Estimating Public and Patient Savings From Basic Research—A Study of Optical Coherence Tomography in Managing Antiangiogenic Therapy

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• PURPOSE: To compare patient and Medicare savings from the use of optical coherence tomography (OCT) in guiding therapy for neovascular age-related macular degeneration (nvAMD) to the research investments made in developing OCT by the National Institutes of Health (NIH) and the National Science Foundation (NSF).

• DESIGN: Observational cohort study.

• METHODS: Main outcome measures were spending by Medicare as tracked by Current Procedural Terminology codes on intravitreal injections (67028), retinal OCT imaging (92134), and anti–vascular endothelial growth factor (anti-VEGF) treatment–specific J-codes (J0178, J2778, J9035, J3490, and J3590). These claims were identified from the Medicare Provider Utilization and Payment Data from the Centers for Medicare and Medicaid Services among fee-for-service (FFS) Medicare beneficiaries from 2012 to 2015; 2008 claims were acquired from the 100% FFS Part B Medicare Claims File. OCT research costs were determined by searching for grants awarded by NIH and NSF from inception to 2015. All costs and savings were discounted by 3% annually and adjusted for inflation to 2015 dollars.

• RESULTS: From 2008 to 2015, the United States government and nvAMD patients have accrued an estimated savings of $9.0 billion and $2.2 billion, respectively, from the use of OCT to guide personalized anti-VEGF treatment. The $9.0 billion represents a 21-fold return on government investment into developing the technology through NIH and NSF grants.

• CONCLUSIONS: Although an overall cost-benefit ratio of government-sponsored research is difficult to estimate because the benefit may be diffuse and delayed, the investment in OCT over 2 decades has been recouped many times over in just a few years through better personalized therapy. (Am J Ophthalmol 2018;185:115–122. © 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)

H EALTHCARE INNOVATION IS OFTEN ASSOCIATED with expensive new medical devices and drugs. For example, in 2000, new cancer drugs were priced from $5000 to $10 000 for a year of therapy. By 2012, prices averaged more than $100 000.[1] With drug prices increasing, technologies that can limit their use through appropriate personalization of care are becoming increasingly important.

Concurrent with the arrival of costly anti–vascular endothelial growth factor (anti-VEGF) biologics to treat neovascular ("wet") age-related macular degeneration (nvAMD), ophthalmologists adopted optical coherence tomography (OCT) to more efficiently use these effective, but expensive, drugs. OCT is the most frequently used imaging technique within the field and aids in the diagnosis and monitoring of diseases such as glaucoma, diabetic macular edema, and nvAMD.[2] The technology uses low-coherence interferometry to rapidly and noninvasively obtain 3-dimensional, micron-resolution images of the retina and choroid.[3,4] First popularized in ophthalmology, the use of OCT is expanding to other medical fields such as cardiology, neurology, gastroenterology, and dermatology, as well as nonmedical applications like industrial nondestructive testing and even art conservation.[5–10]

OCT is used frequently for the diagnosis and management of nvAMD, a potentially blinding condition in which abnormal blood vessels grow and leak fluid into the macula—the central part of the retina responsible for high-acuity vision.[11] Anti-VEGF drugs injected directly into the eye have successfully treated this condition.[12–16] There are 2 commonly used anti-VEGF drugs that are approved by the Food and Drug Administration (FDA) for this indication: ranibizumab (Lucentis; Genentech/ Roche, South San Francisco, California, USA) and

aflibercept (Eylea; Regeneron, Tarrytown, New York, USA). Both of these protein drugs are effective, but they are very expensive at approximately $2000 per dose. A third anti-VEGF drug, bevacizumab (Avastin; Genentech/Roche, South San Francisco, California, USA), is more economical at ~$70 per dose, but bevacizumab is not FDA approved for this purpose despite being the most frequently used drug for nvAMD.[17,18] With FDA-approved monthly injections for ranibizumab and bimonthly injections for aflibercept, the cost for treatment per year, per patient, is $24 000 and $12 000, respectively. Owing to the high cost of these 2 drugs and the increasing incidence of nvAMD as the population ages, ranibizumab and aflibercept accounted for more than 16% of Medicare Part B (drug) spending in 2013, at roughly $2.4 billion.[19]

Before OCT was part of routine clinical practice, physicians were limited to following a fixed, FDA-approved treatment schedule for anti-VEGF drugs to treat nvAMD. For example, the first, now rarely used, anti-VEGF drug to treat nvAMD, known as pegaptanib (Macugen; OSI Pharmaceuticals, Melville, New York), required 1 injection every 6 weeks. Now, OCT has enabled ophthalmologists to personalize anti-VEGF therapy. A patient's anti-VEGF schedule can be individually tailored based on the presence or absence of excess macular fluid, which can be detected with OCT imaging.

