

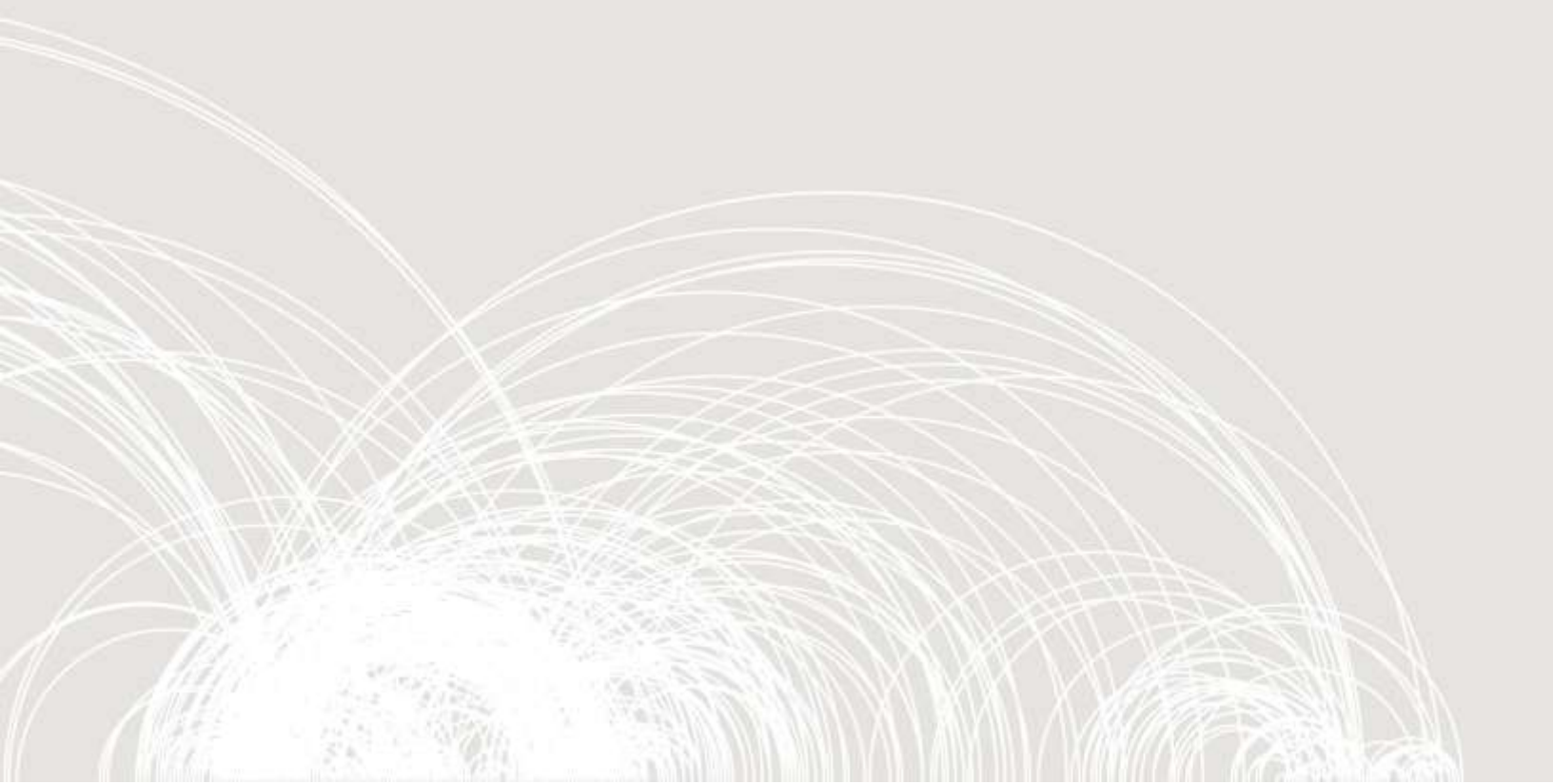
# OFF-LABEL PRESCRIPTION DRUG USE PLAYBOOK

September 2023

## Supply Chain Incentives: Avastin and Lucentis

**Prepared by:**

NORC at the University of Chicago



# Table of Contents

Introduction.....	2
Impact of Incentives.....	3
Production.....	3
Commercialization and Access.....	3
Patient Implications.....	6
Conclusion.....	7
Acknowledgements.....	8

## About This Series

This paper is organized to highlight each medication or therapy in this series in three phases: production, commercialization, and access.


