

THE WHAM REPORT

Societal Impact of Research Funding for Women's Health

IN LUNG CANCER

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Women's
Health
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Matters®

Research Funding for Women's Health: A Modeling Study of Societal Impact

Findings for Lung Cancer

Matthew D. Baird, Annie Chen, Andrew W. Dick, Chloe E. Bird, Melanie A. Zaber,
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RAND Social and Economic Well-Being

WR-A708-4
March 2022

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Published by the RAND Corporation, Santa Monica, Calif. For more information on this publication, visit www.rand.org/pubs/working_papers/WRA708-4.html

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WHAM, whamnow.org, is a 501c3 dedicated to funding women's health research to transform women's lives.

This report was conceived by WHAM in response to the considerable funding gap, historical exclusion, and under representation of women in health research.

As businesswomen, we believed that a focused study showing the impact of accelerating sex and gender-based health research on women, their families and the economy by quantifying costs and economic benefits will be an invaluable accountability index. In other words, if more investment is made in women's health research the plausible assumption is that women would benefit from sex-specific prevention strategies, diagnoses and treatments that reduce their burden of disease and thus improve their well-being and hence the well-being of society.

WHAM commissioned the RAND Corporation to conduct a data-driven study of the economic impact to society of increasing the investment in women's health research. This first research project comprises four disease modules: Alzheimer's Dementia, Rheumatoid Arthritis as representative of Autoimmune Disease,

Coronary Artery Disease, and Lung Cancer as representative of cancer. In the future, we plan to study different socioeconomic groups to the extent that the data are available and detail the global data which expands this research.

To the best of WHAM's and RAND's knowledge, this is the first analysis of its kind to create and calibrate a microsimulation model of investments in health R&D that examines differences for women's health research investment, and should become a seminal part of the arsenal in advocating for increased investment in women's health research. The research methodology and the microsimulation models have been vetted by a diverse panel of experts convened by RAND.

We are so thankful for the dedicated, invested partnership of the research team at the RAND Corporation who conducted the analysis presented here and brought their findings to life.

We encourage other leaders, including advocates, economists, scientists, business leaders, public health experts and policy makers to draw from and act upon the results of this report. Together, we can drive meaningful change.

Carolee Lee

Founder and CEO

Women's Health Access Matters (WHAM)

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Please find additional infographics and social media toolkits on www.thewhamreport.org

The technical specifications for the models are publicly available. Please visit www.thewhamreport.org to learn more about using these data and citing this report.

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WHAM's leadership of this research project was encouraged through the generous support and collaboration from the following organizations:

American Heart Association (AHA) is a relentless force for a world of longer, healthier lives dedicated to ensuring equitable health for all—in the United States and around the world. AHA's signature women's initiative, Go Red for Women® (GRFW), has been the trusted, passionate, relevant force for change to end heart disease and stroke in women all over the world for nearly two decades. GRFW and WHAM will collaborate to directly address the lack of societal level evidence on the economic cost, benefits, and social impact due to the underrepresentation of women in cardiovascular research.

BrightFocus Foundation is a leading source of private research funding to defeat Alzheimer's, macular degeneration and glaucoma. Supporting scientists early in their careers to kick-start promising ideas, BrightFocus addresses a full and diverse range of approaches from better understanding the root causes of the diseases and improving early detection and diagnosis, to developing new drugs and treatments. The nonprofit has a longstanding commitment to funding pioneering, sex-based research in Alzheimer's and related dementias.

Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital, Harvard Medical School is a leading local and national force in advancing the health of women, with a rich history and strong foundation of women's health and sex-differences discovery, clinical care, and advocacy for equity in the health of women and is the Lead Scientific Research Partner of The WHAM

Collaborative. The Connors Center shares the bold vision of improving the health of women and a commitment to joining forces to advance scientific discovery for the benefit of all women.

GO2 for Lung Cancer (GO2) relentlessly confronts lung cancer on every front, every day. Founded by patients and survivors, GO2 is dedicated to increasing survival for those at risk, diagnosed and living with lung cancer. GO2 serves as the "go-to" for assistance across the care continuum and is the source for improving health policies and leading public awareness to shift the disease away from stigma to hope. The Women and Lung Cancer Research and Preventive Service Act provides a foundation for WHAM and GO2 to engage in strong partnership to advance our shared goal of improving health outcomes for women.

La Jolla Institute for Immunology (LJI) is one of the top five research institutes in the world focused on the study of the immune system. LJI is home to three research centers that harness the efforts of collaborative groups of researchers on defined areas of inquiry, to accelerate progress toward the development of new treatments and vaccines to prevent and cure autoimmune conditions, cancer and infectious disease. Together, LJI and WHAM will create a framework for researchers to re-analyze existing data with sex as a biological variable, to work together to spark new projects, to hire new faculty to build key research areas, to communicate via The WHAM Report, and to establish an ignition point for new leadership in the scientific field.

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A Message from WHAM

The research described in this volume was conceived by Women's Health Access Matters (WHAM—whamnow.org). WHAM was created in response to the considerable funding gap, historical exclusion, and underrepresentation of women in health research. WHAM is a 501(c)(3) (www.whamnow.org) dedicated to funding women's health research to transform women's lives.

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The Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital/Harvard Medical School is a leading local and national force in advancing the health of women, with a rich history and strong foundation of women's health and sex-differences discovery, clinical care, and advocacy for equity in the health of women, and is the Premier Partner and the Lead Scientific Research Partner of the WHAM Collaborative for Women's Health Research. The Connors Center shares the bold vision of improving the health of women and a commitment to joining forces to advance scientific discovery for the benefit of all women.

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La Jolla Institute is home to three research centers that focus the efforts of collaborative groups of researchers on defined areas of inquiry to accelerate progress toward the development of new treatments and vaccines to prevent and cure autoimmune conditions, cancer, and infectious disease. Together, we will create a framework for researchers to reanalyze existing data with sex as a biological variable, to work together to spark new projects, to hire new faculty to build key research areas, to communicate via the WHAM Report, and to establish an ignition point for new leadership in the scientific field.

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Executive Summary

The Challenge: Women's health has suffered from insufficient research addressing women. The research community has not widely embraced the value of this research. The impact of limited knowledge about women's health relative to men's is far reaching. Without information on the potential return on investment for women's health research, research funders, policymakers, and business leaders lack a basis for altering research investments to improve knowledge of women's health.

