their PQ work. This subsequent funding has allowed them to continue their work on the evolution of pre-cancers. Although their model system is breast cancer, they believe that their work has implications for the progression of other solid tumors that go through pre-cancer, invasive, and metastatic phases.

PQ Impact

Dr. Y credits the PQ for supporting out-of-the-box thinking to benefit cancer research and would love to see an additional focus on interdisciplinary collaboration through PQ research. Dr. Z believes that the PQ is essential to speeding up novel cancer research approaches and allowing researchers to use alternate methods. They each expressed gratitude for to the PQ initiative for helping them to work together to help answer some of the most urgent and fundamental questions in cancer biology.

PQ Jump Starts Funded Work for Early Stage Investigator

Research Focus

Dr. A's PQ research focused on early breast tumor metastasis to the brain and the tumor microenvironment. Specifically, he has looked at how breast tumor cells interact in the different metastatic environments of the brain, and how to capture that information. At the time of PQ award, he was in the early years of his assistant professorship. Although he had a good understanding of how to perform the work he was interested in, he did not yet have preliminary work as an early stage investigator, and the PQ grant was foundational in the first years that he established his lab.

Dr. A's lab found that metastatic breast cancer cells begin to show neuron-like features in the brain microenvironment, and his work has demonstrated that neurological drugs can be used to slow down metastasis progression. Dr. A believes that the PQ question under which he was funded is essential in his field, but not well studied by traditional cell biology approaches. Because of this, he views the PQ as a high risk, high gain program that provides one of the only mechanisms for his type of work, which is difficult to have funded through traditional R01 mechanisms. He felt that the focus on vision rather than preliminary results in the review process was particularly helpful for him as an early stage investigator and was essential to launching his lab and research program. He also believes that the PQ program is essential for stimulating innovation for questions that are ignored in his field, or which are technically challenging.

Subsequent Funding and Research

The preliminary results from Dr. A's PQ research led to a subsequent R01 grant to study the brain microenvironment and metastasis. His team also has three papers which are in the process of submission, one of which was recently accepted for publication. Now, his lab has two separate additional grants which they have applied for, an R01 and an R21, to study topics related to aging rooted in his initial PQ work. For example, Dr. A utilized single cell sequencing and compared different stages of metastasis to review transcriptome differences. Dr. A believes that the PQ was essential to jump start this work, and later adapt a new single cell technology. Currently his lab is doing extensive single cell sequencing to study the tumor microenvironment, which he says directly led from the PQ grant.

Collaborations

Through the PQ grant, Dr. A's team developed a strong collaboration with computational scientists who specialize in computer imaging analysis. Additionally, because of Dr. A's work focusing on metastasis to the brain, the PQ work led him to the field of neuroscience, and he even attends meetings for the Society of Neuroscience. As a result, his lab has gradually moved to engage with neurodegenerative diseases which intersects well with brain metastasis because both may trigger inflammation. His lab is currently researching metastasis in the aging brain environment.

Appendix C – Evaluation Methods

Ripple Effect relied on existing data and documentation and consultation with NCI staff to inform the study design and methods. We used primarily secondary data sources to assess applicants, awardees, and outputs and PQ scientific outcomes. Methods included quantitative analysis of NIH and other publicly available data, publication analyses and bibliometrics, and content analysis of program documentation (e.g., progress reports). We created and used a comparison group of Research Project Grants to contextualize some of these metrics. We also conducted five interviews with six PQ Principal Investigators (PI) to create in-depth case studies or vignettes on topics of interest. Finally, we convened an expert panel to qualitatively evaluate the publication and bibliometric outcomes of a subset of randomly selected PQs.

The use of multiple data sources allowed us to examine PQ outcomes using multiple quantitative metrics. Using multiple metrics allows for data triangulation, or the validation of findings from more than a single source, to enhance confidence in the study results. This Appendix outlines each evaluation method in detail.

To systematically assess applicants, awardees, and outcomes associated with PQ research over time, the evaluation team retrieved existing data from a variety of NIH and public databases, including IMPAC II, PubMed, and iCite. We only included data on grants that were awarded from Fiscal year 2012 to July 2019. Below, we describe how we abstracted and analyzed data for each source.

Identification of PQ Awardees

The target population for this evaluation included all Contact PIs and Multiple PIs for PQ awards for FY2012 – 2018. NCI provided a list of all awardees and this list was cross-checked against award information available in QVR/IMPACII. We used this list of awardees, along with PQ award numbers when necessary, to identify their subsequent NIH grants, publication history, co-author collaborations, patent applications filed and awarded, and clinical trials.

Selection of the Comparison Group

The PQ Initiative has awarded R01 and R21 grants for cancer research across a range of fiscal years, scientific disciplines, and budget. Ripple Effect and NCI selected a comparison group of NCI grants modeled on several key variables: award type (R01 or R21), cost, and fiscal year of award. After eliminating potential comparison grants based on these variables, we stratified the remaining grants by fiscal year. We then used a random number generator to select a matching number of comparison grants for each fiscal year based on award type. A total of 343 NCI grants were selected for the comparison group. Table 12 provides information on these comparison grants.

Table 12. Comparison Grant Award Type and Cost

Year of Project Start	Number of Randomly Selected NCI R01s	Total Cost Range ($)	Number of Randomly Selected NCI R21s	Total Cost Range ($)
2012	38	354,047 - 558,203	18	193,259 - 221,038
2013	21	336,150 - 597,628	8	172,416 - 210,039
2014	48	341,337 - 605,599	36	189,240 - 211,084

Year of Project Start	Number of Randomly Selected NCI R01s	Total Cost Range ($)	Number of Randomly Selected NCI R21s	Total Cost Range ($)
2015				169,016 - 212,356
2016	32	365,278 - 534,556	17	171,825 - 217,016
2017	34	332,234 - 548,523	12	182,268 - 207,525
2018	31	375,807 - 567,324	7	194,704 - 208,773

Data Sources and Data Abstraction

Data for all components of the evaluation analyses was abstracted from a variety of relevant databases. We identified all publications associated with PQ-funded research and comparison group research with a publication search of the research literature using award numbers. We also identified patents and pending patent applications and clinical trials using award numbers and/or PI names. The team utilized a high-performance web-based analytics platform that allowed for expressive free-text queries and provided sub-second search and retrieval of millions of publications, patents, and grants. Table 13 below provides a summary of the sources from which data were obtained to inform the analyses.

Table 13. Data Sources and Descriptions

Data Source	Description
ClinicalTrials.gov	Clinical trials database
CrossRef	Publications data
iCite	NIH bibliometrics dashboard
NIH ExPORTER/ RePORTER	Research Portfolio Online Reporting Tools (RePORT) Expenditures and Results (RePORTER)
PubMed/Medline	Biomedical publications database
USPTO Database	Patents and patent applications
Web of Science (WoS)	Scientific citation index

Breakdown of Applicants and Awardees Across Early Stage and New Investigators

This analysis explored awardee and applicant investigator status among PQ PIs and awardee status for a comparison group of NCI Research Project Grant (RPG) PIs in FY2012-FY2018. NIH definitions were used to distinguish the awardees who met criteria for being a New Investigator (NI) and an Early Stage Investigator (ESI). Specifically, NIs are those investigators who have not received substantial, independent funding from NIH previously. ESIs are those investigators who have completed their terminal degree and post-graduate clinical training within the past ten years. To be categorized as an ESI, the investigator also could not have successfully competed for a PI/PD for a substantial NIH independent research award. PI status includes the status of Contact PIs and Multiple PIs for this analysis.