Within production, there are critical steps and decisions that manufacturers make regarding research and development, patenting, and manufacturing.

From there, commercialization is intended to look closely at how a product is marketed, labeled, and regulated, and the resultant impact of those decisions on the price of each featured product.

The final step in the process is access, how product acquisition (moving from manufacturer, through wholesalers, and on to pharmacies) and distribution (PBMs, payers, and providers) shapes patient access, which is so often impacted by cost.

## Introduction

Age-related macular degeneration (AMD) is an eye disease that can result in blurring in the center of vision. AMD affects nearly 20 million adults over the age of 40 in the U.S. Of the 20 million, 1.5 million suffer from “vision threatening” AMD, a progression of the disease that typically necessitates treatment and begins to spike in adults over the age of 75.<sup>1</sup> Wet AMD is a vision threatening form of AMD that occurs when the vascular endothelial growth factor (VEGF) protein causes abnormal blood vessels to grow in the wrong place in the eye, eventually resulting in blindness.<sup>2</sup> Genentech, Inc. (“Genentech”, a subsidiary of Roche) developed two drugs, Avastin (bevacizumab) and Lucentis (ranibizumab), that work by seeking out and blocking harmful VEGF molecules. Blocking of VEGF molecules reduces abnormal growth and leakage, helping to stabilize vision loss and, in some cases, improve sight.<sup>3</sup> Both Avastin and Lucentis are physician-administered via injection into the eye, typically in an outpatient setting.

 NORC at the University of Chicago	<b>Avastin (bevacizumab)</b>	<b>Lucentis (ranibizumab)</b>
<b>FDA Approval</b>	FDA-approved as a treatment for colon cancer in 2004, and since then has been used by ophthalmologists to treat wet AMD “off-label”.	FDA-approved in 2006 for use in the eye to treat wet AMD. Lucentis was the first FDA-approved drug for treating wet AMD.
<b>Packaging</b>	When used to treat wet AMD, Avastin is repackaged. The repackaging process involves the manufacturer shipping Avastin to compounding pharmacies, where it is repackaged into smaller doses for the eye and then delivered to doctors’ offices. <sup>1</sup>	Since Lucentis is FDA approved for use in the eye, it is manufactured and delivered to ophthalmologists as eye injectables, usually stored in the ophthalmologist’s office and available for use as needed.

This playbook highlights the practice of “off-label” use – when doctors prescribe a drug to treat a condition for which it is not explicitly approved, but that has shown efficacy in real-world settings and in many cases, clinical trials as well. While off-label use is not uncommon, in the specific case of Avastin and Lucentis, the unique dynamics of the two drugs reveal underlying supply chain incentives that contribute to the persistent use of a higher-cost medication, when a comparable lower-cost option is also available. As such, this playbook details the ways in which those various incentives impact manufacturers, physicians, and payers, and result in the prescribing of both an approved product and an off-label product to treat the same condition, with comparable efficacy yet vastly different price points and Medicare spending implications.

<sup>1</sup> *Prevalence Estimates | Vision and Eye Health Surveillance System | Vision Health Initiative (VHI) | CDC.* (n.d.). <https://www.cdc.gov/visionhealth/vehss/estimates/amd-prevalence.html>

<sup>2</sup> *Treatments for Wet AMD (Advanced Neovascular AMD) | National Eye Institute.* (n.d.). [https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/age-related-macular-degeneration/treatments-wet-amd-advanced-neovascular-amd#:~:text=Wet%20AMD%20\(also%20called%20advanced,the%20back%20of%20your%20eye.](https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/age-related-macular-degeneration/treatments-wet-amd-advanced-neovascular-amd#:~:text=Wet%20AMD%20(also%20called%20advanced,the%20back%20of%20your%20eye.)