Personalized therapy is typically separated into 2 phases. The induction phase of treatment requires monthly injections until the excess macular fluid is resorbed and usually lasts 2–3 months. Then, in the much lengthier maintenance phase, the injection frequency can be reduced as long as OCT imaging shows that macular fluid has not reaccumulated. Two common OCT-guided treatment regimens are known as *pro re nata* (PRN), or "as needed," and "treat and extend" (TAE).[20–22] Although there is still some controversy over whether TAE and PRN regimens are as effective as monthly dosing, most studies have shown noninferiority for these maintenance protocols.[23–26] In the PRN regimen, a patient returns to the clinic once a month for OCT evaluation. If the OCT image indicates the absence of macular fluid, then the patient does not receive an injection; if fluid is present, then an injection is given. In the TAE regimen, when OCT imaging demonstrates resolution of macular fluid, an injection is still given and the visit interval is extended (eg, 2 weeks). For example, if the patient returns after 4 weeks and the fluid has resorbed, then an injection is given and the next appointment is scheduled for 6 weeks. At the 6-week visit, if no fluid is detected by OCT imaging, then an injection is given and the interval is extended to 8 weeks. If at any time OCT imaging identifies the recurrence of macular fluid, then an injection is given and the next appointment interval is decreased (eg, from 8 weeks to 6 weeks). The treatment interval continues to be decreased until the macula is fluid-free once again. TAE and PRN regimens were identified as the preferred practice pattern by 91% of surveyed retina specialists in 2015.[27]

By reducing the number of expensive anti-VEGF injections an nvAMD patient receives, these personalized-treatment protocols cut costs in the healthcare system and reduce the treatment burden on patients and clinicians.[28] Without the high-resolution, noninvasive macular imaging by OCT, these personalized regimens would be significantly more difficult to accomplish because physicians would have to treat according to the fixed-dosing regimen used in the pivotal trials or possibly rely on more invasive and expensive angiography to direct therapy. Here, we examine the cost savings enjoyed by patients and Medicare in treating nvAMD with OCT-enabled personalized-treatment protocols compared with a fixed-treatment schedule. We estimate the return on investment from this single application of the technology relative to the government funding of research in this area and reimbursement for use.

METHODS

- **DEFINITIONS:** Definitions used in our cost analysis are as follows:

(1) Fixed-regimen spending: Defined as total Medicare spending on anti-VEGF drugs and their delivery (ie, intravitreal injection) for the treatment of nvAMD in the absence of OCT. Assumes physicians would need to inject patients at the fixed monthly (ranibizumab) or bimonthly (aflibercept) schedule on the FDA label; bevacizumab is assumed to be delivered on a monthly schedule.

(2) Personalized-regimen spending: The estimated Medicare drug and delivery spending on OCT-guided anti-VEGF treatment for nvAMD, assuming that physicians use PRN and TAE regimens according to practice pattern surveys, and assuming that PRN and TAE regimens requires fewer injections according to our meta-analysis of major published studies.

(3) Actual Medicare spending: The actual Medicare drug and delivery spending on anti-VEGF therapy for nvAMD by Medicare. This is expected to be lower than the above hypothetical calculations (see Discussion).

(4) OCT-related government investment: Limited to the cost of reimbursing clinicians for each OCT image on nvAMD patients, and funding for the development of OCT technology and its clinical applications by the National Institutes of Health (NIH) and National Science Foundation (NSF).

(5) Neovascular AMD patient savings: Savings nvAMD patients experience from the use of OCT in managing their disease, stemming from the 20% copay for each anti-VEGF injection and OCT image under Medicare Part B. For simplicity, assumes the absence of supplementary Medigap insurance.