Our evaluation team retrieved investigator status at the time of application or award from IMPACII. For Contact PIs and Co-PIs that did not have ESI and NI status available in IMPACII, education and award data from QVR was utilized to calculate the ESI and NI status at the time of application based on the NIH definitions. For unawarded applications (n=1,417), there were 40 grants where the PIs reapplied for the

same grant. No PIs reapplied for the same grant more than one time. We have only included the first grant application in this analysis.

Total Volume of Publications Produced by PQ Awardees and Comparison Group

To characterize scientific productivity and impact, the evaluation team analyzed the publications resulting from our search for PQ and comparison group grant numbers within PubMed, in a variety of ways. As general measures of publication productivity, we first counted the total number of PQ- and comparison group associated publications and plotted the publication distributions over time.

Bibliometrics of PQ Associated Publications and Comparison Group

Citation Count and Relative Citation Ratio

We calculated the total number of times that PQ-associated publications were cited in subsequent publications in the research literature. Since the number of citations received is a function of both the number of years since publication and the scientific field in which it was published, we also retrieved relative citation ratios (RCR). This process was repeated for the comparison group. RCR is a measure of scientific productivity, developed by the NIH, calculated by comparing an article's actual citation rate to the expected citation rate based upon the article's co-citation network of NIH-funded publications. Since RCR is both field- and time-normalized, it represents a robust alternative to using raw citation counts and rates. One study found RCR to be correlated with expert rankings and scores in response to the quality and impact of research.[16] An RCR greater than 1 indicates that the publication received above average number of citations, compared to publications in the same field, in the same year. An RCR of 0 indicates that the publication has not been cited. RCR data may not be available for recent publications that have not had sufficient time to accrue citations.

Citation Lag

To approximate the speed with which PQ and comparison group research influenced subsequent research, we calculated the "citation lag," or the number of months between the time of article publication to when it was first cited in a subsequent publication. We removed publications that had missing citation lag data from the PQ and NCI RPG Comparison Group (16%, n=349 and 16%, n=367 respectively). We also removed citation lag data from the PQ and NCI RPG Comparison Group for publications with a negative citation lag (14%, n=297 and 0%, n=0 respectively) or a citation lag of zero (13%, n=276 and 25%, n=583 respectively). Negative citation lags come about when the citing publication cited the electronic version of the focal publication, which was prior to the print publication. A citation lag of zero indicates that the focal paper was cited in the same month as it was published.

Highly Cited Papers

Highly Cited Papers are in the top 1% of their subject area for the publication year, based on Web of Science calculations. WoS identifies "highly cited papers" based on the top 1% of publications by subject area for the publication year.[17] To determine the top 1% of publications, WoS constructs the distribution

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[16] B. Ian Hutchins et al., "Relative Citation Ratio (RCR): A New Metric That Uses Citation Rates to Measure Influence at the Article Level," *PLoS Biology* 14 (2016), https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002541

[17]Clarivate Analytics. *Web of Science Core Collection*. Retrieved on June 10, 2019 from <https://images.webofknowledge.com/images/help/WOS/hs_citation_applications.html>.

of citations received by all publications in 22 subject areas over a ten-year period. Highly cited papers help identify breakthrough research within a research field and are used within WoS to identify the most influential research papers.

Hot Papers

Papers that reach their citation peak very soon after publication, reflected by a rapid and significant number of citations, based on Web of Science calculations. These papers are often key papers in their fields.

Subsequent Grant Funding of PQ Awardees

The evaluation team searched QVR to obtain data on all new grants that have been awarded to each PQ and Comparison Group researcher subsequent to their PQ or comparison award. For each grant awarded, we obtained the administering NIH Institute or Center (IC), amount awarded, and the year in which it was awarded for Contact PIs and C-PIs. In order to ensure that the awards were in fact subsequent to PQ and comparison RPG funding, grants were only included in this analysis if they were received at least one year after the Fiscal Year (FY) in which the PI received the PQ award or RPG award respectively. All P and U sub-awards were removed from the analysis and only the parent award was included. Subsequent funding data was obtained in August 2019, so any applications or awards after August 2019 are not included in this analysis.

Patents and Clinical Trials Associated with PQ Awards

We quantitatively analyzed patent application and award counts as measures of scientific productivity and impact. We searched the US Patent Databases for patent applications and awards that acknowledged PQ grants and patent awards by author name. Similarly, we searched the clinicaltrials.gov database for clinical trials that acknowledged PQ grants.

PQ Themes in Scientific Meetings

Ripple Effect abstracted data on presentations at scientific meetings between FY 2012 and FY 2019 from PQ progress reports obtained from IMPAC II/QVR. Given investigators may not consistently provide a full listing of presentations at scientific meetings in their progress reports, this is likely an underestimation of the total of presentations given at scientific meetings.

External Panel Assessment of Scientific Impact of 10 Select PQ Awards

PQ Selection

For the external expert panel assessments of the outcomes and impacts of the PQ Initiative, Ripple Effect and NCI selected 10 PQs for review. There were 58 unique PQs released from 2011 to 2018. To ensure outcome and impact data was available for the PQs selected we eliminated the 8 PQs that were initially released in the 2017/2018 RFA. Furthermore, of the remaining 50 PQs, PQs with less than four grants awarded by the end of 2018 were eliminated, since the outcomes and impacts of PQs with a small number of grants may be affected by spurious factors, such as investigator behaviors. There were 28 unique PQs that were included in RFAs prior to 2017/2018 and had each four or more grants. We classified the 28 PQs as early (2011 – 2013) or late PQs (2015 – 2016).[18] The year of the PQ was

[18] There were no PQ RFAs in 2014.

determined by the year the PQ was initially included in an RFA. There were 23 Early PQs, issued in 2011, 2012, or 2013 and 5 late PQs issued 2015/2016.

Of these, Ripple Effect randomly selected eight PQs from the group of 23 Early PQs and two from the group of five late PQs. We stratified the PQs by number of grants awarded within the early PQ group and the late PQ group separately (see Table 14). The stratification by time and then by number of grants ensured the PQs selected represented the duration of the program (2011 -2016) and the varying number of grants awarded across the different PQs. Ripple Effect randomly selected two PQs from each quartile from the Early PQ group (23 PQs) and then selected one award from the 50% quartile and one award from top quartile for the late PQ group to select the 10 PQs.

Table 14. Number of Grants Awarded per PQ

Quartile	Number of Grants Awarded Per PQ
Lower	4 – 5 awards
50%	6 – 8 awards
75%	9 to 12 awards
Top	13 – 31 awards

Ripple Effect created a data book (see Appendix E for a sample excerpt)with basic information and outcome data for the 10 PQs and for distribution to the expert panel. The data book included information on publications and bibliometric data for the grants that address the ten PQs. Relevant publications: 1) acknowledged the PQ grant, 2) had a PI or co-PI an author, 3) were clearly supported by grant funding (based on qualitative review of the abstract), and 4) were not reviews, commentaries, editorials, or letters. The grants awarded in 2019 are included in the data book but the publications for those grants were not assessed.