<sup>3</sup> *Comparison of Anti-VEGF Treatments for Wet AMD.* (2020, February 5). American Academy of Ophthalmology. <https://www.aao.org/eye-health/diseases/avastin-eylea-lucentis-difference>

# Impact of Incentives

## Production

### *Research and Development*

While Lucentis has been approved by the Food & Drug Administration (FDA) for the treatment of wet AMD, physicians have prescribed Avastin “off-label”<sup>4</sup>, a practice where a drug initially approved by the FDA for one clinical indication is prescribed by physicians to treat another, unapproved, disease or medical condition. The first published accounts of the use of Avastin for the treatment of macular degeneration came out in 2005, two years into clinical trials for Lucentis.<sup>5</sup> The overlapping timeline shows that Genentech had already been heavily invested in the development of a novel treatment for macular degeneration by the time the off-label use of Avastin for wet AMD was becoming more widespread.<sup>6</sup> Given the number of resources that go into the development of a new drug, it is reasonable to assume that the manufacturer was heavily invested in the continued success of Lucentis, despite learning near to its launch that another product in their portfolio may show promise for the same purpose.

Genentech/Roche never formally submitted Avastin for approval for the treatment of wet AMD to the FDA despite both real-world and clinical trial evidence indicating its value. Given the FDA’s approval of Lucentis and the unique health insurance coverage and reimbursement dynamics, there may have been less financial incentive for the manufacturer to submit for Avastin’s approval.

## Commercialization and Access

### *Labeling*

Off-label use of medications is both legal and common; in fact, one in five prescriptions written today are for off-label use.<sup>7</sup> Before prescribing drugs off-label, physicians review the evidence to assess the drug’s effectiveness in treating the off-label condition. Yet, comparative effectiveness research in this country is limited, and when conducted, statute limits the ways in which Medicare can use that research in making coverage decisions.<sup>8</sup> Arguably one of the most influential comparative effectiveness trials ever conducted in the U.S. compared Avastin to Lucentis in the treatment of wet AMD. The trial study was sponsored by the National Eye Institute, the National Institutes of Health (NIH), and the Department of Health and Human Services (HHS) and found that both treatments have

<sup>4</sup> Office of the Commissioner & Office of the Commissioner. (2018, February 5). *Understanding Unapproved Use of Approved Drugs “Off Label.”* U.S. Food and Drug Administration. <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label>

<sup>5</sup> Moshfeghi, A. A., Rosenfeld, P. J., Puliafito, C. A., Michels, S., Marcus, E. N., Lenchus, J. D., & Venkatraman, A. S. (2006). Systemic Bevacizumab (Avastin) Therapy for Neovascular Age-Related Macular Degeneration. *Ophthalmology*, 113(11), 2002-2011.e2. <https://doi.org/10.1016/j.ophtha.2006.05.070>

<sup>6</sup> Rosenfeld, P. J., Brown, D., Heier, J. S., Boyer, D. S., Kaiser, P. K., Chung, C., & Kim, R. Y. (2006). Ranibizumab for Neovascular Age-Related Macular Degeneration. *The New England Journal of Medicine*, 355(14), 1419–1431. <https://doi.org/10.1056/nejmoa054481>

<sup>7</sup> *Off-Label Drugs: What You Need to Know | Agency for Healthcare Research and Quality.* (n.d.). <https://www.ahrq.gov/patients-consumers/patient-involvement/off-label-drug-usage.html>

<sup>8</sup> Comparative Effectiveness Research, 10 Years After the ACA: Where Do We Go from Here? (2020). *Commonwealth Fund.* <https://doi.org/10.26099/34zd-z807>

equivalent effects on visual acuity improvement when prescribed on the same schedule without marked differences in adverse clinical events.<sup>9</sup>

### Market Share

Numerous other drugs (such as Eylea) used to treat wet AMD have come to market over the past 15 years, creating competition for Lucentis.<sup>10</sup> As market competition has increased, Roche (and Genentech) have experienced Lucentis' sales declines (U.S. sales for Lucentis in Q1 2022 were 21% lower compared to Q1 2021<sup>11</sup>). A 2020 study by Glasser et al., used IRIS Registry data to estimate Medicare Fee-for-Service (FFS) market share for Avastin, Lucentis, and Eylea when treating all types of AMD, diabetic macular edema, and retinal vascular occlusion via intravitreal injection. Eylea had the highest market share (43.3%), followed by Avastin (36.4%) and Lucentis (20.0%).<sup>12</sup>

### Reimbursement and Patient Costs

To understand approximate annual reimbursement to providers (and thus, costs to Medicare and other insurers), it is important to first review the course of treatment. Most drugs used to treat wet AMD (including Avastin and Lucentis) recommend monthly injections for 3-4 months followed by more intermittent injections. Based on a typical course of treatment, NORC will assume 10 injections per year for provider reimbursement calculations.