What We Did: Research impact analysis is a framework for supporting decision making about research funding allocation. Economic modeling aids with such impact analysis. Microsimulation models provide a method of quantifying the potential future impact of additions to research investment. Using microsimulation analyses, we examined the societal cost impact of increasing research funding in lung cancer. We quantified the potential impact of increasing funding on women's health on health outcomes and ultimate societal costs including healthcare expenditures, labor productivity of informal caregivers, and quality-adjusted life years (QALYs). We calculated impacts across 30 years of two funding scenarios: doubling the current percent of the National Institutes of Health extramural lung cancer portfolio devoted to women's health, and tripling that investment. Impact of a current investment was assumed to occur in 10 years, with benefits accruing after that.

Key Takeaways:

- Investing in women's health research is worthwhile over time even if you expect the actual improvements to be small. Assuming health improvements of 0.1 percent or less in terms of age incidence and mortality and quality of life yields the following results:
 - For the US population age 25 and older, over 22,700 years can be saved across 30 years, with substantial gains in health-related quality of life.
 - Approximately 2,500 more labor years valued at \$45 million in labor productivity result from increased work time and longer life.
- Doubling the investment would have an expected ROI of over 1200 percent if it succeeded in generating health improvements of 0.1 percent in mortality and incidence and 0.01 percent in quality-adjusted life years.

The results establish the potential for investment in women's health research on lung cancer to realize gains beyond additional general research investment.

Implications: Large societal gains may be possible by increasing investment in women's health research in lung cancer. The potential to recognize societal gains is greater for research devoted to women's health relative to general research, based on the specifications used here.

We recommend the following policy actions based on this research to inform decisions about research funding allocations:

Policy Implications: The results of these analyses suggest several policy actions to inform decision making about research funding allocations.

Expand the research agenda to address multiple aspects of sex/gender and lung cancer based on the limited evidence base, including:

- the unknown interactions of sex and gender with lung cancer etiology, risk factors, and disease progression to inform treatment and prevention research.
- under-studied interactions of gender and race with lung cancer risk, health care, and disease progression. In particular examine obstacles to access to and use of diagnostic technology, including for personalized medicine.
- differences by sex and gender in lifestyle impacts on disease.
- differences in disease course and outcomes by sex and gender based on different patterns of use of formal and informal caregiving.

Given the findings here of potential for impact on health-related quality of life of women with lung cancer, further study of the relationship of earlier detection for women and improved disease management, in terms of impact on health and quality of life outcomes, can aid with tracking investment impacts in the future. The following recommendations can provide a foundation for support of research funding allocation decisions:

- Raise awareness of differences between the lung cancer course for women and men and the potential for investment to improve disease outcomes and societal impact.
- Raise awareness among the business community of the potential return on investment in women's health research, particularly for women in the workforce.

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Chapter 1. Introduction

Historical exclusion and under-representation of women in health research has resulted in an impoverished evidence base about women's health. Increased awareness of the impact of sex and gender exclusion on health research has led to efforts to include more representative samples. However, the value of this research is not yet widely embraced by the research community, nor is consideration of gender effects part of the culture of science. The impact of this oversight is far-reaching.

Given the evidence that women's health has been historically underfunded, with resulting negative consequences for diagnosis and treatment of diseases among women (Johnson et al., 2014), tracking the dedicated investment to women's health research provides information vital to funders, researchers, and policymakers in terms of planning for investments that can yield the greatest public health benefits.

Given known differences and the potential for unknown differences to affect morbidity and mortality, investment in women's health could be expected to yield a favorable return for society.

The lack of societal-level evidence on the economic costs, benefits, and social impacts of attention to sex and gender in health research is a major obstacle to moving from policies of passive inclusion to active focus on the medical gender gap. In lung cancer, differences by gender have been explored in terms of rates of diagnosis and treatment trajectories (National Cancer Institute, 2018; Rana et al., 2020) but empirical evidence about differences by sex and gender is still limited.

Quantifying the impact of research funding investment is a relatively new area of inquiry (Adam et al., 2018). Hallmarks of ideal systems for comprehensively examining research funding impact include capture of a full set of impacts and benefits, aggregating impacts and also reporting disaggregated impacts, and valuing different impacts in a common currency (Adam et al., 2018). Economic modeling provides a method for achieving these goals. Microsimulation modeling allows a way to address the gap in knowledge about investment in women's health research and to specifically examine impacts of additional investments (see for example, Grant and Buxton (2018)). Impacts can be quantified in economic terms. Inclusion of impacts on health-related quality of life is a relatively recent addition to the comprehensive impacts examined in research impact analysis (Grant and Buxton, 2018). Understanding the impact of the disease and potential disease mitigation on health-related quality of life as well as other health outcomes ensures outcomes beyond those that are readily monetized are appropriately considered and included.

To address this gap, we used microsimulation modeling to explore the potential for enhanced investment in women's health research, in terms of the economic wellbeing of women and for

the US population, using existing studies examining sex or gender differences (Quigley et al., 2020; Rana et al., 2020; Yu et al., 2014; Schütte et al., 2018). Women's health research as used here refers both to analyses that address sex/gender within general sample or population studies, and to research focusing on women specifically. Our microsimulation model approach contributes to the existing body of literature by allowing us to project the future impact of funding on health outcomes and changes in societal burden from lung cancer (Yabroff et al., 2008; Yabroff and Kim, 2009).

The analyses presented here quantify costs and benefits of investment in women's health research in lung cancer. The models used for this examination address the contribution of research to disease burden and to societal productivity costs and benefits. Quantifying societal costs alongside disease burden is key.

We used current levels of funding from the National Institutes of Health (NIH) as the "base case" with comparisons to doubling and tripling the level of research funding currently invested in women-focused research. We assumed that impacts of increased funding occur through innovations that reduce age incidence of disease and disease mortality and improve health-related quality of life. We quantified the innovations through costs of informal and paid caregiving, work productivity for informal caregivers, and healthy life-years gained or lost.

In the US, the universe of funding for research on lung cancer extends beyond NIH and includes other major funders and advocacy organizations like the American Cancer Society, the biopharmaceutical industry, and philanthropic organizations ("Making Progress: Making a Difference," 2020). NIH's share of lung cancer research investment is large, however, and provides a starting point for understanding investments in health research generally and women's health research in particular.¹

Women are disproportionately represented among nonsmokers with lung cancer, with nonsmoking men representing just 2-6% of total lung cancer cases among men, but nonsmoking women representing approximately 20% of cases (North and Christiani, 2013). The differences not attributable to tobacco exposure may indicate different disease pathophysiology (e.g., Sun, Schiller and Gazdar (2007). The role of estrogen in lung cancer is still being evaluated but evidence supports its relationship to pathology (Rodriguez-Lara and Avila-Costa, 2021).