For each publication, the data book included the number of citations that the publication received (as of July 7, 2019) and the Relative Citation Ratio (RCR). For each grant, we calculated the average RCR and average number of citations per publication as overarching measures of influence. Note, RCR is not available for publications published in 2018 and 2019. For consistency and to avoid diluting the average number of citations per publication with newer publications that have not had as much time to be cited, publications without an RCR were omitted from both the average RCR and average number of citations per publication.

Expert Panel Selection

Ripple Effect and NCI worked together to compile a list of scientists with expertise in each of the selected 10 PQ topics based on professional knowledge and a review of the literature in each scientific area. Panelists could not have received PQ funding or served on a PQ review panel to be eligible to participate. Ripple Effect used potential panelists' institution information to ensure there was geographic diversity in the panel selection. Ripple Effect delivered a consent form to each scientific expert once they agreed to serve on the external expert assessment panel. The consent form included language to verify the selected panelist had no conflict of interest with the PQ Initiative. We selected a total of eight experts to review the first five PQs on Panel Day 1 and eight experts to review the remaining five PQs on Panel Day 2. Each panelist received a $200 honorarium per day of participation. All panelists are listed in Appendix D.

Expert Panel Implementation and Analysis

Ripple Effect hosted two expert panels, each of which reviewed five PQs, on May 7, 2020 and May 22, 2020. Approximately two weeks before each panel, Ripple Effect distributed the data books to the panel via email with instructions for review. The panels were held virtually via Zoom meeting and were moderated by a trained scientific moderator provided by Ripple Effect. The moderator used a semi-structured interview guide (see Appendix F) to help facilitate the conversation. Each panel lasted approximately 5 – 6 hours.

The expert panels were recorded with permission of the panelists and a trained scientific notetaker took notes on panelist responses throughout the panel sessions. Panel recordings were not transcribed but were used to assist the notetakers in clarifying any feedback that was unclear or was not fully captured. A senior qualitative analyst analyzed the panel notes using basic thematic analysis to elicit major themes that emerged from the discussions.

Vignettes

The evaluation team conducted five informal telephone interviews with a six PQ PIs or Co-PIs to gain in-depth information about their perceptions and experiences related to PQ initiative. Potential participants were extracted from evaluation outcomes with a focus on those PIs who had gone on to receive subsequent NIH funding or those who appeared to engage in new collaborations through the PQ initiative. A qualitative analyst reviewed the notes resulting from these interviews to create case studies focused on research highlights for each. *Please note the investigators' names have been redacted for public posting.*

Appendix D – External Panel Members

Table 15. PQ External Panel Members

Panelist	Affiliation
Dmitri Artemov	Johns Hopkins Medicine
John Baron	University of North Carolina at Chapel Hill
Kristy A. Brown	Weill Cornell Medicine
Deirdre Cohen	NYU Langone Health
Gina DeNicola	Moffitt Cancer Center
Nadine Hempel	Penn State
Cindy Reinhart King	Vanderbilt University
Bonnie Spring	Northwestern University Feinberg School of Medicine
Fengyi Wan	Johns Hopkins University
Shoumeng Wang	University of Michigan

Appendix E – Sample PQ Excerpt from External Panel Data book

Provocative Questions Program Overview

In 2011 the National Cancer Institute (NCI) established the Provocative Questions (PQ) Initiative. This program was created to support research projects designed to use innovative research strategies to solve specific problems and paradoxes in cancer research identified by the NCI as "Provocative Questions" (PQs). The PQs were created to challenge cancer researchers to think about and elucidate specific problems in key areas of cancer research that are deemed important but have not received sufficient attention in general cancer research.

NCI has facilitated workshops with experts from the extramural research community to identify and prioritize these compelling but understudied problems in cancer research. PQs come from various fields of cancer research and all are framed to inspire interested scientists to conceive new approaches or feasible solutions. NCI publishes PQs that are published in Request for Applications (RFA) Funding Opportunity Announcements (FOAs). Some questions were reissued by one to two additional RFAs.

Objective of Evaluation

As part of an overall assessment of program outcomes and impacts, NCI and Ripple Effect are convening an expert panel to evaluate the outcomes and impacts of 10 randomly selected PQs. The panel will consider three overarching questions for each PQ:

(1) How do the grants for each PQ constitute significant research progress?
(2) How has the PQ research served as a foundation for subsequent research?
(3) How has the PQ research stimulated research in an important and under-studied area?

Additionally, the panel will consider whether NCI should continue to support the PQ program, based on the outcomes of the PQ research.

Publications Data

This data book includes information on publications for the grants that address the ten PQs. Publications published as of July 7, 2019 were considered for inclusion. Relevant publications: 1) acknowledged the PQ grant, 2) had a PI or a co-investigator as an author, 3) were clearly supported by grant funding (based on qualitative review of the abstract), and 4) were not reviews, commentaries, editorials, or letters. For grants with no publications included in the data book, those that did not have any publications as of July 7, 2019 (indicated by “None”) are distinguished from those that had at least one publication but none that met the inclusion criteria (indicated by “No relevant publications”). Note that grants awarded in 2019 are included in the data book but the publications for those grants were not assessed.

For each publication, we included the number of citations that the publication received (as of July 7, 2019) and the Relative Citation Ratio (RCR). The RCR is citation-based measure of scientific influence. It is calculated as the citations received per year for each paper, normalized to the citations per year received by NIH-funded papers in the same field and year. A paper with an RCR of 1.0 has received the same number of cites/year as the median NIH-funded paper in its field, while a paper with an RCR of 2.0 has received twice as many cites/year as the median NIH-funded paper in its field. For each grant, we calculated the average RCR and average number of citations per publication as overarching measures of influence. Note, RCR is not available for publications published in 2018 and 2019. For consistency and to avoid diluting the average number of citations per publication with newer publications that have not

had as much time to be cited, publications without an RCR were omitted from both the average RCR and average number of citations per publication.

**The title, abstract, PubMed link, and publication metrics was provided for each publication in the full data book – this truncated version just includes total numbers of publications and citations per award.*

PQ Description

Why don't more people alter behaviors known to increase the risk of cancers? **(first issuance of question)**

How do decision making processes influence habitual behaviors, and how can that knowledge be used to design strategies that lead to adoption and maintenance of behaviors that reduce cancer risk? **(text modifications for second issuance of question)**

How do cognitive processes such as memory and executive function interact with emotional or habitual processes to influence lifestyle behaviors and decisions, and can we use this knowledge to design strategies to change behaviors that increase cancer risk? **(text modifications for third issuance of question)**

Background

A wealth of epidemiological research shows that certain modifiable and habitual behaviors are linked to increased cancer risk; these include tobacco use, UV exposure and obesity-related behaviors such as overeating and physical inactivity. Despite awareness of the link between these behaviors to the risk of cancer and other diseases, many individuals find it difficult to change those behaviors. Research on basic decision-making processes, emotion, and motivation, could shed light on why people fail to alter behavioral patterns and could inform the development of interventions to increase healthy behaviors and ultimately improve cancer outcomes.

