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# NBER NATIONAL BUREAU OF ECONOMIC RESEARCH BULLETIN ON AGING AND HEALTH

## The Effects of Stimulant Medications for ADHD

In recent years, mental disabilities have overtaken physical disabilities as the leading cause of activity limitations for children. One of the most prevalent mental conditions affecting children is Attention Deficit Hyperactivity Disorder (ADHD). As the number of children diagnosed with the condition has increased, so too has the use of stimulant medications such as Ritalin to treat the condition. In 2011, eleven percent of U.S. children ages 4 to 17 had ever been diagnosed with ADHD and more than half were taking stimulant medication.

Although stimulant medication is recommended as a treatment for ADHD by the National Institute of Mental Health, its use remains controversial. One concern is short- and long-term side effects, which may include physical effects such as decreased appetite, insomnia, and growth deficits as well as mood changes such as anxiety and depression. Adding to the unease is the relative lack of evidence on the educational benefits of medication use. Solid evidence can be difficult to come by because few studies follow children long enough to observe longrun outcomes and treatment decisions are made by families, raising the possibility that any relationship between medication use and outcomes may reflect family characteristics rather than the causal effect of treatment.

In their recent study "Do Stimulant Medications Improve Educational and Behavioral Outcomes for Children with ADHD?" (NBER Working Paper 19105), researchers Janet Currie, Mark Stabile, and Lauren E. Jones aim to help fill this gap.

The authors examine the effect of a policy change in Quebec, Canada that greatly expanded insurance coverage for prescription medications. Using data from the National Longitudinal Survey of Canadian Youth, the authors follow a sample of children from 1994 to 2008, enabling them to observe long-term educational outcomes. Their data includes an assessment of ADHD symptoms for all respondents, avoiding the issue that some types of children may be more likely to have been diagnosed with ADHD, as well as information on medication use at each survey wave until the children are 15 years old.

The policy change is a 1997 law that made prescription drug insurance coverage mandatory in Quebec. The law established a public plan for those without drug insurance, with premiums scaled according to income and collected with the provincial income tax to ensure compliance. The enactment of the law led to a rapid increase in drug coverage, from 55 percent of the population in 1996 to 84 percent in 1998, rising to 89 percent by 2003. In the rest of Canada, by contrast, drug coverage rose more slowly and gradually, from 65 percent in 1996 to 76 percent in 2003.

The authors first examine whether the policy change led to an increase in the use of stimulant medication (Ritalin) in Quebec, relative to the rest of Canada. Naturally, medication use may have risen in the rest of Canada during this time as well, due to the gradual spread of insurance or greater acceptance of this treatment. Therefore, the authors use a triple You can sign up to receive new Bulletin issues and can access current and past issues electronically, at no cost, by going to: http:// www.nber.org/aginghealth

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difference specification that focuses on those children most likely to benefit from increased stimulant use in response to the policy change: those with the worst initial ADHD symptoms.

The authors find that the law increased the use of Ritalin in Quebec by 1.15 percentage points for a child with an average level of ADHD symptoms and by even more for children with more severe symptoms. Since the baseline use of Ritalin in the sample is about 2 percent, this represents a reasonably large effect.

Next, the authors turn to exploring the effect of the law and resulting increase in medication use on other outcomes. They find that behavioral outcomes are negatively affected in the medium run, as the law is associated with an increase in the probability of grade repetition, lower math scores, and a deterioration in relationships with parents.

Finally, the authors explore the long-

term effects of the policy. Consistent with the medium-term findings, the policy is associated with an increased probability of suffering from depression and a decreased probability of post-secondary education in girls. The authors employ a number of checks to verify that their results are not driven by greater access to drugs to treat physical health conditions, other contemporaneous policy changes, or chance.

In short, the evidence suggests that the increased access to stimulant medication that resulted from Quebec's insurance law had some negative effects on behavioral outcomes, consistent with known side effects, and did not improve academic outcomes. The authors suggest that one possible explanation for this surprising finding is that "medication is a substitute for other types of cognitive and behavioral interventions that might be necessary to help the child learn. By making children less disruptive, ADHD medication could decrease the attention that they receive in the average classroom and reduce the probability of receiving other services."