Through analyses that quantify costs and socio-economic benefits, these models examine the impact of increased sex- and gender-based health research on women, their families, and the economy. The goal of the analyses is to serve as a foundation for developing a concrete,

¹ Terminology: We follow terminology guidance from the NIH, which states the following: "'Sex' refers to biological factors and processes (e.g., sex chromosomes, endogenous hormonal profiles) related to differentiation between males (who generally have XY chromosomes) and females (who generally have XX chromosomes). 'Gender' refers to culturally and socially defined roles for people, sometimes but not always along the lines of a gender binary (girls and women, boys and men). Gender incorporates individuals' self-perceptions (gender identity); the perceptions, attitudes, and expectations of others (gender norms); and social interactions (gender relations)." We combine sex and gender research in our examination.

actionable research and funding agenda. The analyses are intended to demonstrate the potential impacts of increased funding for research on women's health and thereby inform funders', legislators', and the business community's prioritization of research funding allocations.

Chapter 2. Methods

We used microsimulation models to address the impact of funding for women's health research in lung cancer. The models followed a cohort representing the U.S. population of individuals who have or could develop lung cancer, age 25 and older. The youngest age of 25 reflects the fact that lung cancer affects adults, and this captures the working-age population and older. The cohort assumed 100 percent mortality at age 99. The model simulated the progression of each person's health in the sample over a 30-year time horizon; the models generated the relevant costs associated with the development of health. We generated a model to first reflect the *status quo* of the disease and then re-simulated the model under the assumption that increased investment improves health outcomes and thus lowers costs. This approach allowed us to directly estimate how costs evolve with health innovation and allows exploration of the associated return on the research investments.

Base Case

Creating a realistic microsimulation model requires calibrating several functions that define how health evolves and the relationship with changes in health and costs. Where possible, we calibrated these functions using estimates from the research literature. This approach has the primary advantage of relying on best-available, peer-reviewed estimates; an added benefit is efficiency in terms of estimates for each function in the model.

However, we could not calibrate every parameter of the model from the literature; in some cases, we had to create our own estimates. Ultimately, we required data that included measures of employment, medical expenditures, health condition incidence, and baseline demographics such as age and gender. The data set also needed to include a large sample to ensure substantial detection of each condition within the population.

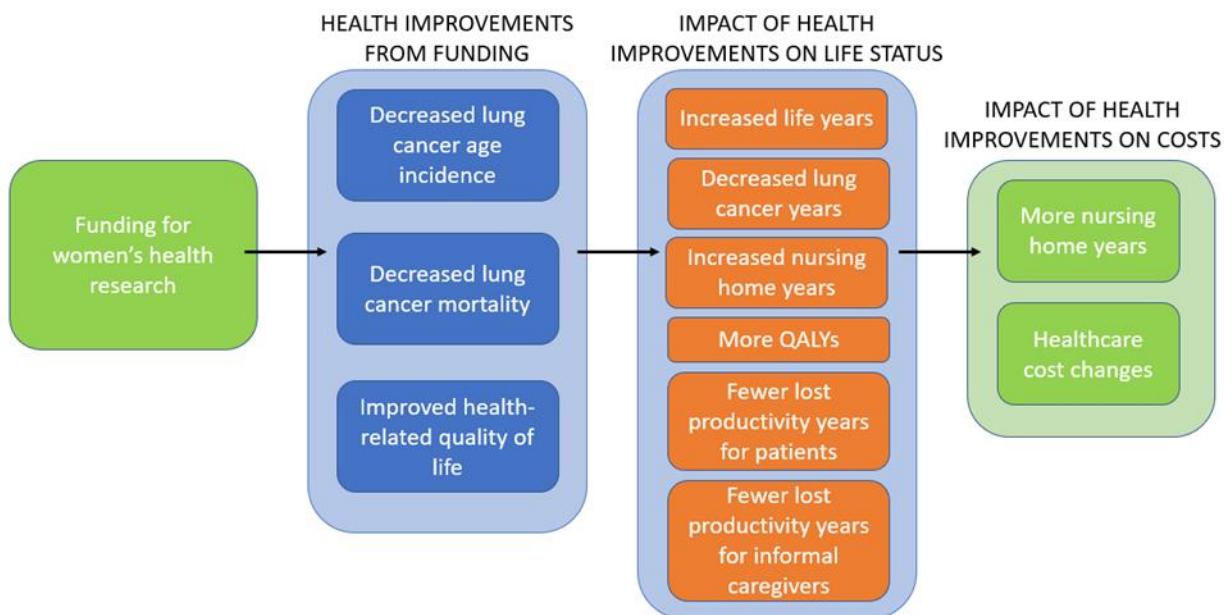
We considered several data sources; the Medical Expenditure Panel Survey (MEPS) best fit these criteria. Among our options, the MEPS has the largest sample and range of ages, the clearest diagnosis indicators, and detailed data on medical expenditures. It also meets our primary criterion of having detailed employment and income data for all household members. We used the MEPS data in several instances to parameterize functions we could not observe in the literature. See the Technical Appendix A for details of the dataset considered.

We estimated baseline healthcare costs from the *status quo* simulation model. Note that these baseline healthcare costs are not intended to capture all potential healthcare costs, direct and indirect. Instead, the baseline healthcare costs are with respect to the relevant inputs.

Lung Cancer Model

Our primary strategy was to create a model that allows us to take assumptions about current funding levels, input what the literature tells us about how funding affects health outcomes and translate that information into predicted economic outcomes of funding changes. We quantified the impact of funding on health outcomes, and on specific changes in societal burden like reduced workforce participation of informal caregivers, through an economic microsimulation model. By tying different funding scenarios to incurred societal burden, the model quantifies how funding amounts impact societal burden of lung cancer in terms of health expenditures, caregiver time loss, and lost life years. The impact on quality-adjusted life years (QALYs), and not just on absolute lost life years, is important to quantify, given the ways in which the disease affects individuals. The QALY is one way in which monetary value can be assigned to disease impact (Grant and Buxton, 2018). The approach to relating funding to health improvements, life status, and costs is summarized in Figure 1 as the conceptual model guiding this work. The model represents the hypothesis of improved health as a result of increased funding for women's health research – decreased age incidence of lung cancer, decreased mortality, and improved health-related quality of life. While the hypotheses related to improved health relate to lower costs for some aspects of healthcare, we are associating decreased mortality with more time in nursing homes. That is, reduced mortality associated with lung cancer could result in other chronic disabling diseases to emerge among those who would otherwise have died from lung cancer, resulting in net increase in nursing home years.

Figure 1. Conceptual Model of Research Funding Impacts for Lung Cancer



Background on Model Components

The model was built with the following components: age incidence profiles, mortality, non-nursing home healthcare costs, informal care status, and nursing home care costs. Patient-level disease burden components were the age incidence and quality-adjusted life years. Societal-level disease burden components were the healthcare costs associated with institutionalization, all other healthcare costs, and informal caregiver lost productivity. Data sources for model components are presented in Figure 2.