Feasibility

Opportunities exist to leverage methodological perspectives and tools from sciences (e.g., marketing and consumer science, industrial and organizational psychology, neuroscience) far afield of traditional cancer research to understand and change behaviors known to increase cancer risk.

Implications of Success

Reduced cancer morbidity and mortality as a result of modified health behaviors associated with disease risk.

Grants

R01CA170128: Primary Investigator: Barbara Lee Frederickson
R01CA170297: Primary Investigators: Caryn Lerman; Joseph Kable
R01CA170336: Primary Investigator: Daniel Petereit
R01CA180015: Primary Investigator: Emily Falk
R01CA180030: Primary Investigators: Ivan De Araujo; Dana Small
R01CA184779: Primary Investigator: Michael Andrew Sayette
R01CA184781: Primary Investigator: Jason Robinson
R01CA185378: Primary Investigator: Mark Landau
R21CA184834: Primary Investigator: Seung Lark Lim
R21CA190093: Primary Investigator: Stephen Jeffrey Wilson

R01CA170128

Title: Promoting Cancer-related Behavior Change through Positive Emotions
Primary Investigator: Barbara Lee Frederickson
Year awarded: 2012
Abstract: The American Cancer Society estimates that 62% of all cancers could be prevented altogether through lifestyle change. Despite good intentions, people's attempts to alter their behaviors known to increase cancer risk - related to diet, physical activity, tobacco, and alcohol use - often fail, which ultimately increases their risks for various cancers. In response to NCI's Provocative Question 4, the overarching goal of the proposed research is to investigate the role of positive emotions in facilitating successful lifestyle change, defined as long-term adherence to cancer- preventive behaviors (e.g., nutritious eating, physical activity, tobacco, and alcohol use). An innovative upward spiral model of lifestyle change integrates multiple streams of research in basic behavioral and brain sciences to position positive emotions as key active ingredients that not only seed non-conscious motivational pulls toward newly-adopted cancer-preventive behaviors, but also reshape key biopsychosocial resources in ways that increase the subsequent positive emotion yield of multiple cancer-preventive behaviors, creating a self- sustaining dynamic system. A longitudinal, dual-blind, placebo-controlled field experiment tests this new model by targeting three Specific Aims. These aims are: (1) to identify biopsychosocial resources that moderate the link between cancer-preventive behaviors and their positive emotion yield; (2) to test whether and how positive emotions, experienced in daily life, produce a psychological propensity for wellness through the combined presence of (a) increases in non-conscious motives for cancer-preventive behaviors and (b) increases in biopsychosocial resources; and (3) to test whether positive emotions and a psychological propensity for wellness predict increasing and sustained cancer-preventive behaviors and improved health-related outcomes at 18-month follow-up. The proposed study tests the novel upward spiral model in daily life with densely repeated measures and physiological, behavioral, endocrine, and self- report indices of health-related outcomes. This program of translational research stands to reshape public health interventions and unlock hidden opportunities to drastically reduce the incidence of cancer. PUBLIC HEALTH RELEVANCE: Unhealthy lifestyles contribute to many cancers and other costly chronic diseases. Lifestyle change is thus vital to reduce cancer incidence, yet most attempts at lifestyle change fail. Understanding how positive emotions create non-conscious motives for long-term adherence to cancer-preventive behaviors is needed to unlock evidence-based health interventions to promote health and save money and lives.

Publications:

8 publications with an average relative citation ratio of 2.20 and 8 citations per publication on average.

R01CA170297

Title: Retraining Neurocognitive Mechanisms of Cancer Risk Behavior

Primary Investigator: Caryn Lerman; Joseph Kable

Year awarded: 2012

Abstract: This study addresses the provocative question: Why don't more people alter behaviors known to increase cancer risk? (PQ4). Emerging work in behavioral economics has shed light on the critical role of reward-based decision-making processes in health risk behavior. In parallel, research in cognitive neuroscience has clarified the central role of the dorsolateral prefrontal cortices (DLPFC) in cognitive control during decision-making. Thus, we propose to integrate these lines of research and advance the science of behavior change by testing whether enhancement of DLPFC function via neurocognitive training improves decision-making processes that contribute to risk behavior. Young adults (ages 18-30; n=150) will participate in a five-week web-based neurocognitive training program or a cognitive stimulation (control) condition, based on random assignment. The evidence-based neurocognitive training focuses on enhancement of targeted cognitive processes to facilitate self-control and goal-directed behavior: sustained attention, working memory, and response inhibition. This intervention, shown to be highly effective for cognitive remediation in neuropsychiatric illness, has been adapted as a web-based tool for the proposed study to enhance cognitive function in healthy subjects. Importantly, our pilot data support the feasibility, high levels of compliance, and beneficial effects on neurocognitive performance. Our primary aim is to evaluate effects of neurocognitive training on neural activity and decision-making behavior. Our secondary aim is to examine the neurobehavioral mechanisms that mediate effects of neurocognitive training, including changes in executive cognitive function. Changes in decision-making processes and neural activity associated with neurocognitive training will be assessed at baseline and post-training by acquiring functional magnetic resonance imaging (fMRI) while participants perform reward-based decision-making tasks, specifically delay discounting and risk sensitivity. Cognitive performance will be assessed at these time points using a validated battery of tasks, in order to examine mediation effects. A three-month follow-up assessment will test the durability of the effects of neurocognitive training beyond the training period. Thus, this application breaks new scientific ground by applying novel concepts and tools from the field of cognitive neuroscience to accelerate the study of basic mechanisms of behavior change. These data will inform the development of novel and more comprehensive interventions for behavior change (e.g., combining neurocognitive training with existing behavioral interventions). As a basic mechanism study, the knowledge generated will be relevant to multiple health risk behaviors, enabling a potentially broad impact on cancer prevention. PUBLIC HEALTH RELEVANCE: The proposed study investigates the basic behavioral and brain mechanisms underlying decision-making processes that contribute to cancer risk behaviors. The science is built upon a firm foundation of empirical evidence supporting executive cognition as a target for behavior change interventions, thus driving the field forward from observational data to clinical intervention. The novel web-based neurocognitive training intervention is "portable" and can be easily translated to clinical and public health practice.

Publications:

2 publications with an average relative citation ratio of 2.58 and 8 citations per publication on average.