The authors caution that their study "does not shed light on the question of whether optimal medication use would be beneficial." Many children in their sample appear to take medication in a haphazard manner and the dose taken may not be calibrated to achieve optimal results. "What our results do speak to is the effect of a large increase in the use of ADHD medications in a community, given the usual standard of care available to Quebec children. In Quebec, as in the U.S., any doctor can prescribe Ritalin, and it is not necessary to have expertise treating ADHD. Hence it is not surprising that some use is sub-optimal. Our results suggest that observers of the large increases in the use of medication for ADHD in the U.S. are right to be concerned."

The authors acknowledge funding from the Canadian Institutes of Health Research.

### Regional Variation in Health Care: Physician Beliefs or Patient Preferences?

Health care analysts have long been puzzled by the existence of substantial regional variation in health care expenditures. In the Medicare population, for example, regional averages of priceadjusted per-patient expenditures range from under \$7,000 to nearly \$14,000, differences that cannot be explained by regional variation in patient illness or income.

In "Physician Beliefs and Patient Preferences: A New Look at Regional Variation in Health Care Spending" (NBER Working Paper 19320), researchers David Cutler, Jonathan Skinner, Ariel Dora Stern, and David Wennberg explore the causes of this phenomenon.

There are a number of possible explanations. On the demand side, patient preferences may play a role. Some patients facing a serious illness may prefer to try every possible treatment while others would prefer palliative care and comfort. If patients with similar preferences are grouped in the same geographic area, this could generate regional variation in spending. Differences in price and income, by contrast, are unlikely to be important in the Medicare context, where all patients essentially have access to the same, fairly generous insurance.

There are also possible supply-side explanations. Monetary incentives are one, as physicians may encourage patients to consume more health care if doing so raises physician income. But this alone cannot explain the observed regional variation in spending, since reimbursement rates do not vary much across areas. Alternatively, physicians may have differing beliefs about the efficacy of certain treatments. If physician beliefs are geographically correlated — for example, because many physicians in a given area received their training at the same medical school — this could create regional variation in spending.

The approach employed by the authors to distinguish between these competing hypotheses involves using "strategic surveys" that employ clinical vignettes to elicit information on physician beliefs and patient preferences. The authors analyze survey responses of over 1300 primary care physicians and cardiologists in 64 Hospital Referral Regions (HRRs). The vignettes present the physicians with hypothetical elderly patients suffering from conditions such as heart failure and ask the physicians how they would treat them. The authors characterize physicians as "cowboys" if they consistently and unambiguously recommend intensive care beyond clinical guidelines and as "comforters" if they consistently recommend palliative care for the severely ill.

On the patient side, the authors consider the preferences of over 1400 Medicare beneficiaries surveyed in the same set of HRRs. Respondents were asked questions relating to their preferences for unnecessary care and end-of-life care, such as whether they would like a test or cardiac referral even if their primary care physician did not think they needed one and whether they would want to be put on a respirator if it would extend their life for a short time.

There are a several key findings from these surveys. On the patient side, nearly three-quarters of patients would want an unnecessary test and over half would want an unneeded referral; in an end-oflife situation, about half would choose comfort over aggressive treatment. The physician survey revealed that nearly onequarter of cardiologists would recommend more frequent follow-up visits than called for in current guidelines, while less than 1 percent would recommend fewer. By contrast, only 9 percent of primary care physicians would recommend more frequent follow-up visits than called for in practice guidelines and an equal number would recommend less frequent visits. There is substantial variation in all of these measures across HRRs, suggesting they could contribute to regional variation in spending.

To explore this hypothesis, the authors match their physician and patient survey data to Medicare expenditure data, focusing on expenditures in the last two years of life for beneficiaries with various fatal illnesses, and estimate models

relating HRR-level expenditures to the survey measures. They find that average expenditures in an HRR rise with the percent of physicians that are cowboys—i.e. those that recommend more intensive care than clinical guidelines would suggest—and fall with the percent that are comforters—i.e. those who recommend more low-cost, palliative care for very sick patients. The estimated effects are large: a 10 percentage point increase in cowboys raises expenditures by 7.5 percent, while a 10 point increase in comforters lowers expenditures by 4.1 percent. A 10 percentage point increase in physicians recommending more frequent care than guidelines suggest is associated with an increase of 9.5 percent in end-of-life spending. However, the authors find a very modest relationship between regional patient preference measures and spending.