In Medicare, physicians are paid 106% of the Average Sales Price (ASP) for Part B drugs like Lucentis and Eylea.<sup>13</sup> In 2023, Medicare is estimated to reimburse providers \$1,186 and \$1,797 for Lucentis and Eylea, per injection, respectively, with per year reimbursement totaling \$11,860 and \$17,967.<sup>14</sup> The previously referenced 2020 study by Glasser<sup>15</sup> notes that as a repackaged drug, Avastin's Medicare reimbursement cannot be directly determined from publicly available ASP files and instead varies by Medicare Administrative Contractor (MAC). The following Avastin reimbursement figures are taken from the Glasser study and were obtained from a representative MAC (Wisconsin Physician Services), likely reflective of the 2019 rate. Avastin's reimbursement per dose, derived from these figures, is \$90,

<sup>9</sup> *Avastin and Lucentis are equivalent in treating age-related macular.* (2015, August 31). National Institutes of Health (NIH).

<https://www.nih.gov/news-events/news-releases/avastin-lucentis-are-equivalent-treating-age-related-macular-degeneration>

<sup>10</sup> Drugs competing with Lucentis: Eylea (Afilbercept), Beovu (brolucizumab-dbl), and Vabysmo (Faricimab-svoa). The three aforementioned drugs are all biologics and were approved in 2011, 2019, and 2022, respectively. Additionally, Lucentis biosimilars Byooviz (2021) and Cimerli (2022) have also been FDA-approved to treat wet AMD in the United States.

<sup>11</sup> Jeremias, S. (2022, April 26). *Despite Overall Increases, Blockbuster Roche Products Take Hit from Biosimilars.* Center for Biosimilars.

<https://www.centerforbiosimilars.com/view/despite-overall-increases-blockbuster-roche-products-take-hit-from-biosimilars>

<sup>12</sup> Glasser, D., Parikh, R. B., Lum, F., & Williams, G. (2020). Intravitreal Anti-Vascular Endothelial Growth Factor Cost Savings Achievable with Increased Bevacizumab Reimbursement and Use. *Ophthalmology*, 127(12), 1688–1692.

<https://doi.org/10.1016/j.ophtha.2020.06.012>

<sup>13</sup> Though in effect as of March 2023, this playbook does not factor sequestration into provider reimbursement calculations. Sequestration is a term to describe an automatic reduction of spending by the Federal Government to meet budget goals. In this case, it's reducing the amount Medicare will pay in appropriations to providers by 2% for each fiscal year. Sequestration does not apply to patient coinsurance or copayment.

<sup>14</sup> *2023 ASP Drug Pricing Files | CMS.* (n.d.). <https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2023-asp-drug-pricing-files>

<sup>15</sup> Glasser, D., Parikh, R. B., Lum, F., & Williams, G. (2020b). Intravitreal Anti-Vascular Endothelial Growth Factor Cost Savings Achievable with Increased Bevacizumab Reimbursement and Use. *Ophthalmology*, 127(12), 1688–1692.

<https://doi.org/10.1016/j.ophtha.2020.06.012>

with per year reimbursement totaling \$900.<sup>16</sup> Based on these calculations, Lucentis costs Medicare approximately 13 times more per year than Avastin.

Given the large price difference and the similar clinical efficacy, one might expect the lower-cost, clinically effective Avastin to be the more commonly prescribed treatment for wet AMD. However, this is not the case due to perverse market forces. In practice, this pricing model means that a higher cost drug will translate to higher revenue for prescribing physicians. Financial incentives to prescribe higher-cost drugs over lower-cost alternatives result in deleterious effects on patient access to drugs like Avastin (which comes with a substantially lower price), thereby costing patients and the health care system millions more in health care spending.

