Lessons from the Impact of Price Regulation on the Pricing of Anticancer Drugs in Germany

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The impact of price regulation on the pricing of anticancer drugs in Germany: an empirical analysis

Abstract

The 2011 German Pharmaceutical Market Restructuring Act (AMNOG) aimed to achieve drug prices more closely aligned with their clinical benefits, without sacrificing innovation and patient access. Under AMNOG, manufacturers freely set prices of newly-authorized drugs during the first year on the market. Benefit assessments are then carried out during this period and used in price negotiations between manufacturers and representatives of the statutory health insurers. Using data on anticancer drugs launched in Germany from 2002-2017 (N=57), we found that implementation of AMNOG was associated with drug prices more closely aligned with clinical benefit. We did not find evidence that manufacturers responded by setting higher launch prices. Price negotiations led to a 24.5% decrease in negotiated prices relative to launch prices, and for products with added benefit, we found a positive association between an additional life-year gained and negotiated price.

Spending on pharmaceuticals has increased dramatically in recent years,(1) with total expenditures projected to reach $1.4 trillion worldwide by 2020 (2). Such spending has historically been highest in the US. Over the past 15 years, US per capita pharmaceutical spending has almost doubled, from $665 in 2002 to $1,208 in 2016 (1), a phenomenon mainly driven by higher prices rather than by increased prescribing rates (3).

Anticancer drugs now account for approximately 12% of US pharmaceutical spending (1,4), with expenditures predicted to grow by 12-15% annually over the next five years (4,5). Inflation- and benefit-adjusted launch prices of anticancer drugs increased by 10% annually from 1995 to 2013 (6), and an additional average 18% markup has been reported within eight years after launch (7), all of which has raised concern about the sustainability of drug price growth.

Currently, there are no mechanisms for directly regulating drug prices in the US. High prices have been linked to reduced access (8,9) and worse patient adherence (10–12), and consequently to negative health outcomes (10) and increased health care spending (11). Thus, addressing high brand-name prescription drug prices continues to be the subject of ongoing political (13) and academic (9,14,15) discussions, with proposed solutions featured prominently in the platforms of several 2020 presidential candidates (16). In response, pharmaceutical industry representatives have raised concerns that any restraints on drug pricing might hamper investment in innovation (14) or delay or reduce patient access to certain drugs (17).

European countries began implementing regulatory interventions to rein in growing pharmaceutical spending and price increases as early as the 1990s and have served as models for proposed changes in the US (18). Over time, three main approaches have emerged. Some countries — most

prominently England — conduct economic evaluations that compare incremental cost-effectiveness ratios and willingness-to-pay thresholds to inform binary (yes/no) coverage and reimbursement decisions related to pharmaceutical products (19). Other countries, like Austria, use external reference pricing, basing their prices on those charged in comparable markets (20). Finally, countries like Germany apply two-stage approaches in which evidence-based clinical benefit assessments are followed by price negotiations (19). The German approach is particularly relevant for potential policy interventions in the US, since Germany also has a multi-payer health insurance system and a large domestic pharmaceutical industry (21,22). Pharmaceutical spending levels in Germany are among the highest in Europe (at $777 per capita in 2016 versus a European Union-wide average of $536 per capita), but are still much lower than in the US (1).

In 2011, Germany launched a major drug pricing reform in reaction to steadily-rising pharmaceutical expenditures. The German Pharmaceutical Market Restructuring Act ("Arzneimittelmarktneuordnungsgesetz," known by the acronym "AMNOG") was introduced to align prices and reimbursement more closely with expected treatment benefits, with the stated goals of ensuring patient access to the best available medicines and providing reliable conditions that promote innovation (23). The AMNOG process for post-market, comparative effectiveness-based drug price regulation takes place after a product has been authorized for use in the European Union by the European Medicines Agency (EMA). Under AMNOG, manufacturers set prices freely for a drug's first year on the market. During this time, new drugs' additional therapeutic benefits relative to existing standards of care are formally assessed by a non-profit, non-governmental research body, the Institute for Quality and Efficiency in Health Care (IQWiG), and by a regulatory agency, the Federal Joint Committee, the highest

decision-making body of Germany's joint self-government of physicians, dentists, hospitals, and health insurers.

Based on the outcome of this benefit assessment, prices are negotiated between manufacturers and the umbrella organization of German statutory health insurers (SHIs) (24). For drugs without sufficient clinical evidence of therapeutic benefit beyond the standard of care (e.g., if no clinically or patient-relevant advantage can be shown, or if the evidence is considered to be of inadequate quality), an upper bound on reimbursement is set at the cost of the existing standard of care. Negotiated prices of drugs found to have additional therapeutic benefit (in which the drug's benefit may be determined to be "not quantifiable," "minor," "considerable," or "major") may receive reimbursement premiums above the cost of the current standard of care. Generally, the greater the additional therapeutic benefit, the greater the negotiated price premium (25). Because additional benefits assigned to new products may vary across different patient subgroups, such as patients above and below a certain age, negotiated prices may constitute "mixed prices" that weight different levels of added benefit by the sizes of the respective patient subgroups in the population. If negotiations fail, a price is set by arbitration (27,28).