Next, the authors explore what fac-

tors affect physician beliefs. Older physicians are more likely to be cowboys and to recommend extra follow-up care, while men are less likely to be comforters. Board certification, a marker of quality, is associated with a reduced likelihood of being a cowboy or recommending more frequent follow-up care, consistent with earlier work showing that lower quality physicians spend more treating identical patients. Physicians in solo or 2-person practices are more likely to be cowboys, as are cardiologists who report that they accommodate the wishes of referring physicians. Yet the lion's share of differences in how doctors say they would treat patients are not explained by financial, organizational, or other factors, and likely results from differences in beliefs.

Finally, the authors use their results to estimate that, were physicians to follow professional guidelines, end-of-life Medicare expenditures would be 36 percent less, and overall expenditures would be 17 percent less. These results lead them to conclude "individual physician beliefs regarding treatment options can explain a substantial degree of regional variation in utilization among the U.S. Medicare population." While the authors note that economic incentives are not unimportant, the presence of large regional variation in environments where economic incentives are muted is consistent with a large role for physician beliefs. As yet, we know little about how physician beliefs arise and can be shaped, making this a productive area for future work.

The authors acknowledge funding from the National Institute on Aging (grants T32-AG000186-23 and P01-AG031098 to the NBER and P01-AG019783 to Dartmouth) and from the Laboratory for Economic Applications and Policy (LEAP) at Harvard University to Skinner.

### The Recent Slowdown in Health Care Spending: Explanations and Predictions

Health care expenditures in the U.S. have grown faster than GDP for many decades, leading to concerns about the long-term sustainability of public and private insurance programs. Yet over the past decade, the growth in health care spending has moderated, leading to much speculation about whether the era of rapidly rising costs may finally be coming to an end or whether this is merely a short-term phenomenon driven by the recent recession.

In "Is This Time Different? The Slowdown in Health Care Spending" (NBERWorkingPaper 19700), researchers Amitabh Chandra, Jonathan Holmes, and Jonathan Skinner explore the causes of the recent slowdown and ask whether it is likely to continue.

The authors begin by noting that the recent slowdown in health care spending and utilization is not the first such episode, as health care costs grew more slowly than GDP in the early 1990s before resuming more rapid growth later that decade. They also point out that the U.S. health care system is an aggregation of three different systems — private insurance, Medicare, and Medicaid. These systems differ in their means of controlling costs, and the authors argue that it is necessary to look at trends in utilization, prices, and technological development within each system in order to understand past and future spending growth.

What role has the recession played in the spending slowdown? Studies estimating the relationship between GDP growth and health care spending have yielded a wide range of results. One explanation for this, the authors suggest, is that different components of health care spending are affected differently by an economic downturn. Medicare is largely insulated from recession-related budget cuts, and the authors show that there is no empirical relationship between Medicare expenditures and GDP growth. Private health insurance spending, by contrast, is strongly associated with GDP growth. Medicaid spending is in between, as policy makers tend to cut provider reimbursements and limit covered services when state government budgets are tight, but economic downturns also make more people eligible for Medicaid coverage. A study cited by the authors suggests that there remains a roughly 1 percentage point drop in health care costs even after accounting for the effect of the weak economy.

Another leading explanation for the slowdown in spending is the Affordable Care Act (ACA). As the slowdown predates the ACA's passage by several years, the ACA is unlikely to be the only reason that cost growth has moderated, but the law may have been a factor over the past few years and its effect could potentially grow in the future. One change that is already being phased in is lower payments to Medicare Advantage plans and providers and to hospitals with poor quality indicators. However, other provisions of the ACA, such as the extension of insurance to dependents up to age 26, and the expansion of Medicaid coverage, are likely to increase costs. In the future, the law's support of Accountable Care Organizations (ACOs), which offer a new way of organizing and reimbursing health care, may also save money, but this is as yet largely untested. In sum, more time is needed before

the ACA's effect on costs can be definitively determined.

Moving away from these usual suspects, the authors identify three other explanations as leading contributors to the cost slowdown. The first is higher patient cost-sharing, as more employers offer high-deductible insurance plans and the share of the working-age population that is uninsured continues to climb. The second is state-level efforts to curb Medicaid cost growth by cutting provider fees and limiting access to specialists and other high-cost services. The third is a decrease in pace of technological growth, particularly for the Medicare population. Drug spending moderated and even fell in 2012, as generic drugs claimed a larger share of the market and relatively few new blockbuster drugs were introduced. Among Medicare patients, the use of some popular treatments including heart stents, coronary bypass surgery, and hip and knee replacements declined. The authors estimate that cuts to Medicaid providers reduced the annual growth in health care spending by 0.5%, while decreased utilization due to higher costsharing for the privately insured and access restrictions for Medicaid patients reduced spending by a further 0.4%.