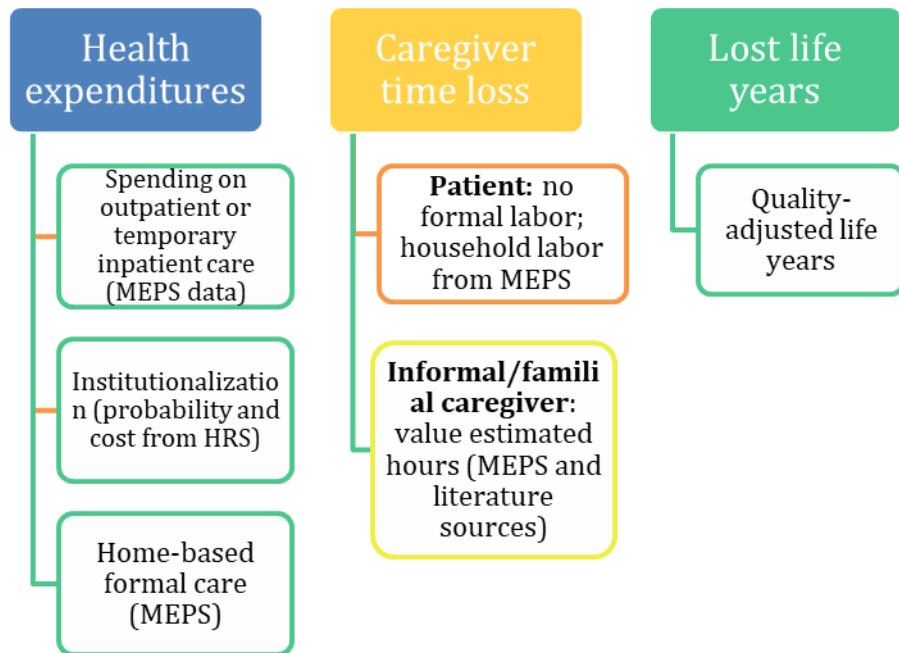
Disease burden extends to other family members beyond the patient and was represented as informal caregiver lost labor force participation in the model (Committee on Family Caregiving for Older Adults, 2016). The earnings profiles, stratified by age, quantify earnings over a working career and enabled us to see the effect of personal and family health issues as well as caregiving responsibilities on earnings.

Details of all model components are presented in Technical Appendix B.

Calculations involving population earnings ordinarily adjust by race and ethnicity and gender, given differences by these variables in earnings. We chose to instead use earnings of non-Hispanic white males as the basis for the earnings calculations in these models, regardless of gender and race/ethnicity composition of the informal caregiving population. This choice avoids current time disparities in earnings to be propagated into an assumed future. Doing so avoids the gender and race-based labor market discrimination that is inherent in the differential, and lower, earnings for women and for non-Hispanic white males. Specifically, the earnings used for self and for informal caregivers were based on those of non-Hispanic white males, instead of on race and gender specific earnings, representing an assumption of earnings equality.

The age incidence profiles provided a layer of information regarding when in a person's life the health conditions of interest occur and when they affect quality of life, care, and employment as a function of age and gender. The impacts were on informal caregiver earnings loss, quality of life, and probability and type of care. Care status and mortality were functions of age, gender, and disease status.

Figure 2. Quantifying Societal Burden of Lung Cancer



Finally, expenditures were a function of age, gender, lung cancer status, and care status. The model accounts for uncompensated costs of labor and household management in the form of informal care, which may represent a spouse or dependents engaged in caregiving. Reductions in own-earnings due to lung cancer may occur for two reasons: first, we accounted for reduction in earnings for all individuals below age 65 based on estimates in earnings differentials for individuals with and without lung cancer. Second, those that die before age 65 are assumed to additionally have an earnings loss equal to the unconditional average earnings for non-Hispanic white men (that is, including the fact that some individuals do not work, and have zero earnings).

We used prior research on funding investment return as a basis for assumptions on return on research investment, that is, the impact of funding levels on health outcomes (Grant and Buxton, 2018). The return on research investment calculation was a function of the following specific health outcomes: age incidence of disease, improved detection rates and earlier detection in the disease course, and reduced mortality due to disease. Following analyses in which the return on research investment was permitted to vary, we constrained the model to determine inputs that would yield an expected return on investment of 15 percent, in line with findings from several therapeutic areas (Grant and Buxton, 2018).

Taken together, these components enabled us to simulate the effects of increasing funding for health research on women in terms of economic outcomes. These economic outcomes included the monetary value of workers being able to stay in the labor force longer as a result of decreased caregiving burden.

Time Horizon

The representative cohort of 999,565 lives was moved through a 30-year time horizon, with impact of investment expected 10 years from initiation. We created the representative sample based on the U.S. age and gender distribution for individuals ages 25 and older as well as initial existing disease rates by age and gender. We chose a 10-year investment impact time point based on existing research on time from investment to healthcare impacts (Cruz Rivera et al., 2017; Hansen et al., 2013; Scott et al., 2014). Given the small health improvement assumed with each scenario, we chose the lower end of the literature estimates of time from investment to impact. The 30-year model time horizon permits accrual of impacts for the 20 subsequent years, within the lifespan of the majority of the cohort.

Investment Impacts

The model provides information on return on investment (ROI) associated with multiple innovation impacts. Models address each of the three main impacts separately and then address all three impacts occurring together:

1. decreased age incidence of disease (probability of onset at a given age)
2. decreased mortality rates for lung cancer patients given age and gender
3. improvements in health-related quality of life, with the assumption that reduction in symptoms and more functional independence would account for more quality-adjusted life-years (QALYs).

We investigated different levels of aggregate health improvement in each of the three health inputs described above, starting with very small improvements, ranging from 0.01 percent to 1 percent. We simulated the model and estimated the costs and ROIs under two assumptions about health improvements. The first assumption was for a targeted investment in women's lung cancer research with an impact for women three times larger than that for men. Any investment in research focused on women was expected to yield results relevant for women, but this assumption included the likelihood that a portion of that research will benefit both women and men. The second assumption was a representation of general investment in lung cancer research with equal research impact on women and men. Given the limitations of "general" research with regard to understanding women's health historically, this assumption is a likely overestimation of the impact of "general" research on women's health. For both differential and equal impact, we assume that the average return is still the same. For example, when considering an average health improvement of 1 percent, the equal impact assumes that both women and men realize a 1 percent improvement, whereas the three-times larger version assumes that women realize a 1.5 percent improvement and men realize a 0.5 percent improvement, averaging approximately to a population-level 1 percent improvement.