• STUDY DESIGN: We used the free-to-access Medicare Provider Utilization and Payment Data 2012–2015: Physician and Other Supplier Public Use Files (Physician and Other Supplier PUF), and previously published data from the 2008 100% fee-for-service (FFS) Part B Medicare Claims File, both from the Center for Medicare and Medicaid Services (CMS), as our primary sources of Medicare data.[29,30] Similar databases from 2009 to 2011 were not used in this analysis because they are not publicly available. The files contained information on all Medicare Part B claims provided to FFS Medicare beneficiaries, representing ∼70% of the Medicare beneficiary population. Medicare Advantage beneficiaries are not included in these datasets.[31]

All anti-VEGF drug claims were identified by treatment-specific J-code: J9035, J3490, and J3590 for bevacizumab; J2778 for ranibizumab; J0178 for aflibercept. Though J3490 and J3590 are unclassified drug and biologic J-codes, respectively, previous work has shown that these codes are overwhelmingly paired with International Classification of Diseases (ICD-9) code 362.52—exudative senile macular degeneration.[18,29] Because all bevacizumab codes are used in reimbursement for other indications (eg, cancer), codes for 2012 through 2015 were limited by provider type (ie, ophthalmology). Codes J3490 and J3590 were further limited to providers with an average Medicare-allowed payment amount of less than 2 times the Medicare reimbursement rate—equal to the Average Sales Price (ASP) + 6%.[17,32] The total number of patients receiving each drug in 2012–2015 was found by summing each provider's count of unique beneficiaries paired with an anti-VEGF J-code. The number of patients using ranibizumab and bevacizumab in 2008 was found in the literature and assumed to increase linearly to 2012 (Table S1; Supplemental Material available at AJO.com).[29]

Spending on intravitreal injection (delivery) of anti-VEGF drugs was identified by Current Procedural Terminology (CPT) code 67028. Previous work has shown that CPT code 67028 is overwhelmingly paired with ICD-9 code 362.52—exudative senile macular degeneration.[18]

We obtained consumer price index data to adjust government research expenditures and medical care consumer price index data to adjust Medicare spending for inflation to 2015 dollars.[33] Starting from the earliest investment in OCT (1995), we discounted all future expenditures and savings by 3% annually to account for the time value of money.[34]

• FIXED-REGIMEN SPENDING: Fixed-regimen Medicare spending on anti-VEGF drugs and their delivery were calculated using the number of nvAMD patients on each drug in a given year, the Medicare reimbursement rate for each drug (ASP + 6%) and injection, and the FDA-approved number of injections per year (12 for bevacizumab and ranibizumab, 6 for aflibercept). Owing to sequestration, Medicare reimbursement was ASP + 4%

in 2013.[17,32,35] Total fixed-regimen spending on each anti-VEGF drug and its delivery was found by summing all years.

• PERSONALIZED-REGIMEN SPENDING: We performed a meta-analysis of the literature to determine the number of injections per year an average nvAMD patient would receive on the PRN or TAE treatment protocols during the maintenance phase of his or her therapy. The maintenance phase is defined as the period after the induction phase, when newly diagnosed patients receive a series of 1–3 monthly anti-VEGF injections to bring the disease under control. The meta-analysis was performed by a PubMed search using the terms "(("PRN" or "treat and extend" or "inject and extend" or "as needed") AND (ranibizumab or aflibercept or bevacizumab) AND AMD)." Articles that had patients undergoing intravitreal injections of 0.5 mg ranibizumab, 1.25 mg bevacizumab, or 2.0 mg aflibercept using TAE or PRN regimens for treatment of nvAMD were included. All evaluated papers were in English and had their references to related articles examined. Manuscripts with non-treatment-naïve patients, or with patients suffering nvAMD secondary to another condition or receiving anti-VEGF treatment in conjunction with another procedure, were excluded. Of the initial 121 papers that met our search criteria, 38 were included in the meta-analysis ("Supplemental Material 1: List of references used in meta-analysis" and Table S3; Supplemental Material available at AJO.com).

We estimated the percentage of Medicare patients treated with TAE or PRN protocols by using survey data from retinal specialists (Table S4; Supplemental Material available at AJO.com).[27,36,37] We calculated the protocol-independent number of injections a Medicare beneficiary received of a drug in a given year using the meta-analysis and survey data ("Supplemental Material 2: Calculation of protocol-independent number of anti-VEGF injections per drug, per year"; Supplemental Material available at AJO.com). The protocol-independent number of injections was then applied to determine the personalized-regimen Medicare spending on anti-VEGF drugs and their delivery by multiplying by the fixed-regimen drug and delivery spending total, and dividing by the percentage of patients treated under PRN or TAE protocols.