Will health care costs continue to

grow at a similar rate or revert to long-term trends? The authors use three approaches to explore this question. The first is to examine what new treatments are in the technology pipeline. Historically, technological innovation has been the largest contributor to cost growth, thus future innovations will play a key role in future cost growth. While drug development has been slow in recent years, there are new treatments for heart disease and cancer that are likely to add substantially to costs in the coming years. Some, such as proton beam therapy for prostate cancer patients, have not been proven to be effective yet are very expensive; each new proton beam facility costs hundreds of millions of dollars. The authors suggest that, compared to other countries, the U.S. is more likely to adopt high cost treatments with little proven value, as Medicare is legislated to pay for any treatments that do not cause harm and private insurers often follow suit.

Second, the authors look at trends in the value of health care stocks, and conclude there is little evidence that the market believes that the rate of technological progress is slowing. Third, the authors use their own estimates of future growth in prices and utilization as well as the effect of the aging population to predict an annual real growth in health care spending of 1.2 percent above GDP growth. This is lower than the historical growth rate and relatively similar to the current rate. At this rate, the health care sector would grow from 17.9 percent of GDP today to 23 percent in 2032.

As the authors note, this estimate "is not a cause for celebration," as growth at this rate would require some combination of tax increases or drastic cuts in non-health care spending to continue to be able to fund Medicare and Medicaid. But "more optimistically, we also recognize that the structure and balance of power among providers and insurers may be undergoing fundamental changes...Similarly, accountable care organizations in Medicare and the move towards bundled payments could encourage providers to switch from expensive and unproven therapies to cheaper ones." In the end, the authors caution that any policy solutions "must be concerned about the long-term technology pipeline that will continue to deliver new technology with large price tags but with the potential for very modest health benefits."

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### **NBER Profile:** Sherry Glied

Sherry Glied is Dean of New York University's Robert F. Wagner School of Public Service and a Research Associate in the NBER's Programs on Health Care, Health Economics, and Children. From 1989–2013, she was Professor of Health Policy and Management at Columbia University's Mailman School of Public Health.

Professor Glied served as Assistant Secretary for Planning and Evaluation at the U.S. Department of Health and Human Services from 2010 through 2012. She had previously served as Senior Economist for health care and labor market policy on the President's Council of Economic Advisers in 1992–1993, under Presidents Bush and Clinton, and participated in the Clinton Health Care Task Force. She is a member of the Institute of Medicine of the National Academy of Sciences, and of the National Academy of Social Insurance, and has been a member of the Board of AcademyHealth, and of the Congressional Budget Office's Panel of Health Advisers.

Professor Glied received a B.A. in economics from Yale University, an M.A. in economics from the University of Toronto, and a Ph.D. in economics from Harvard University.

Dr. Glied's principal areas of research are in health policy reform and mental health care policy. She is the author of a book on health care reform, *Chronic Condition*, the co-author (with Richard Frank) of *Better But Not Well: Mental Health Policy in the U.S. since* 1950, and the co-editor (with Peter C. Smith) of *The Oxford Handbook of Health Economics.* 



Glied lives in New York City with her husband, daughter, and son. She is an avid sculler and an opera fan.

## Abstracts of Selected Recent NBER Working Papers

#### WP 19216

#### David Neumark, Patrick Button Did Age Discrimination Protections Help Older Workers Weather the Great Recession?

We examine whether stronger age discrimination laws at the state level moderated the impact of the Great Recession on older workers. We use a difference-in-difference-in-differences strategy to compare older workers in states with stronger and weaker laws, to their younger counterparts, both before, during, and after the Great Recession. We find very little evidence that stronger age discrimination protections helped older workers weather the Great Recession, relative to younger workers. The evidence sometimes points in the opposite direction, with stronger state age discrimination protections associated with more adverse effects of the Great Recession on older workers. We suggest that this may be because during an experience like the Great Recession, severe labor market disruptions make it difficult to discern discrimination, weakening the effects of stronger state age discrimination protections, or because higher termination costs associated with stronger age discrimination protections do more to deter hiring when future product and labor demand is highly uncertain.