Based on preliminary findings we selected a mixed scenario for our primary base case. We found that improvements in incidence and mortality had to be large relative to improvements in

QALYs to have a substantively important effect on the outcomes. The final base case scenario then is 0.1% improvement in incidence and mortality combined with a 0.01% improvement in QALY, using the women's impact 3 times that of men. See Table 1.

Table 1. Investigated Health Improvement Scenarios

Health Improvement Assumption	Assumption: Impact on Women 3 Times that of Men	Assumption: Equal Impact by Sex
0.01%	Scenario 1	Scenario 2
0.02%	Scenario 3	Scenario 4
1%	Scenario 5	Scenario 6
Primary base case assumption: 0.1% incidence and mortality improvement with 0.01% QALY improvement	Scenario 7	Scenario 8

Value of Investing in Women's Health Research

Using the simulated health and cost outcomes, we examined ROIs under either doubling or tripling of the NIH portfolio of women-targeted lung cancer research across the scenarios. To further understand investment impact, we also examined probability of success. To do so, we additionally framed the ROIs in the context of uncertainty of investments. That is, we calculated the minimum probability of success of the investment to generate an expected ROI of 15% for a given health improvement.

The benchmark for the baseline percentage of research on women's health was funding levels for lung cancer research within the funded portfolio of the NIH. To estimate this level we retrieved all titles and abstracts for the lung cancer area using NIH RePORTER, the publicly available interface of funded extramural NIH projects (National Institutes of Health, 2020b). The terms used to search the retrieved titles and abstracts to determine the total number of women-focused projects were "women", "sex", "gender", and "female." Projects without these terms in the title or abstract were excluded from the "women-focused research" set examined (N=56,612). The RePORTER search identified 8,515 lung cancer projects from 2008 to 2019; 10.8% of the total number of funded projects were women-focused projects and 14.9% of the total dollar amount of the portfolio was women-focused. Total project funding level was calculated based on the NIH Research, Condition, and Disease Categorization (RCDC) codes (National Institutes of Health, 2020a).

The total funding level between 2008 and 2019 for lung cancer was \$3,284,089,672 dollars for an annual average of \$40,889,414, with 14.9 percent of the budget allocated to women-focused projects (Sekar; National Institutes of Health, 2020a). This 14.9 percent increment was added to the 2019 amount, to double the level of investment in women's health research. All costs are presented as 2017 USD.

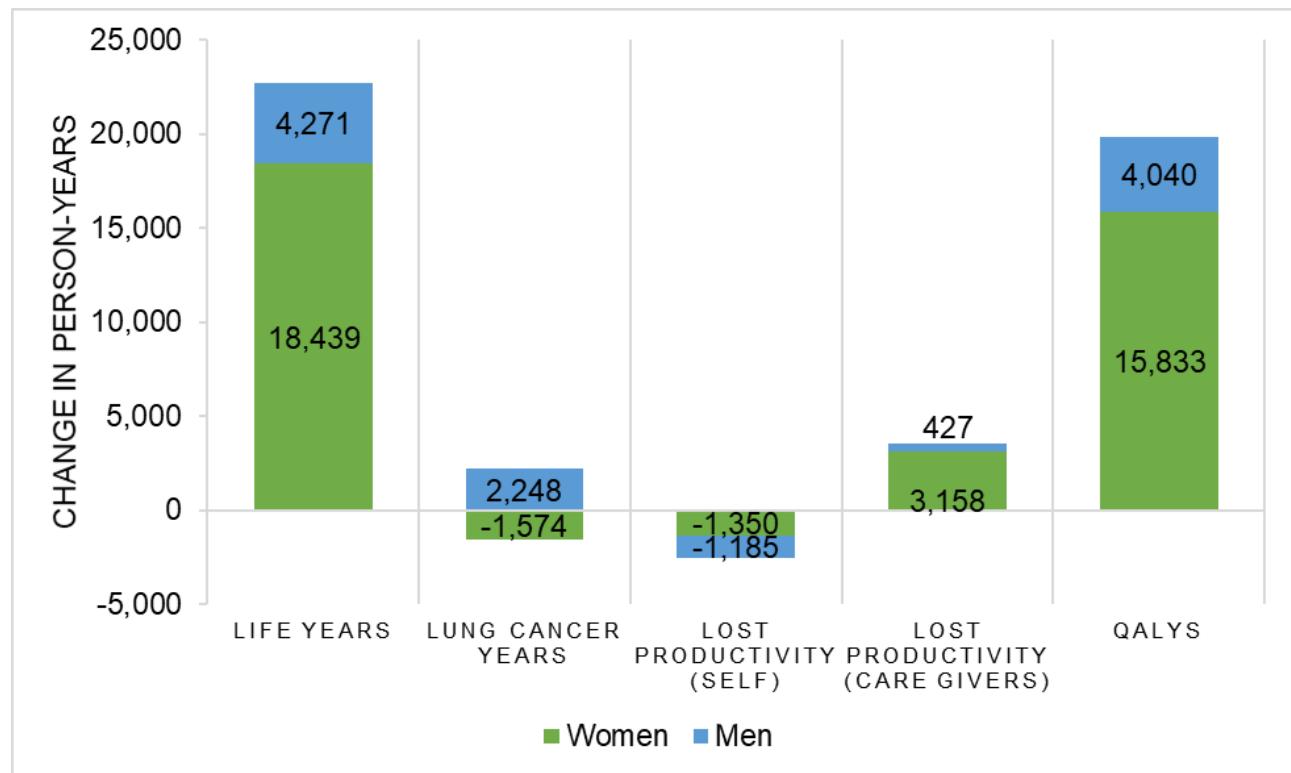
Chapter 3. Results

We present the health and economic improvements and resulting impact on costs for the primary base case specification: a 0.1 percent average health improvement in mortality and incidence, and a 0.01 percent QALY improvement, with three times the impact for women as for men. Different funding scenarios are compared to provide context for these results. Finally, we present the resulting ROIs and probability of success necessary to have an expected ROI of 15 percent.

Impact on Health and Economic Outcomes for Scenario 7

Figure 3 presents the simulated improvements in the health and economic outcomes and the resulting impact on costs, scaled up from the model cohort to the US population, ages 25 and older, of approximately 225 million people. We discuss each cost impact in turn below.

Figure 3. Health and Economic Improvements Under Scenario 7 (0.1% Impact in Mortality and Incidence, and 0.01% QALY Improvement, Three Times Larger for Women than Men), for US Population Age 25 and Older



NOTE: Based on US population age 25 and older of around 225 million.