• ACTUAL MEDICARE SPENDING: Actual Medicare spending for ranibizumab (J2778), aflibercept (J0178), and intravitreal injection of anti-VEGF drugs (67028) was found using the Medicare Part B National Summary Data File.[38] Medicare spending on bevacizumab provided in this dataset could not be used because the codes are not limited to the treatment of nvAMD. Instead, the Physician and Other Supplier PUF dataset was used to find the actual Medicare spending for ophthalmic use of bevacizumab from 2012 through 2015 by multiplying a provider's line service count by the average Medicare-allowed
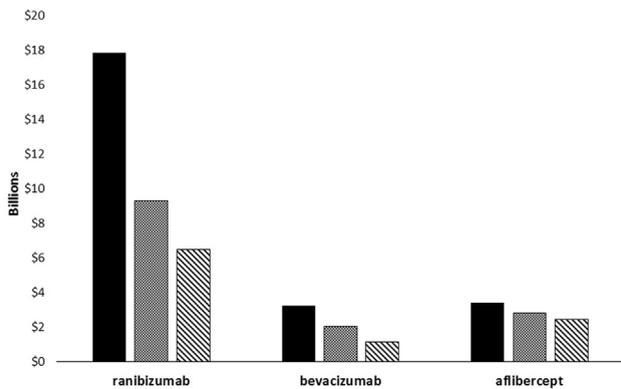
FIGURE 1. Hypothetical vs actual drug and delivery expenditures on anti–vascular endothelial growth factor therapy for neovascular age-related macular degeneration, 2008–2015. Fixed-regimen spending is shown in black, personalized-regimen spending is depicted with a cross-hatch pattern, and actual spending is shown in a striped pattern. Aflibercept spending is limited to 2013–2015.

payment and summing. Actual Medicare spending on ophthalmic use of bevacizumab in 2008 across all J-codes was previously published and assumed to increase linearly to 2012 (Table S2; Supplemental Material available at AJO.com).[29] Injection costs were distributed based on the percentage of patients using each anti-VEGF drug.

• OPTICAL COHERENCE TOMOGRAPHY–RELATED GOVERNMENT INVESTMENT: Research spending by NIH and NSF on OCT was determined via an NIH RePORTER and NSF Award search using the term "optical coherence tomography" in the title and abstract of every grant from inception to 2015.[39,40] Spending on OCT imaging reimbursement was determined by calculating the number of patients under PRN and assuming they would receive imaging with OCT once a month. Patients under TAE were assumed to receive imaging every time they received an injection. The total number of images was then multiplied by the allowed charge for OCT, which was found using the Healthcare Common Procedure Coding System (HCPCS) code 92135 for 2008–2010 and 92134 for 2011–2015.[35]

• NEOVASCULAR AGE-RELATED MACULAR DEGENERATION PATIENT SAVINGS: Copay by nvAMD patients for their anti-VEGF therapy on a fixed-injection schedule was calculated for each drug using the FDA-approved number of injections per year.[41] Copay by nvAMD patients on a personalized-injection schedule was determined for each drug using the average number of injections and OCT images a patient received. The average number of injections was found by averaging the protocol-independent number of injections across all years (see personalized-regimen spending section). The average number of OCT images was determined by assuming patients under a PRN protocol received 1 scan per month, whereas patients under a TAE protocol received 1 scan per injection. Patient savings was found by subtracting the cost of treatment on a personalized-injection schedule from the cost on a fixed-injection schedule.

RESULTS

• HYPOTHETICAL VERSUS ACTUAL MEDICARE SPENDING: Our analysis is based on FFS Medicare claims, which represents ∼70% of the Medicare beneficiary population (∼37.4 million people in 2015), from 2008 and 2012–2015.[29–31] Where necessary, we assumed linear increases in patient totals and anti-VEGF drug spending from 2008 to 2012 (see Methodology). Figure 1 consists of data for ranibizumab and bevacizumab from 2008 to 2015 and for aflibercept from 2013 to 2015. Fixed-regimen spending over these time frames for ranibizumab, bevacizumab, and aflibercept was calculated to be $17.8 billion, $3.2 billion, and $3.4 billion, respectively.