R01CA170336

Title: American Indian mHealth Smoking Dependence Study

Primary Investigator: Daniel Petereit

Year awarded: 2012

Abstract: Northern Plains American Indians have the highest tobacco use compared with other American Indians and non-Hispanic Whites. Notably, the rate for tobacco related cancers also are higher among Northern Plains American Indians as compared to American Indians living in other regions and for non-Hispanic Whites living in the Northern Plains and elsewhere in the US. Although awareness of these elevated rates of tobacco-related cancers is well known throughout American Indian communities, Northern Plains American Indian adults continue to use tobacco. In addition, Northern Plains American Indian patients with cancer continue to smoke despite knowing that this behavior is related to cancer recurrence, new cancers, and other chronic illnesses. Rapid City Regional Hospital's (RCRH) mission is to reduce cancer mortality among American Indians in the Northern Plains. In 2002, Dr. Petereit, the PI for this project, developed the Walking Forward Program which is designed to address cancer disparities among Western South Dakota tribes. To accomplish this, Community Research Representatives have been hired to work with the reservation-based Cheyenne River Sioux, Rosebud Sioux, and Pine Ridge Lakota Sioux and the Rapid City urban Indian community. This study will focus on American Indians living on the Cheyenne River, Rosebud and Pine Ridge Reservations. The proposed project, "American Indian mHealth Smoking Dependence Study (PQ4)," is designed to answer the research question, "Why don't Northern Plain American Indians alter tobacco use behaviors known to increase the risk of cancer?" The study is based on the Theory of Planned Behavior and uses a phase- based framework. mHealth (mobile health), the use of wireless devices such as cell phones to provide health- related information, will facilitate attainment of project aims as it offers a low-cost, efficient way to provide health-related messages to rural and other populations. This will be feasible for this study as access to wireless technology is rapidly increasing among Northern Plains American Indians. The specific aims for the study are: Aim 1: Measure factors that predict smoking behaviors among Northern Plains American Indians; Aim 2: Identify issues and risk factors related to smoking persistence and high relapse behaviors, regardless of knowledge about smoking hazards, among Northern Plains American Indians; and Aim 3: Using the Theory for Planned Behavior, develop and adapt existing tobacco cessation interventions for use with adult Northern Plains American Indians who smoke cigarettes daily. Outcome data will reveal predictors of intention to quit smoking, successful quit attempts, and relapse. Other social cognitive variables that ensure initial quit attempts are translated into longer term abstinence will be identified. Study results will impact tobacco use among Northern Plains American Indians by providing insight into designing effective cessation interventions for this population. PUBLIC HEALTH RELEVANCE: The prevalence of smoking among Northern Plains American Indians is of epidemic proportion and on the rise. Consequently, they also have high cancer mortality rates. This project is designed to understand continued tobacco use by Northern Plains American Indians despite knowledge of its cancer risks and to identify the types of interventions most effective for smoking cessation success in this population.

Publications:

2 publications with an average relative citation ratio of 0.16 and 2 citations per publication on average.

R01CA180015

Title: Neural Predictors of Receptivity to Health Communication and Behavior Change

Primary Investigator: Emily Falk

Year awarded: 2013

Abstract: Promoting physical activity and decreasing sedentary behavior are key goals in the fight against cancers; physical activity is associated with lower risk of several cancers [1-10], and lower overall morbidity and mortality [11-26]. Thus, theory-driven initiatives to change these behaviors are essential [1-10, 26-40]. PQ#3 highlights the necessity for new perspectives on the interplay of cognitive and emotional factors in promoting behavior change. Current theories, which focus primarily on predictors derived from self-report measures, do not fully predict behavior change. For example, recent meta-analyses suggest that on average, variables from the Theory of Planned Behavior account for ~27% of the variance in behavior change [41, 42]. This limits our ability to design optimally effective interventions [43] and invites new methods that may explain additional variance. Our team has shown that neural activation in response to health messages in hypothesized neural regions of interest can double the explained variance in behavior change, above and beyond self-reports of attitudes, intentions, and self-efficacy [44, 45]. We now propose a next leap, inspired by PQ3, to identify how cognitive and affective processes interact in the brain to influence and predict behavior change. Our core hypothesis is that the balance of neural activity in regions associated with self-related processing versus defensive counterarguing is key in producing health behavior change, and that self-affirmation (an innovative approach, relatively new to the health behavior area [46]) can alter this balance. Self-affirmation theory [47] posits that people are motivated to maintain a sense of self-worth, and that threats to self-worth will be met with resistance, often in the form of counterarguing. One common threat to self-worth occurs when people are confronted with self-relevant health messages (e.g. encouraging less sedentary behavior in overweight, sedentary adults). This phenomenon speaks to a classic and problematic paradox: those at highest risk are likely to be most defensive and least open to altering cancer risk behaviors [48]. A substantial, and surprisingly impressive, body of evidence demonstrates that affirmation of core-values (self-affirmation priming) preceding messages can reduce resistance and increase intervention effectiveness [46, 49-53]. Uncovering neural mechanisms of such affirmation effects [46], has transformative potential for intervention design and selection. To test our conceptual assumptions and core hypothesis we will: (1) Identify neural signals associated with processing health messages as self-relevant versus counterarguing; (2) Test whether self-affirmation alters the balance of these signals; (3) Use these neural signals to predict physical activity behavior change, above and beyond what is predicted by self-report measures alone. Our approach is innovative methodologically (using fMRI to understand and predict behavior change), and conceptually (self-affirmation may dramatically increase intervention effectiveness). Benchmarks will include objectively measured decreases in sedentary behavior in affirmed vs. control subjects (using accelerometers), and increases in predictive capacity afforded by neuroimaging methods, compared to self-report alone.

Publications:

7 publications with an average relative citation ratio of 1.90 and 14 citations per publication on average.

R01CA180030

Title: The Gut-Brain Axis: A Novel Target for Treating Behavioral Alterations

Primary Investigator: Ivan De Araujo; Dana Small

Year awarded: 2013

Abstract: Our proposal addresses NCI's Provocative Question #3 (Group A): We designed a strategy to change cancer- inducing dietary habits, which is based on rescuing normal neural activity in brain circuits of overweight/obese individuals. The relevance of our proposal to cancer prevention is demonstrated by epidemiological studies establishing that several forms of cancer could be prevented by the adoption of healthier dietary habits, with up to 20% of cancer-related deaths being potentially attributable to obesity alone. In both rodents and humans, excessive intake of dietary fats leads to dysregulated neuronal function in dorsal striatum. This diet-derived striatal deficiency leads to an impaired ability to learn about the negative outcomes of one's actions which, in turn, results in the expression of impulsive behaviors such as excessive caloric intake. Our strategy builds on previous animal studies demonstrating that prolonged exposure to a high-fat diet substantially reduces the intestinal synthesis of appetite-regulating lipid messengers. Since our previous work had established that gut- brain signals regulate neurochemical activity in dorsal striatum, we set fort the central hypothesis that rescuing gut-brain communication will restore striatal function. As a corollary, we predict that rescuing gut-brain communication will enhance the ability to learn about negative outcomes, thereby reducing impulsivity behavioral scores and increasing compliance with a low-calorie diet. Accordingly, our Specific Aims are as follows: Specific Aim 1 (Mechanistic studies): To identify which gut N-acylethanolamines rescue striatal function and reduce impulsivity in high-fat fed mice, and to determine the neural and molecular mechanisms of their action; Specific Aim 2 (Translational studies): To determine whether gut N-Acylethanolamines precursors rescue striatal function and reduce impulsivity scores in overweight/obese human subjects. We thus propose that the gut-brain axis is a novel target for treating behavioral alterations in the obese, the normalization of which may greatly contribute to reducing cancer-related dietary habits.

Publications:

5 publications with an average relative citation ratio of 3.38 and 20 citations per publication on average.