Increased Life Expectancy:

We estimated that the base case scenario health improvement results in more years of life from lowering the onset of lung cancer and the mortality rate for lung cancer patients. Specifically, we found that women realize almost 18,500 more life years from innovations, while men realized over 4,200 more life years from innovations, for a total of over 22,700 more life years. This is small for the overall US population over age 24, approximately 225 million people, tracked through 30 years. Put another way, this represents an average additional extension of life by 15 days per patient, or one additional life year for one out of every approximately 24 lung cancer patients.

Decreased Disease Burden:

Scenario 7 health improvements also generated a reduction in lung cancer disease burden in terms of life years with lung cancer for women, a function of both shorter disease duration as well as a reduction in age incidence. Women have nearly 1,600 fewer life years with lung cancer, and men had over 2,200 more life years with lung cancer.

Lost Productivity (Self):

We examined the impact of the lung cancer health improvements on employment productivity for the patients. There are two ways in which the health improvements increase employment and earnings of the lung cancer population. First, fewer years of disease create less lost earnings given the earnings penalty for lung cancer patients. Second, more years of life also allows for more years of work. In both cases, the effect is limited to those that are age 65 or younger. We estimate that these effects yield around 1,350 more equivalent years of work for women, and 1,185 years for men.

Caregiver Productivity:

We also investigated the change in productive years of caregivers, which is a function of changes in formal and informal care. We find the effect to be small but in the direction opposite of that hypothesized in the conceptual model: the increase in lost years (or fewer productive years) is around for 3,200 years for caregivers of female patients and 400 years for caregivers of male patients. These are due to more years of life given the health improvements, but more of those years at a functional level requiring informal caregiving.

Increased Quality of Life (Measured in Equivalent QAL Ys):

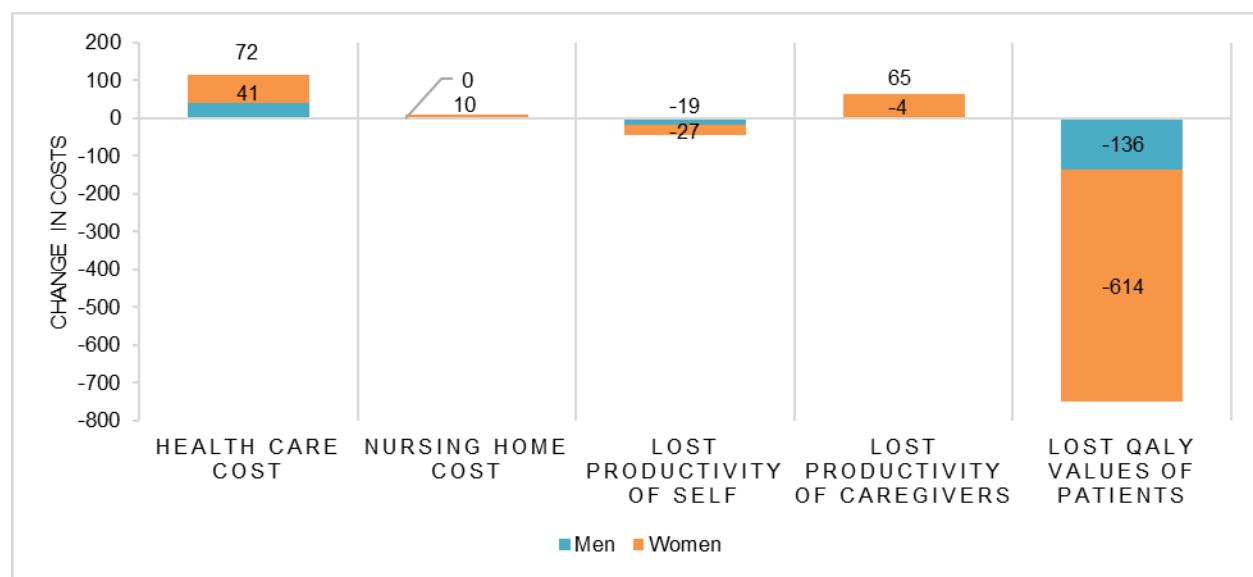
While we measured an increase of around total life years due to the health improvement in the base case scenario, this does not capture the fact that these health improvements are also related to higher quality of life. In fact, unlike the prior metrics, this is the only one affected by each of the three health improvements. Delayed onset reduces the years of lung cancer burden,

which increases quality of life. Decreased mortality rates lead to more years alive, which increases quality of life. For each health improvement level tested we included an assumption of increased quality of life for lung cancer patients from the health improvements, representing potential innovations that decrease the burden of the disease. For these reasons, the QALYs represent a large effect, with around 19,900 more year-equivalent of a fully-healthy adult. Of these, approximately 80 percent are from women patients, and 20 percent from men.

Impact on Cost Outcomes for Scenario 7

With the health and economic outcomes in the *status quo* and improved health base case scenario estimated, we can calculate the costs and changes in costs. These are presented in Figure 4.

Figure 4. Change in Costs Under Base Case (Scenario 7) 0.1% Health Impact for Mortality and Incidence, 0.01% Impact for QALYs; Three Times Larger Impact for Women than Men

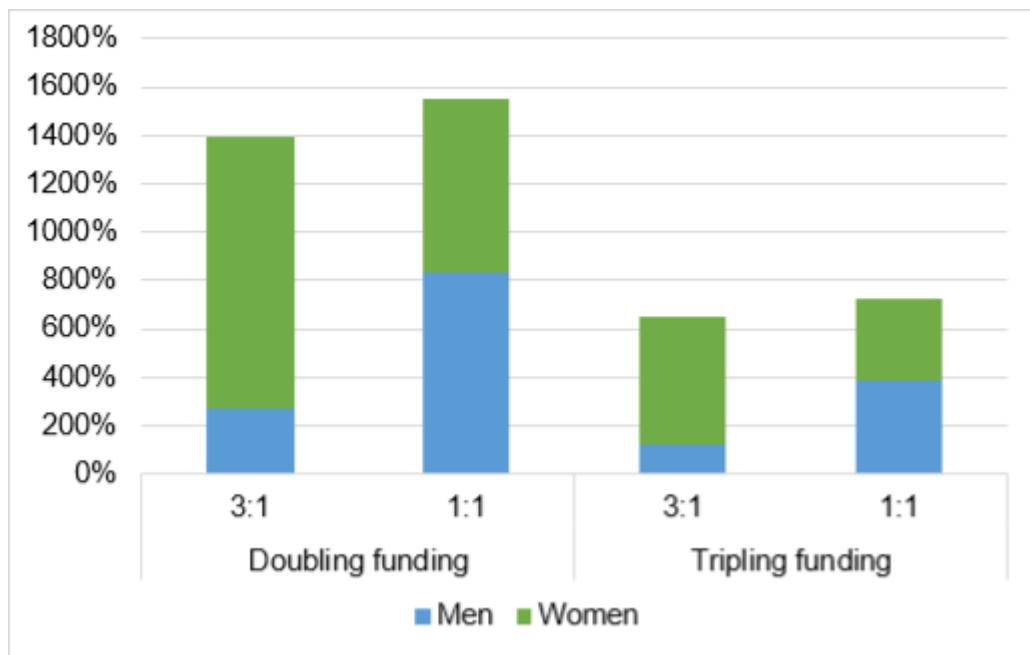


The overall reduction in costs was around \$610,911,000 net present value across the 30 years. Around 81 percent of the costs are from female patients, and 19 percent from male patients. Furthermore, as shown in Figure 4, almost all of the cost-reductions arise from fewer lost QALYs (from improved quality of life and more life years), while approximately 7 percent come from fewer lost years of workforce productivity of patients. Nursing home costs, direct health care costs, and lost productivity of caregivers are significantly smaller relative to the first two factors.