To understand cost to Medicare beneficiaries, it is important to recall that both Lucentis and Avastin are administered by physicians in an outpatient setting, and are thus covered under Medicare Part B. Medicare covers 80% of the Part B drugs' cost, and beneficiaries are responsible for the remaining 20% as coinsurance, after meeting their deductible (i.e., \$226, in 2023).<sup>17,18</sup> After meeting their deductible, and depending on the physician's choice of therapy, patients may face annual out-of-pocket spending of \$3,157 for Lucentis versus \$108 for Avastin.

The previously cited Glasser study's main purpose was to model Medicare Part B and patient savings that would be achievable via increased payment rates to physicians for Avastin. The working assumption of the study was that increasing Avastin reimbursement to physicians (and thus improving the provider's margin<sup>19</sup>) would incentivize providers to prescribe Avastin over Lucentis and Eylea, and that the increased reimbursement amount for Avastin would be more than offset by the significant cost difference compared to Lucentis and Eylea, saving Medicare and patients money. The study modeled multiple scenarios that factored in various increases to Avastin reimbursement as well as the effect of hypothetical increases in Avastin's market share. One model showed that if Avastin reimbursement was increased such that its margin matched Eylea's, and if Avastin's market share increased by 10%, annual Part B savings would amount to \$468 million, and patients could save \$119 million in annual copayments.

In addition to the perverse incentives described above, there are other factors that influence provider prescribing decisions. Training, clinical preference, academic literature, manufacturers' marketing efforts, and communication about the risks and benefits of drugs can all play a part in prescribing patterns. Similarly, patient coverage of certain medications, system affiliation, and participation in

<sup>16</sup> Figures here represent one possible pricing scenario, based on the best available data at the time of publication. Individual payment rates are subject to various other factors and may vary considerably. We use these numbers as a good-faith estimate to illustrate the potential differential.

<sup>17</sup> *2023 Medicare Parts A & B Premiums and Deductibles 2023 Medicare Part D Income-Related Monthly Adjustment Amounts* | CMS. (2022, September 27). <https://www.cms.gov/newsroom/fact-sheets/2023-medicare-parts-b-premiums-and-deductibles-2023-medicare-part-d-income-related-monthly>

<sup>18</sup> Deductible: The amount you pay for covered health care services before your insurance plan starts to pay. With a \$2,000 deductible, for example, you pay the first \$2,000 of covered services yourself. After you pay your deductible, you usually pay only a copayment or coinsurance for covered services.

<sup>19</sup> Because Avastin is a repackaged drug, Medicare reimbursement cannot be directly determined from publicly available ASP files and instead varies by Medicare Administrative Contractors (MAC) allowable amounts. Glasser's study "calculated the Medicare (Avastin) allowable required to equalize the dollar margin over cost with (Eylea), the highest cost alternative...The resulting Medicare allowable that would equalize the dollar margin over cost between the 2 drugs is \$125.78."

value-based or at-risk payment models impact which drug a patient is prescribed.<sup>20</sup> Clinicians must ultimately balance all these factors to prescribe the drug that is best suited to treat their patient.

As mentioned above, value-based or risk-bearing payment models where payments are tied to quality and health outcomes or where payments are capped at a maximum, may encourage administration of highly effective and less costly therapies. Recent research has demonstrated that making this prescribing switch would result in median savings to an individual Medicare Accountable Care Organization (ACO) of \$816,000 annually.<sup>21</sup> Further, that same research found that 25% of ACOs that met savings thresholds for Medicare missed out on qualifying for the shared savings bonus payment paid back to the ACO—but would have qualified for the bonus payment if more wet AMD patients attributed to that ACO were treated with Avastin over higher-cost therapies.<sup>22</sup>

## Patient Implications

*Note: Patient scenarios are meant to be illustrative only. The goal of these scenarios is not to provide exact prices, but to demonstrate the patient experience while accessing their medications and the ways these prices are impacted by upstream incentives. Prices are based on publicly available information when possible (and cited accordingly) and based on good faith estimates when prices were not available.*

In the scenarios below, we follow the journey of a 72-year-old male recently diagnosed with wet AMD, who has traditional Medicare and no Medicare Supplemental insurance. These scenarios will differ primarily on the financial structure and incentives of the care setting to treat the same medical condition with different drug therapies—Avastin versus Lucentis. This difference will result in substantially different drug costs for Medicare (total cost) and the patient (out-of-pocket).