R01CA184781

Title: Smartphone Delivered Attentional Bias Modification Training for Smokers

Primary Investigator: Jason Robinson

Year awarded: 2014

Abstract: More than 70% of smokers who receive first-line therapies relapse within 6 months. Thus, alternative, and complementary smoking-cessation therapies are needed. Given its success in treating anxiety and alcohol disorders, Attentional bias modification (ABM), a computer-delivered intervention, has been proposed to treat nicotine dependence. ABM reduces the attentional bias (AB) towards smoking cues that develops over time as a result of conditioning processes through which smoking cues become strongly motivationally salient. ABM with smokers has been attempted, but with limited success. We have identified three weaknesses with the smoking ABM approaches to date: (1) Existing smoking ABM studies have relied on only a single laboratory training session, falling short of a realistic and generalizable assessment of the technique's potential to influence neurobiological mechanisms

associated with AB and smoking behavior; (2) No published smoking ABM study has evaluated the generalizability of ABM to AB experienced in multiple environments, to AB across multiple modalities, and to alter AB in the long-term; (3) No previous study has examined the potential additive benefits of ABM on first-line smoking cessation therapy. The objective of this application is to determine the feasibility of smartphone-delivered, in-home ABM to reduce AB to smoking cues and to modify smoking behavior in the short- and long-term. Participants will be 250 treatment-seeking smokers, who will receive 8 weeks of NRT after completing either ABM (AB away from smoking cues and toward neutral cues) or sham training daily for 2 weeks. The first aim of this study is to identify the impact of in- home ABM on AB and the second aim is to identify the impact of in-home ABM on smoking behavior. The significance of this project is a new non-pharmacological intervention that normalizes AB and smoking behavior in treatment-seeking smokers that can be used as an adjunct to first-line cessation therapies. The innovations of this project are as follows: 1) we will be the first to administer multiple-session n-home ABM training using smartphones which offers the potential of maximizing ABM's effects to smokers' naturalistic environments; 2) we will be the first to evaluate the impact of ABM in conjunction with a first-line smoking cessation therapy (NRT); 3) we will be the first study to directly assess the generalizability of ABM on AB measured using multiple modalities, including central nervous system indicators of changes using ERP methodology, which its high spatial resolution is ideal for examining early attentional processes that RT cannot duplicate and 4) by using multiple sessions, we will be able to assess trajectories of change in AB over time to determine the optimum number of ABM training sessions. We anticipate that our study will have a positive impact on smoking cessation treatment by identifying an innovative low-cost intervention that alters AB and smoking behavior in treatment-seeking smokers, which would suggest a promising new avenue for future smoking cessation clinical trials.

Publications:

4 publications with an average relative citation ratio of 1.75 and 11 citations per publication on average.

R01CA185378

Title: Cognitive and Emotional Processes of Metaphoric Cancer Communications

Primary Investigator: Mark Landau

Year awarded: 2014

Abstract: Changing lifestyle behaviors has been estimated to substantially reduce the incidence of many types of cancer. Health communicators have therefore sought to create messages that motivate recipients to adopt and maintain lifestyle behaviors that reduce cancer risk. Associated research reveals that such messages are especially effective when they change both emotions and cognitions about cancer. Specifically, motivating messages increase recipients' emotional worry that cancer threatens their well-being, and also strengthen their cognitions that a recommended cancer-prevention behavior is effective at reducing cancer risk (response efficacy) and lies within their power to implement (self-efficacy). Despite these critical insights, messages often fall short of their potential to change lifestyle behaviors. One potentially important reason for this limited impact is that communication strategies overlook the role of abstractness in the public's understanding of cancer. Research shows that abstract, remote threats elicit low worry; also, people tend to lack confidence in the efficacy of behaviors that solve problems in abstract, unobservable ways. Therefore, developing communication strategies that guide the design of concretizing cancer messages represents a low-cost and potentially powerful means for enhancing message impact. The proposed project offers a novel integration of growing research in

psychology showing that metaphor is a mental tool that helps people to grasp abstract ideas in terms that are more concrete. Applying this research to cancer communication leads to the hypothesis that messages that use metaphor to compare cancer risks to concrete hazards, and to compare cancer prevention behaviors to concrete prevention practices, will elicit an energizing level of cancer worry and strengthen efficacy cognitions. This knowledge of how metaphor-induced emotions and cognitions interactively influence behavior suggests new strategies for creating metaphoric messages that will be uniquely effective at motivating behaviors that reduce cancer risk. The proposed project examines the motivating effect of metaphoric cancer messages on prevention behaviors in five programmatic experimental studies. All five studies are designed to illuminate how this effect is driven by interacting emotional and cognitive processes. They also examine for whom such messages will be particularly effective and the specific features of the messages that determine when they motivate prevention behavior. The studies are designed to inform the impact of metaphoric messages across a range of cancer communication contexts. They test predictions with regard to skin, lung, and colon cancer, and they assess both short- and longer-term health behavior change in both field and laboratory settings. If the project aims are achieved, this research will provide a critical foundation for understanding how to foster health behavior change and productive health decision making that can markedly reduce cancer diagnosis and progression.

Publications:

2 publications with an average relative citation ratio of N/A and N/A citations per publication on average.

R21CA184834

Title: Neural Predictors of Self-Regulation of Smoking Urges At A Stressful Moment

Primary Investigator: Seung Lark Lim

Year awarded: 2014

Abstract: We propose to determine the neurobiological mechanisms that predict self-regulation of smoking urges while a person is under stress. Even after quitting or deciding to quit, the cravings for tobacco continue, particularly when exposed to acute stress. During stressful situations, self-control can fail, often resulting in a relapse. Previous behavioral and neuroimaging studies have not provided specific information about the neurobiological basis of self-control that could be used to prevent a self-control failure (i.e., relapse) at a particular moment (e.g., a single puff after abstinence). If smoking lapses are predictable before they actually occur, clinical interventions might be provided ahead of time as often imagined in science-fiction films (e.g., "Minority Report"). We will study how and why self-regulation fails by using a brain-as-predictor functional magnetic resonance imaging (fMRI) approach and our custom-made MRI-compatible electronic cigarette delivery system that allows us to investigate "real" smoking decisions during fMRI scans. The main goal of this research is to elucidate the precise psychological and neurobiological mechanisms of self-control of smoking urges under cognitive overload and emotional distress on a moment-to-moment basis. Forty tobacco-dependent smokers (e10 cigarettes/day; 18-50 years old) will be recruited from the local community. While in the fMRI scanner, subjects will make real choices regarding whether or not to take a puff of an electronic cigarette in three different types of dual-task conditions; working memory (WM), emotional distress (ED), and fixation control (FC). Stressful cognitive overload will be induced by a concurrent WM task and emotional distress will be induced by threat of electric shock stimulation. We hypothesize that (1) the moment-to-moment brain signals in affective (increased craving-related activity) and cognitive (decreased self-control-related activity) brain regions will predict subsequent self-regulation failures (lapses), and (2) cognitive overload and affective distress will modulate the pattern of functional connectivity of brain

activation that predicts trial-by-trial self-regulation outcomes. The knowledge gained from our study that predicts real smoking-regulation choices will have strong ecological validity and provide valuable transformative information for developing novel clinical interventions that may prevent smoking lapses before they actually occur. Beyond smoking cessation treatments, our project outcomes will inform understanding of other self-control related maladaptive lifestyle behaviors (e.g., obesity, alcohol abuse, etc.) that increase one's risk for cancer.