ROI under Different Scenarios

We calculated the ROI that would result from doubling or tripling the women's portion of the lung cancer portfolio under the base case scenario health improvements. Under this scenario of a 0.1 percent health improvement in terms of mortality and incidence, with 0.01 percent QALY improvement, doubling the women-targeted portion of the portfolio results in a ROI of 1,394 percent, and 647 percent for tripling the budget.

Figure 5. Return on Investment For Doubling and Tripling Funding for Women's Health Research



NOTE: Based on assumption of 0.1% health improvement in mortality and disease incidence and 0.01% improvement in QALY.

Overall ROI is high for any increased funding scenario. Women recognize proportionately more benefits of research directed at women, but all scenarios examined here lead to large returns on investment. The 1:1 scenarios are based on the assumption that the same investment increase in dollars focused on women's-targeted research will have the same average health improvement as general research. Given that gender-specific research has historically focused more on men than on women, and general research often is actually focused on men, this assumption may not be true. Potential drivers of ROI for investment require review of the assumptions about relative benefit of the investment by sex and gender.

Calculation of Probability of Success Needed for an Expected ROI of 15 Percent

The returns on investment presented in the prior section implicitly assume that the investment *will be* successful. In reality, investments bear risk, and this holds true for investments in lung cancer research. We thus reframe the returns into a simple model of uncertainty, where with probability (P) that the investment succeeds in bringing to bear the scenario's health improvement, and with probability (1-P) that it fails and costs remain the same, except with the additional borne cost of the investment. We then can calculate the probability of success (P) that equates to an expected return on investment of 15 percent. These results are presented in Table 2. The target of 15 percent was chosen based on similar return on research investment in a range of therapeutic areas (Grant and Buxton, 2018).

Table 2. Probability of Success of Investments Needed for 15 Percent Expected ROI

Scenario	Health Improvement (%)	Women's Impact	Minimum Probability of Success Needed for	
			Doubling Investment	Tripling Investment
1	0.01	3 to 1	77.55%	155.11%
2	0.01	Equal	46.69%	93.37%
3	0.02	3 to 1	19.31%	38.62%
4	0.02	Equal	23.16%	46.31%
5	1	3 to 1	0.39%	0.77%
6	1	Equal	0.39%	0.79%
7	Mortality, incidence: 0.1; QALY: 0.01	3 to 1	0.05%	0.11%
8	Mortality, incidence: 0.1; QALY: 0.01	Equal	0.06%	0.11%

Chapter 4. Discussion

Small investments in lung cancer research on women are likely to yield large societal gains. The very high return on investment from assumptions of relatively small overall health improvement support the potential for these gains from research. The very low probability of success required for research in lung cancer to yield a 15% return on investment provide further support. The overall magnitude of impact is greater than similar research on impact of research investment (Luce et al., 2006).

The results can aid with establishing the value of new interventions, offering a method for disaggregating impact by stakeholders types and by different societal payers. The assumptions used for these microsimulation models yield high return, with healthcare cost and productivity loss reductions but most of the gains are due to improved health-related quality of life.

All models involve assumptions, by design. The assumptions made for the models reported here were in general selected to return more conservative results, that is, results that bound the lower end of possibilities for investment in women's health research. These assumptions are discussed in turn.

Investment size: The size of the investment increments examined in these models is relatively small. The ROI is a function of the size of the investment and the magnitude of health improvements. The very small health improvements examined here make the direction of impacts robust to smaller overall investments.

Accrual of health improvements to women compared to men: The main results reported here assumed that dollars invested in women's health research would yield greater benefits for women than men but that all people would recognize health benefit from the investment. The two main scenarios examined were one in which the investment in women's health research was assumed to yield greater benefit for women but some benefit for men in terms of health improvements, and the other in which the research investment was assumed to yield equal benefits for women and men. The second scenario can be considered a "general investment" case and is a form of the *status quo*. A key caveat is that the *status quo* disadvantages women. That is, gender neutral or gender inclusive research yields results that are less applicable to women than to men. The comparison of a 3:1 benefit, favoring women, likely underestimates the actual benefit to women of research investment in women's health research, as relative benefit for women may be higher. The overall model assumption also keeps the proportion of the investment in women's health research to well less than 50 percent of the total portfolio amount. The results are therefore likely an underestimate of the potential societal impacts. The comparison case of equal benefit accruing to women and men is likely an overestimate of the impact of women, given historical disadvantage to women's health of research that does not expressly address women. The true ratio of benefit for the base case is not known, but the ratio of

1:1 is not an underestimate of the relative benefit to men. For these reasons, the comparison is likely skewed toward understatement of the value of investment in women's health research. That we find approximately equal returns on investment from a women-targeted investment as from a general one is thus indicative of a baseline that suggests if we adopted more realistic parameters (such as women-targeted research having a larger average health improvement than general research), the ROI would thus be higher from women-targeted research.

Time horizon: Estimates for the time from investment to discernible impact of investment for health research center on 13 to 25 years (Cruz Rivera et al., 2017; Hansen et al., 2013; Scott et al., 2014). Future research may involve acceleration of that timeline. The speed with which treatments and vaccines are being developed to address the current COVID-19 pandemic may be a bellwether for research time horizons, demonstrating the potential for shorter timelines for peer review and publication of research results. The models examined here assumed 10 years from present day investment to future realization of health impacts. However, the models were based on a single cohort, without replacement. While impacts were scaled up to the US population, cumulative impacts of health improvements may be greater longitudinally than presented here.

The benchmark for additive investments in women's health research is relatively small compared to the size of the lung cancer portfolio of research that NIH funds. The potential for both smaller and larger investments is worth investigating, although the doubling and tripling scenarios examined here provide some benchmarks for interpreting potential benefit relative to investment size.