Based on our meta-analysis of the literature and practice pattern survey data of retinal specialists (Tables S3 and S4 in the Supplemental Materials), we calculated personalized-regimen spending by Medicare to be $9.3 billion, $2.0 billion, and $2.8 billion for ranibizumab, bevacizumab, and aflibercept, respectively.[27,36,37] Compared to the fixed-regimen spending totals, OCT-guided personalized-treatment regimens enabled Medicare to save $10.3 billion on anti-VEGF therapy costs for nvAMD from 2008 to 2015. Fewer injections of ranibizumab are responsible for 83% of the calculated savings.

Actual Medicare spending was $6.5 billion for ranibizumab, $1.1 billion for bevacizumab, and $2.4 billion for aflibercept, for a total of $10.0 billion. This is $4.1 billion (29%) less than our calculated personalized-regimen spending total (Figure 1).

• GOVERNMENT INVESTMENT VERSUS SAVINGS: Figure 2 highlights 3 government budget categories related to OCT and its use in anti-VEGF therapy for nvAMD: Medicare savings from fewer drug injections ($10.3 billion, Figure 1); reimbursement on OCT imaging used to monitor nvAMD; and the investment made by NIH and NSF to develop OCT from an academic laboratory curiosity to an effective clinical tool. Using the meta-analysis and survey data, we calculated that the cost of using OCT imaging to guide anti-VEGF treatment decisions from 2008 to 2015 was $0.8 billion. NIH and NSF spent ∼$0.4 billion on basic and clinical research toward the development of OCT from 1995 to 2015.[39,40] After summing these 3 budget categories, the United States government has saved $9.0 billion, a return on its investment in OCT research of ∼2100%.
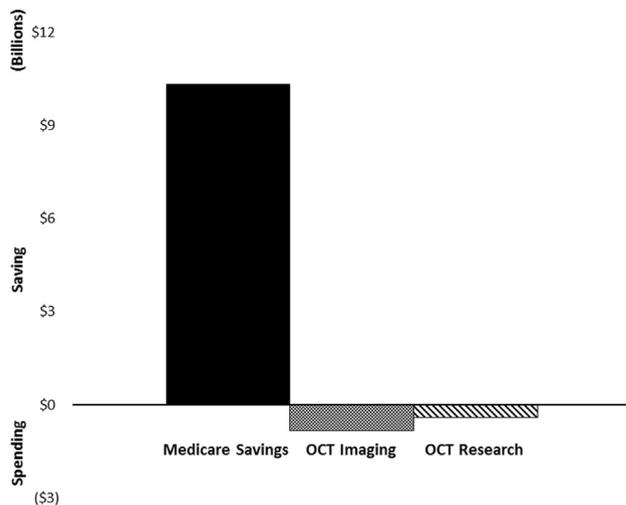
FIGURE 2. Government investment in optical coherence tomography (OCT) vs savings from OCT-guided anti–vascular endothelial growth factor therapy for neovascular age-related macular degeneration. Medicare savings is from 2008 to 2015 owing to reduced drug and delivery costs. Medicare spending on reimbursing clinicians for OCT imaging is from 2008 to 2015, while research spending on OCT by the National Institutes of Health and National Science Foundation is from 1995 to 2015.

● PATIENT SAVINGS: Anti-VEGF drugs, their injection, and OCT imaging are covered under Medicare Part B, which requires beneficiaries to copay 20% of the Medicare-approved amount in the absence of supplementary Medigap insurance.[41,42] On a fixed-injection schedule, patients on ranibizumab, bevacizumab, and aflibercept would have an average copay of $3693, $342, and $1568, respectively, per year for their anti-VEGF therapy from 2008 to 2015 (Table). On an OCT-guided, personalized-injection schedule, annual patient copay spending on treatment was reduced by $1918 for ranibizumab, $94 for bevacizumab, and $306 for aflibercept. Taken together, OCT has enabled nvAMD patients to save over $2.2 billion by avoiding 17.7 million anti-VEGF injections from 2008 to 2015.

DISCUSSION

OUR ANALYSIS SHOWS THAT INNOVATIVE TECHNOLOGY can significantly reduce healthcare costs and improve patient care. OCT-enabled personalized-treatment protocols allow clinicians to manage their patients' nvAMD using significantly fewer injections of anti-VEGF agents than approved by the FDA, which saves patients and taxpayers billions of dollars. In addition, patient burden is reduced through fewer trips to the clinic and needles into the eye, while physicians benefit from having timely information on treatment efficacy with which to advise the patient and then personalize management decisions.