Publications:

3 publications with an average relative citation ratio of 0.58 and 4 citations per publication on average.

R21CA190093

Title: FMRI Neurofeedback and Decision-Making in Habitual Cigarette Smokers

Primary Investigator: Stephen Jeffrey Wilson

Year awarded: 2014

Abstract: Cigarette smoking is the leading preventable cause of cancer in the United States. Helping smokers quit thus is one of the most effective means for reducing cancer burden in this country. Because most smokers find it incredibly difficult to stop smoking, enhancing the motivation to remain abstinent from cigarettes is widely seen as an essential step for improving their chances of success. Attempting to motivate quitting smokers to remain abstinent using nondrug rewards (e.g., money) is a particularly common intervention strategy. Although the use of nondrug rewards to aide quitting smokers is grounded in sound behavioral principles, mounting evidence indicates that nondrug rewards may be the least effective at reinforcing abstinence precisely when they are needed most (i.e., when smokers are tempted by an opportunity to smoke). Namely, simply anticipating having access to cigarettes in the near future appears to dampen the response to nondrug rewards in brain regions supporting reward valuation and motivational processing. This blunting is associated with a corresponding decrease in the willingness to resist smoking for a nondrug incentive, thus directly undermining the effectiveness of reward-based approaches to promoting cigarette abstinence. The proposed research addresses RFA-CA-13-017 (PQA1): Research Answers to NCI's Provocative Questions-Group A (PQA1) by testing the novel hypothesis that increasing brain responses to nondrug rewards may be an effective way to enhance the influence that such stimuli have on behavior in smokers. We propose to examine this idea using a technique called real-time functional magnetic resonance imaging (fMRI) neurofeedback. Real-time fMRI neurofeedback is a type of biofeedback that involves training individuals to control brain responses by presenting them with information about ongoing brain activity. Daily smokers (n=90) will be randomly assigned to three groups (intervention, sham neurofeedback control, and no feedback control; n=30 each). Those in the intervention group will receive valid real-time fMRI neurofeedback aimed at training them to volitionally increase activity in brain reward regions. The control groups will undergo nearly identical procedures but receive sham [placebo] neurofeedback and no neurofeedback, respectively. We hypothesize that only smokers provided with valid neurofeedback will learn to reliably and voluntarily increase activation in reward-related brain regions using cognitive strategies (Aim 1). We predict that this learning will be durable, such that smokers will be able to continue using cognitive strategies to increase reward-related brain activity after neurofeedback is removed (Aim 2). We also predict that this learning will be functional, such that clinically-relevant decision making (the willingness to choose a nondrug reward over smoking) is influenced when smokers use the same strategies outside of the scanner (Aim 3). If successful, the proposed study will open new

avenues for using neurofeedback to expedite scientific discovery and facilitate the development of effective smoking interventions that can be used by smokers on a broad scale.

Publications:

3 publications with an average relative citation ratio of 0.29 and 2 citations per publication on average.

Appendix F – External Panel Discussion Guide

1. **Provocative Question (Most Recent): What mechanisms of action of standard-of-care cytotoxic, radiologic, or targeted therapies affect the efficacy of immunotherapy?**
    - **a.** How does the presented data on outcomes suggest significant research progress in the field of cancer immunotherapy?
    - **b.** Describe the 3 most significant outcomes in the field of cancer immunotherapy.
    - c. How has the PQ research provided a foundation for subsequent research?
    - d. Have the PQs stimulated innovative research in an important and under-studied area?

2. **Provocative Question (Most Recent): Can tumors be detected when they are two to three orders of magnitude smaller than those currently detected with in vivo imaging modalities?**
    - a. How does the presented data on outcomes suggest significant research progress in the field of tumor biology or cancer research in general?
    - b. Describe the 3 most significant outcomes in the field of tumor biology.
    - c. How has the PQ research provided a foundation for subsequent research?
    - d. Has the PQ stimulated innovative research in an important and under-studied area?

3. **Provocative Question (Most Recent): What is the molecular mechanism by which a drug (such as aspirin or metformin) that is chronically used for other indications protects against cancer incidence and mortality?**
    - a. How does the presented data on outcomes suggest significant research progress in the field of cancer treatment?
    - b. Describe the 3 most significant outcomes in the field of cancer treatment.
    - c. How has the PQ research provided a foundation for subsequent research?
    - d. Have the PQs stimulated innovative research in an important and under-studied area?

4. **Provocative Question (Most Recent): Are there new technologies to inhibit traditionally "undruggable" target molecules, such as transcription factors, that are required for the oncogenic phenotype?**
    - **a.** How does the presented data on outcomes suggest significant research progress in the field of cancer drug development and discovery?
    - **b.** Describe the 3 most significant outcomes in field of cancer drug development and discovery.
    - **c.** How has the PQ research provided a foundation for subsequent research?
    - **d.** Has the PQ stimulated innovative research in an important and under-studied area?

5. **Provocative Question (Most Recent): How do microbiota affect the response to cancer therapies?**
    - a. How does the presented data on outcomes suggest significant research progress in the field of cancer microbiome?
    - b. Describe the 3 most significant outcomes in the field of cancer microbiome.
    - c. How has the PQ research provided a foundation for subsequent research?
    - d. Has the PQ stimulated innovative research in an important and under-studied area?

6. **Provocative Question (Most Recent): How do decision making processes influence habitual behaviors, and how can that knowledge be used to design strategies that lead to adoption and maintenance of behaviors that reduce cancer risk?**
    a. How does the presented data on outcomes suggest significant research progress in the field of cancer prevention?
    b. Describe the 3 most significant outcomes in the field of cancer prevention.
    c. How has the PQ research provided a foundation for subsequent research?
    d. Is there evidence from the abstracts provided that the PQs stimulated innovative research in an important and understudied area?
        i. From what you know about the broader field, is there evidence that the PQ altered the trajectory of the research field?

7. **Provocative Question (Most Recent): What in vivo imaging methods can be developed to determine and record the identity, quantity, and location of each of the different cell types that contribute to the heterogeneity of a tumor and its microenvironment?**
    e. How does the presented data on outcomes suggest significant research progress in the field of tumor biology?
    f. Describe the 3 most significant outcomes in the field of tumor biology.
    g. How has the PQ research provided a foundation for subsequent research?
    h. Is there evidence from the abstracts provided that the PQs stimulated innovative research in an important and understudied area?
        i. From what you know about the broader field, is there evidence that the PQ altered the trajectory of the research field?

8. **Provocative Question (Most Recent): How does obesity contribute to cancer risk?**
    i. How does the presented data on outcomes suggest significant research progress in the field of cancer prevention field?
    j. Describe the 3 most significant outcomes in the field of cancer prevention field.
    k. How has the PQ research provided a foundation for subsequent research?
    l. Is there evidence from the abstracts provided that the PQs stimulated innovative research in an important and understudied area?
        i. From what you know about the broader field, is there evidence that the PQ altered the trajectory of the research field?