#### WP 19218

#### Thomas Buchmueller, Sean Orzol, Lara D. Shore-Sheppard

#### The Effect of Medicaid Payment Rates on Access to Dental Care Among Children

Historically, low Medicaid reimbursement rates have limited the willingness of health care providers to accept Medicaid patients, leading to access problems in many communities. This problem has been especially acute in the case of dental care. We combine data from several sources to examine the effect of payment rates on access to dental care among children on Medicaid and on dentists' participation in the program. The main utilization analysis is based on data from the Survey of Income and Program Participation combined with data on Medicaid payment rates and private market dental fees for the years 2001 to 2010. Conditioning on state fixed effects, we find a modest, but statistically significant, positive relationship between Medicaid payment rates and several measures of dental care utilization. We find a comparable effect in aggregate data reported by state Medicaid programs. The most likely explanation for this result is that higher fees increase the number of dentists that accept Medicaid patients. We test this hypothesis directly using data from annual surveys of dentists conducted by the American Dental Association between 1999 and 2009. The results indicate a positive and statistically significant effect of Medicaid payment rates on whether a dentist treats any publicly insured patients and the percent of the practice's patients who have public insurance. Similar to the utilization results, the magnitude of the effect is relatively small. As a result, the estimates imply that increasing Medicaid payments to the level of private market fees would increase access to care, but the incremental cost of the additional visits induced would be very high.

#### WP 19247

#### Mireilla Jacobson, Tom Y. Chang, Joseph P. Newhouse, Craig C. Earle, M.D. Physician Agency and Competition: Evidence from a Major Change to Medicare Chemotherapy Reimbursement Policy

We investigate the role of physician agency and competition in determining health care supply and patient outcomes. A 2005 change to Medicare fees had a large, negative impact on physician profit margins for providing chemotherapy treatment. In response to these cuts, physicians increased their provision of chemotherapy and changed the mix of chemotherapy drugs they administered. The increase in treatment improved patient survival. These changes were larger in states that experienced larger decreases in physician profit margins. Finally while physician response was larger in more competitive markets, survival improvements were larger in less competitive markets.

### WP 19287 Christopher J. Ruhm Recessions, Healthy No More?

Using data from multiple sources, over the

1976-2009 period, I show that total mortality has shifted over time from strongly procyclical to being essentially unrelated to macroeconomic conditions. The relationship also shows some instability over time and is likely to be poorly measured when using short (less than 15 or 20 year) analysis periods. The secular change in the association between macroeconomic conditions and overall mortality primarily reflects trends in effects for specific causes of death, rather than changes in the composition of total mortality across causes. Deaths due to cardiovascular disease and transport accidents continue to be procyclical (although possibly less so than in the past), whereas strong countercyclical patterns of cancer fatalities and some external sources of death (particularly those due to accidental poisoning) have emerged over time. The changing effect of macroeconomic conditions on cancer deaths may partially reflect the increasing protective influence of financial resources, perhaps because these can be used to obtain sophisticated (and expensive) treatments that have become available in recent years. That observed for accidental poisoning probably has occurred because declines in mental health during economic downturns are increasingly associated with the use of prescribed or illicitly obtained medications that carry risks of fatal overdoses.

#### WP 19335

David E. Bloom, Elizabeth T. Cafiero, Mark E. McGovern, Klaus Prettner, Anderson Stanciole, Jonathan Weiss, Samuel Bakkila, Larry Rosenberg The Economic Impact of Non-Communicable Disease in China and India: Estimates, Projections, and Comparisons

This paper provides estimates of the economic impact of non-communicable diseases (NCDs) in China and India for the period 2012–2030. Our estimates are derived using WHO's EPIC model of economic growth, which focuses on the negative effects of NCDs on labor supply and capital accumulation. We present results for the five main NCDs (cardiovascular disease, cancer, chronic respiratory disease, diabetes, and mental health). Our undiscounted estimates in-

#### Additional NBER Working Papers on Health and Aging

A complete list of all NBER Working Papers, with searchable abstracts, and the full texts of Working Papers issued since November 1973 are available at http://www.nber.org/papers.html to anyone located at a university or other organization that subscribes to the Working Paper series. dicate that the cost of the five main NCDs will total USD 27.8 trillion for China and USD 6.2 trillion for India (in 2010 USD). For both countries, the most costly domains are cardiovascular disease and mental health, followed by respiratory disease. Our analyses also reveal that the costs are much larger in China than in India mainly because of China's higher income and older population. Rough calculations also indicate that WHO's Best Buys for addressing the challenge of NCDs are highly cost-beneficial.