The worldwide impact of OCT on human health and healthcare delivery would have been much slower to evolve, if at all, without long-term government research funding. Although the first paper to use the term "optical coherence tomography" was published in 1991, widespread adoption of the technology in the clinic occurred only after an additional decade of government-supported development.[4] Our calculations show that this investment over decades has been repaid 21-fold by savings to Medicare from fewer injections of anti-VEGF drugs over just 8 years. Meanwhile, OCT manufacturing has grown to be a sizable industry in its own right, supporting thousands of private-sector jobs through an instrument market with a revenue of ∼$750 million a year.[2,43]

Our analysis has several limitations that could lead to over- or underestimation of the cost savings from OCT-guided anti-VEGF treatment regimens. Our calculations assumed full compliance with either fixed or personalized regimens. Outside of clinical trial settings, studies have suggested that patients may be undertreated.[25] Reasons why patients may miss injections include intolerance of discomfort, inconvenience, disappointment by failure to recover useful vision, other pressing medical issues, and inability to secure transportation or afford the copay. Undertreatment likely contributes to why actual Medicare spending on anti-VEGF medication is lower than our calculated costs. Switching drugs may also lower actual Medicare spending compared to our calculations, which assume patients stick with the same drug throughout the year. Our calculations used practice patterns based on a survey of retina specialists, which may not accurately represent the actual practice pattern on a per-patient basis. Our cost-saving calculations were limited to actual and estimated FFS Medicare claims data from 2008 through 2015; FFS Medicare claims data are not yet available for 2016. Furthermore, we did not have data for the 30% of Medicare beneficiaries using Medicare Advantage or any patient under private insurance. Aflibercept was approved by the FDA in late 2011, but it did not receive its own J-code until 2013. Clinicians using the drug in 2012 likely filed it under the unclassified biologics code J3590, which is also used for bevacizumab. Because it was impossible separate usage of the 2 drugs under the same code, we limited our patient count to medical practices with an average Medicare reimbursement of 2 times the ASP + 6% of bevacizumab. Thus, injections of aflibercept in 2012 were not captured in this analysis. For these reasons, the full savings from OCT may be substantially higher. For simplicity, we assumed that all Medicare patients did not have Medigap insurance. As many patients do have supplementary insurance, our patient-savings totals are likely overstated. Finally, we restricted our analysis to OCT usage related to nvAMD only. OCT and anti-VEGF agents are also used in the treatment of retinal vein occlusion and diabetic macular edema, but FDA approvals for these indications were recent.[44,45] There is not yet sufficient information on the

TABLE. Medicare Beneficiary Copay Spending for Anti-Vascular Endothelial Growth Factor Therapy on Fixed- or Personalized-Injection Schedules

	Drug		
	Ranibizumab	Bevacizumab	Aflibercept
Number of patients	995 396	2 020 091	446 915
Average number of annual injections on personalized-injection schedule	5.6	6.7	4.7
Drug copay cost	$288	$9	$242
OCT imaging copay cost	$6	$6	$6
Injection copay cost	$20	$20	$20
Fixed-injection schedule annual patient copay	$3693	$342	$1568
Personalized-injection schedule annual patient copay	$1776	$247	$1262
Annual patient savings	$1918	$94	$306
Total cohort savings	$1 908 804 551	$190 892 790	$136 910 501
Total injections avoided	6 370 534	10 706 482	580 990

OCT = optical coherence tomography.

evolving practice patterns for us to calculate the cost savings associated with the use of OCT in making treatment decisions for these conditions. In addition to anti-VEGF therapy, OCT is used to guide treatment in a wide range of retinal and optic nerve diseases with potential for cost savings by avoiding unnecessary surgery or drugs. OCT is also used outside the eye, such as in the monitoring and placement of coronary stents.[8] Although evaluation of these examples and others is beyond the scope of this analysis, their exclusion suggests our calculations represent a lower boundary on the savings (and intangible benefits) attributable to OCT.

Contrary to many of today's headlines that highlight the cost of high-tech medicine, there exist examples of innovation—like OCT—that make healthcare more affordable. Funded by modest investments in research by taxpayers over 20 years, such innovation has paid for itself and continues to yield billions of dollars in healthcare savings for patients and insurers. We hope that highlighting the impact of OCT on patient health and public spending encourages further government investment in biomedical research—even in these budget-constrained times.

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