The potential impact of health improvements on patient functioning are fundamental to the results for health care costs and caregiver productivity, and the results here, while small, point to slightly more lost caregiver productive years, while the model included the hypothesis of fewer lost productive years for caregivers. The differential impacts on informal caregiving depending on size of health improvements points to the importance of identifying policy scenarios to pursue pending different health innovation scenarios. For example, policies that address the transitions between formal long-term care and informal caregiving deserve close attention when planning for future public health impacts of research investment. Home health reimbursement and workforce readiness may be critical to address if innovations increase the informal care burden by extending time in non-severe but highly functionally impaired stages. Longer life span for women may exacerbate the informal caregiving need.

One key consideration in modeling based on labor force participation and earnings is selection of earnings profiles. We chose to apply earnings of non-Hispanic white males for all races/ethnicities and genders in the informal caregiving population. This has the advantage of avoiding assumed ongoing bias but does represent a departure from the strict matching of other economic modeling studies.

Health research investments impact society through many pathways. The models examined here focused on a small but important subset of potential impacts on population health based on investment in women's health research. While a cure and/or preventive intervention may be

possible for lung cancer over the coming decades, these analyses assume relatively small health impacts from research investment. More optimistic scenarios are not unreasonable.

Limitations

This examination should be interpreted with reference to potential limitations. These results are dependent on the underlying assumptions about uncertain impact of investment. As noted above, the models present a realistic but not overly optimistic view of the potential for increased research investment. For example, we do not model severity progression or treatment and remission explicitly. A preventive intervention or disease-eliminating intervention is certainly possible as well and could yield more positive impacts than presented here.

While the keyword approach for identifying women-focused research was simple, comprehensive, and consistent with other such searches, the selected keywords may have over- or under-included relevant research. Given the recent requirement to include sex-based analyses in NIH funded research beginning in 2016, many projects may have a women-focused research goal within a set of larger goals, leading to undercounting of women-focused research investment. This suggests that our estimates of overall funding levels for women-focused research are low, and the increments used to project the impacts of doubled and tripled funding scenarios on health and societal outcomes are conservative. Future impacts of research may differentially accrue to women based on this requirement.

There were additional limits to the modeling and simulations. Microsimulations are an exercise in trade-offs, where simplifications made for tractability of the model may weaken the ability of the model to capture the relevant dynamics. In some cases, decisions to simplify were reflections of our inability to obtain reliable parameters from the literature or have the necessary data to estimate. For example, while we have estimations of formal home care costs conditional on receiving formal home care, we chose not to simulate the status of receiving formal home care; instead, we use the average health care cost that covers formal home care in our model. We also did not estimate the costs for temporary skilled nursing home stays, including those after exit from hospitalizations. Furthermore, our results depend on some of the more subjective model decisions we made, including how many years to simulate the model forward (we chose 30 years), whether to bring new people into the cohort as they age into the relevant time-frame (we modeled without replacement), and how many years after the investment until the impact was realized (we assumed 10 years). We also had to simplify the model to assume that the full health improvements were realized at once at that 10-year mark instead of introducing time-gradient for small improvements and bringing the innovations up to scale.

The analyses here do not reference transgender or other sex and gender identities. This is not to deemphasize the importance of wider consideration of sex/gender identities but the focus here is on a first view of the under-resourced area of women's health.

Policy Implications

The results of these analyses along with review of the literature suggest several policy actions to inform decision making about research funding allocations.

1. Expand the research agenda to address multiple aspects of sex/gender and lung cancer based on the limited evidence base, including:
 - a. the unknown interactions of sex and gender with lung cancer etiology, risk factors, and disease progression to inform treatment and prevention research;
 - b. the potential for early detection of disease to improve outcomes for women given the potential for later detection among nonsmokers and disproportionate representation of women among nonsmokers with lung cancer;
 - c. under-studied interactions of gender and race with lung cancer risk, health care, and disease progression. In particular examine obstacles to access to and use of diagnostic technology, including for personalized medicine;
 - d. differences by sex and gender in lifestyle impacts on disease;
 - e. differences in disease course and outcomes by sex and gender based on different patterns of use of formal and informal caregiving.

Given the findings here of potential for impact on health-related quality of life of women with lung cancer, further study of the relationship of earlier detection for women and improved disease management, in terms of impact on health and quality of life outcomes, can aid with tracking investment impacts in the future. The following recommendations can provide a foundation for support of research funding allocation decisions:

1. Raise awareness of differences between the lung cancer course for women and men and the potential for investment to improve disease outcomes and societal impact.
2. Raise awareness among the business community of the potential return on investment in women's health research, particularly for women in the workforce.

Chapter 5. Conclusion

Understanding the full range of societal impacts from health research investment requires consideration of multiple factors and, given the uncertainty of the future, requires assumptions. Differences in etiology, detection, care access, and treatment by sex and gender are well documented in lung cancer and can provide specifics to inform an agenda for research on women's health. In conjunction with detailing the research agenda, the financial investment needed to realize the goals of that agenda requires planning. Investing more in research on women's health is likely to deliver net positive societal impacts. Clear understanding of the potential for investment can improve decisions about where and how to invest, to recognize positive impacts for women and for society as a whole.

Acknowledgments

We gratefully acknowledge the following researchers who contributed to this work: Denise Quigley, Hamad Al-Ibrahim, Jamie Ryan, Alejandro Becerra-Ornelas, Sangita Baxi, and Monica Rico. We also gratefully acknowledge Patricia Stone, Columbia University, for access to the CMS data via NIH-NINR (R01NR013687), Study of Infection Management and Palliative Care at End of Life Care (SIMP-EL). We also gratefully acknowledge the reviewers for this work, Pei-Jung Lin, Center for the Evaluation of Value and Risk in Health, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center; Sandra Berry, RAND Corporation; and Susan Straus, PhD, and Laurie Martin, ScD, RAND Corporation.

Technical Appendix A: Selection of Data Sources

Table A1. Availability of Key Variables Among Potential Data Sources

	Panel Study of Income Dynamics	National Longitudinal Survey of Youth, 1979	Medical Expenditure Panel Survey
N	24,000 people	12,686 people	30,000 households
Age ranges	Born 1951-present	Born 1957-1964	Range of ages
Health spending	Yes (aggregated)	No	Yes
Health condition limits activities	Yes	Snapshot	Yes
Extra care needed	Snapshot	No	Yes
Disability insurance participation	Yes	Yes	No
Paid nurse to come to home this year	Yes	No	Yes

NOTE: “Snapshot” indicates a variable is capture incidentally (e.g. in a single year or at milestone ages) rather than every survey wave (annual/biennial).

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