#### WP 19373

#### Benjamin Handel, Jonathan T. Kolstad Health Insurance for "Humans": Information Frictions, Plan Choice, and Consumer Welfare

Traditional models of insurance choice are predicated on fully informed and rational consumers protecting themselves from exposure to financial risk. In practice, choosing an insurance plan from a set of complex non-linear contracts is a complicated decision often made without full information on several potentially important dimensions. In this paper we combine new administrative data on health plan choices and claims with unique survey data on consumer information and other typically unobserved preference factors in order to separately identify risk preferences, information frictions, and perceived plan hassle costs. The administrative and survey data are linked at the individual level, allowing in-depth investigations of the links between these micro- foundations in both descriptive and choice-model based analyses. We find that consumers lack information on many important dimensions that they are typically assumed to understand, perceive high plan hassle costs, and make choices that depend on these frictions. Moreover, in the context of an expected utility model, including the additional frictions that we measure has direct implications for risk preference estimates, which are typically assumed to be the only source

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of persistent unobserved preference heterogeneity in such models. In our setting, we show that incorporating measures of these frictions leads to meaningful reductions in estimated consumer risk aversion. This result has both positive and normative implications since risk aversion generally has different welfare implications than information frictions. We assess the welfare impact of a counterfactual menu design and find that the welfare loss from risk exposure when additional frictions are not taken into account is more than double that when they are, illustrating the potential importance of our analysis for policy decisions.

#### WP 19393

#### Liran Einav, Amy Finkelstein, Paul Schrimpf

#### The Response of Drug Expenditures to Non-Linear Contract Design: Evidence from Medicare Part D

We study the demand response to non-linear price schedules using data on insurance contracts and prescription drug purchases in Medicare Part D. Consistent with a static response of drug use to price, we document bunching of annual drug spending as individuals enter the famous "donut hole," where insurance becomes discontinuously much less generous on the margin. Consistent with a dynamic response to price, we document a response of drug use to the future out-of-pocket price by using variation in beneficiary birth month which generates variation in contract duration during the first year of eligibility. Motivated by these two facts, we develop and estimate a dynamic model of drug use during the coverage year that allows us to quantify and explore the effects of alternative contract designs on drug expenditures. For example, our estimates suggest that "filling" the donut hole, as required under the Affordable Care Act, will increase annual drug spending by \$180 per beneficiary, or about 10%. Moreover,

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almost half of this increase is "anticipatory," coming from beneficiaries whose spending prior to the policy change would leave them short of reaching the donut hole. We also describe the nature of the utilization response and its heterogeneity across individuals and types of drugs.

#### WP 19430

in practice.

#### Eric Budish, Benjamin N. Roin, Heidi Williams

Do Fixed Patent Terms Distort Innovation? Evidence from Cancer Clinical Trials Patents award innovators a fixed period of market exclusivity, e.g., 20 years in the United States. Yet, since in many industries firms file patents at the time of discovery ("invention") rather than first sale ("commercialization"), effective patent terms vary: inventions that commercialize at the time of invention receive a full patent term, whereas inventions that have a long time lag between invention and commercialization receive substantially reduced-or in extreme cases, zero-effective patent terms. We present a simple model formalizing how this variation may distort research and development (R&D). We then explore this distortion empirically in the context of cancer R&D, where clinical trials are shorter — and hence, effective patent terms longer-for drugs targeting late-stage cancer patients, relative to drugs targeting earlystage cancer patients or cancer prevention. Using a newly constructed data set on cancer clinical trial investments, we provide several sources of evidence consistent with fixed patent terms distorting cancer R&D. Back-of-the-envelope calculations suggest that the number of life-years at stake is large. We discuss three specific policy levers that could eliminate this distortion—patent design, targeted R&D subsidies, and surrogate (non-mortality) clinical trial endpoints-and provide empirical evidence that surrogate endpoints can be effective

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