9. **Provocative Question (Most Recent): How does mitochondrial heterogeneity influence tumorigenesis or progression?**
    m. How does the presented data on outcomes suggest significant research progress in the field of tumor biology field?
    n. Describe the 3 most significant outcomes in the field of tumor biology field.
    o. How has the PQ research provided a foundation for subsequent research?
    p. Is there evidence from the abstracts provided that the PQs stimulated innovative research in an important and understudied area?
        i. From what you know about the broader field, is there evidence that the PQ altered the trajectory of the research field?

10. **Provocative Question (Most Recent): How can the physical properties of tumors, such as a cell's electrical, optical or mechanical properties, be used to provide earlier or more reliable cancer detection, diagnosis, prognosis, or monitoring of drug response or tumor recurrence?**
    q. How does the presented data on outcomes suggest significant research progress in the field of tumor biology field?
    r. Describe the 3 most significant outcomes in the field of tumor biology.
    s. How has the PQ research provided a foundation for subsequent research?
    t. Is there evidence from the abstracts provided that the PQs stimulated innovative research in an important and understudied area?
        i. From what you know about the broader field, is there evidence that the PQ altered the trajectory of the research field?

11. **Discussion of all PQs:**
    u. Have these PQs stimulated innovative research in important and under-studied areas?
        i. Which ones were more effective and why?
        ii. Which ones were less effective and why?
        iii. What are some characteristics of successful questions?
        iv. What are some characteristics of less successful questions?
    v. Based on the outcomes and impacts of these PQs, should NCI continue to support the PQ program? Why or why not?

Appendix G – Brief Long-Term Evaluation Plan

Recommended Evaluation Approach

As the PQ initiative approaches its tenth year since initiation, it is important to continue to consider and plan for future evaluations of the initiative to measure its short-term and long-term impact on the cancer research community. Drawing on the lessons learned from this evaluation and past evaluations, the evaluation team recommends the following evaluation questions, methods, and metrics to assess long-term outcomes of the PQ Initiative.

The overall objective of a long-term evaluation of the PQ initiative will be to assess PQ outcomes to date and identify areas to improve the design of the initiative. The evaluation should consider: (1) major PQ program research outcomes; (2) community involvement; (3) new and retired PQs; and (4) programmatic aspects that should be sustained or improved in future iterations of the program.

Proposed Evaluation Questions

1) What are the major research outcomes achieved by PQ initiative?
    a. What are the research outcomes achieved by the PQ initiative to date?
    b. What is the impact of the PQ initiative's scientific accomplishments?
    c. To what extent have the scientific findings of the PQ initiative expanded our understanding of PQ topics?

2) How has community involvement impacted the PQ initiative?
    a. How is community involvement (e.g., workshops) beneficial to the PQ initiative?
    b. What challenges does the initiative face regarding community involvement?
    c. How could community input be improved in the future?

3) To what extent has the PQ initiative met its goals in supporting understudied areas of cancer research?
    a. What is the rate of new and continuing questions for each RFA issuance?
    b. How have the methods or findings of PQ research contributed to subsequent research in novel or understudied areas?

4) How can the PQ initiative be improved in the future?
    a. What are the strengths and challenges of current processes to choose, revise, and retire PQs?
    b. How has the current structure of the PQ initiative facilitated or hindered the desired research?
    c. What should be the focus or scientific scope of PQ research for future iterations?

Proposed Evaluation Methods and Metrics

Q#	Primary and Secondary Questions	Indicators/ Performance Metrics	Methods
1	**What are the major research outcomes achieved by PQ initiative?**		
1a	What are the research outcomes achieved by the PQ initiative to date?	Number of publications over time, publication lag Number of patents Clinical trials Specific examples of outcomes (e.g., novel findings, new methods)	Data retrieval from relevant databases Interviews with PQ PIs, NCI staff, and other stakeholders Survey of PQ PIs
1b	What is the impact of the PQ Initiative's scientific accomplishments?	Citation metrics (i.e., RCR, citation lag, percent cited/uncited publications, journal impact factor, highly cited/hot papers) Previous and subsequent grants Specific examples of the impact of research outcomes	Data retrieval from relevant databases Interviews with PQ PIs, NCI staff, and other stakeholders Survey of PQ PIs Scientific content analysis of previous and subsequent grants for a sample of PQ awardees
1c	To what extent have the scientific findings of the PQ initiative expanded our understanding of PQ topics?	Trends in PQ topic literature over time PQ awardee contributions to PQ topic literature Specific examples of the impact of research outcomes	Data retrieval from relevant databases Publication MeSH term analysis Literature review and synthesis with citation tracking Interviews with PQ PIs, NCI staff, and other stakeholders
2	**How has community involvement impacted the PQ initiative?**		

Q#	Primary and Secondary Questions	Indicators/ Performance Metrics	Methods
2a	How is community involvement (e.g., workshops) beneficial to the PQ initiative?	Perspectives on community involvement Processes and procedures for PQ selection	Interviews with PQ PIs, NCI staff, and other stakeholders Survey of PQ PIs Focus groups with workshop attendees and/or focused scientific panel Content analysis of program documentation
2b	What challenges does the initiative face regarding community involvement?	Descriptions of challenges	Interviews with PQ PIs, NCI staff, and other stakeholders Survey of PQ PIs Focus groups with workshop attendees and/or focused scientific panel
2c	How could community input be improved in the future?	Suggestions for improvement	Interviews with PQ PIs, NCI staff, and other stakeholders Survey of PQ PIs Focus groups with workshop attendees and/or focused scientific panel
3	**To what extent has the PQ initiative met its goals in supporting understudied areas of cancer research?**		
3a	What is the rate of new and continuing questions for each RFA issuance?	Number/rate of new questions over time Number/rate of retired questions over time Number/proportion/funding dedicated to each PQ	Quantitative analysis of program information In-depth review and analysis of progress reports Data retrieval from relevant databases Publication MeSH term analysis and timeline

Q#	Primary and Secondary Questions	Indicators/ Performance Metrics	Methods
		Summary of findings to date for the full history of each PQ Trends in cancer research literature over time, pre-and post-mature PQs	
3b	How have the methods or findings of PQ research contributed to subsequent research in novel or understudied areas?	Descriptions/vignettes of junior investigators moving into malaria research (if available)	Interviews with PQ PIs, NCI staff, and other stakeholders Survey of PQ PIs
4	How can the PQ initiative be improved in the future?		
4a	What are the strengths and challenges of current processes to choose, revise, and retire PQs?	Perspectives on strengths and challenges	Interviews with PQ PIs, NCI staff, and other stakeholders
4b	How has the current structure of the PQ initiative facilitated or hindered the desired research?	Perspectives on current structure of the initiative	Interviews with PQ PIs, NCI staff, and other stakeholders Survey of PQ PIs Focus groups with workshop attendees and/or focused scientific panel
4c	What should be the focus or scientific scope of PQ research for future iterations?	Perspectives on future focus Emerging trends to explore Current gaps in PQ topic areas	Interviews with PQ PIs, NCI staff, and other stakeholders Survey of PQ PIs Focus groups with workshop attendees and/or focused scientific panel Literature review