### Scenario 1

The patient seeks care from an ophthalmology practice that is not participating in value-based or at-risk payment models. The ophthalmologist prescribes Lucentis, which has a higher drug price and reimbursement rate at ASP +6% (106% of drug cost).

The Medicare allowed amount for Lucentis is \$1,186. For a typical patient, the recommended course of treatment includes 10 injections per year, for a total of \$11,860. The patient would be responsible for their Part B deductible of \$226 (if not already met) plus a 20% coinsurance on the remaining cost. This comes to a total annual out-of-pocket spend of \$2,553.

### Scenario 2

The patient seeks care from an ophthalmologist who participates in a Medicare Shared-Savings ACO. If the Medicare ACO meets quality standards while also lowering health care spending for its attributed

<sup>20</sup>Davari, M., Khorasani, E., & Tigabu, B. M. (1970). Factors Influencing Prescribing Decisions of Physicians: A Review. *Ethiopian Journal of Health Sciences*, 28(6). <https://doi.org/10.4314/ejhs.v28i6.15>

<sup>21</sup> Muhlestein, D., Chopra, A., Lester, C., & Kitterman, K. (2020). ACOs and Age-Related Macular Degeneration (AMD): Practice Patterns Impact Savings. In *www.carejourney.com*. CareJourney. Retrieved March 22, 2023, from <https://carejourney.com/wp-content/uploads/2020/05/ACOs-and-AMD.pdf>

<sup>22</sup> Ibid.

population, the ACO qualifies to keep a portion of the savings that it generates. One value-based care strategy employed by the ophthalmologist is to prescribe Avastin over Lucentis, given Avastin's equivalent clinical efficacy and lower cost.

The Medicare allowed amount for Avastin is \$90. Effective treatment consists of 10 annual doses, totaling \$900. The patient would be responsible for their Part B deductible of \$226 (if not already met) plus a 20% coinsurance on the remaining cost. This comes to a total annual out-of-pocket spend of \$361.

Scenario 1	Scenario 2
Lucentis	Avastin
The Medicare allowed amount for Lucentis is \$1,186 per treatment.	The Medicare allowed amount for Avastin is \$90 per treatment.
Recommended course of treatment includes 10 injections per year, for a total of \$11,860.	Recommended course of treatment includes 10 injections per year, for a total of \$900.
Assuming the patient has not met their annual deductible, patient is responsible for deductible of \$226 plus 20% coinsurance on the remaining cost. This comes to a total annual out-of-pocket spend of \$2,553.	Assuming the patient has not met their annual deductible, patient is responsible for deductible of \$226 plus 20% coinsurance on the remaining cost. This comes to a total annual out-of-pocket spend of \$361.

## Conclusion

Avastin and Lucentis have demonstrated equal efficacy in the treatment of wet AMD, however Avastin has a significantly lower price point. Yet, the presence of this lower cost treatment alternative has not significantly impacted the price of Lucentis, nor has it diminished demand for the higher-priced product. There are several mechanisms driving this, including the unique scenario of Avastin being both an off-label treatment and it being produced by the same manufacturer, as well as payment incentives embedded within the health care system that reimburse providers at higher rates when more expensive drugs are administered. This has significant implications both for overall health care spending, as well as patient out-of-pocket costs.



## Acknowledgements

This research was made possible with support from Arnold Ventures.

### **ABOUT NORC**

NORC at the University of Chicago is an objective, nonpartisan research organization that delivers insights and analysis decision-makers trust. NORC partners with government, corporate, and nonprofit clients around the world to inform the critical decisions facing society. From groundbreaking longitudinal work like the General Social Survey to quick-turnaround studies that use our AmeriSpeak panel, NORC pursues hundreds of projects in any given year. In the process, we develop innovative research methods and analytical tools, advance principles of scientific integrity and collaboration, and support evidence-based policymaking and program development.