Previous research on the AMNOG process has summarized the Federal Joint Committee's decisions (29), compared decision-making between the Federal Joint Committee and other institutions (30–33), assessed the role of specific types of evidence such as quality of life in AMNOG process outcomes (34), and analyzed determinants of price negotiation results (25,35). We sought to add to this growing body of knowledge by assessing whether the AMNOG process has led to pricing that is more aligned with a drug's clinical benefit and how much is being paid for an added unit of health gain. Specifically, if the AMNOG process were working as intended,

one would expect to see a (stronger) positive correlation between drug prices and added clinical benefit after AMNOG implementation. Further, there is no evidence on how AMNOG's introduction has impacted the price-setting behavior of manufacturers. A particular concern is that the AMNOG process might incentivize manufacturers to increase launch prices to offset anticipated future discounts resulting from price negotiations (36,37). This study aims to answer these questions empirically, identifying the impact of AMNOG implementation, to provide policy guidance for German authorities as well as other countries that may consider adopting aspects of Germany's system for drug pricing.

Data and Methods

Sample selection

We focused on the market for anticancer drugs because of its substantial size and because overall survival and progression-free survival are common primary endpoints used to measure incremental health benefits and conduct comparative effectiveness in oncology (38).

We identified anticancer drugs that were launched in Germany between 2002 and 2017 using annual reports on the German prescription drug market ("Arzneiverordnungsreport") (N=110) (39) and categorized them as having launched in the pre-AMNOG period (2002-2010) or the AMNOG period (2011-2017) (Exhibit 1). We restricted the sample to each product's first EMA-approved indication, and to those products that were demonstrated to extend patients' overall or progression-free survival (6). We excluded vaccines (N=2), palliative treatments (N=2), diagnostics (N=1), and products primarily intended for the treatment or prevention of side effects (N=5).

Exhibit 1 approximately here

Data sources and extraction

For each new product, we extracted outcome data from the initial
marketing authorization assessment reports publicly available on the
EMA's website (40). We extracted data on median overall survival, or, if
overall survival was not assessed, progression-free survival, from both
the intervention and control groups of randomized controlled trials
(RCTs) to determine each drug's incremental health benefits. We converted
reported times (sometimes presented in days or weeks) to months by
assuming that a month has an average of 30.5 days. If results from more
than one RCT were reported in regulatory documents, we selected the
results associated with the larger trial or the broader indication. If an
RCT had more than two interventional arms, we selected the trial arms
with the most favorable results (6). We excluded products with
authorizations based on single-arm trials (N=19), with trials showing no
survival benefits (N=5), in which survival was not assessed (N=11), and
in which overall or progression-free survival benefits were reported as
probabilities instead of median times (N=4).

We extracted data on each drug's launch price and negotiated price
from the Rote Liste (41), a comprehensive directory of prescription drug
prices in Germany. We excluded products for which we could not find price
data (N=4) and calculated treatment costs based on net wholesale prices
to establish comparability of prices over time. To calculate treatment
costs for each product, we extracted data on treatment durations and
dosing from the initial marketing authorization assessment reports (40)
or from the product label, if necessary. We calculated treatment costs
based on the assumption that only full packages of medicines could be
purchased (i.e., rounding up quantities needed to the next multiple of

package size). For products for which dosages depended on body surface area or weight, we based our calculations on German population averages (42), with body surface areas calculated according to Mosteller (43). We adjusted treatment costs for inflation using data from the German Federal Statistical Office (44) and converted Euros into US dollars using exchange rates reported by Eurostat (45). We calculated the incremental treatment cost of a product as the difference between the costs of therapy for the intervention and control groups in clinical trials, which permitted a comparison of additionally realized overall or progression-free survival gains with the costs associated with those gains.

As in Howard et al. (2015), we collected control variables that might be associated with a drug's value, which we grouped into six categories: 1) product characteristics, including side-effects, route of administration, and indication, (2) disease severity, (3) quality of clinical data, (4) market characteristics and marketing opportunities, including competition, market size, production costs, and economies of scale, (5) authorization pathways, and (6) benefit assessment. We obtained information on these control variables from the EMA's website (40), the Federal Joint Committee's website (46), and a cancer registry maintained by the Robert-Koch Institute (47).

A full list of study sample drugs, excluded drugs, an overview and description of all control variables, and details on how these variables may have influenced a drug's value (and thus our findings) is presented in the Appendix.

Analytic plan

Based on available data, we estimated the amount paid for an additional life-year gained for products that were assessed as having added benefit over the contemporaneous standard of care during AMNOG period.

Next, we conducted regression analysis to assess manufacturers'
launch-price-setting behavior. We modeled the relationship between
incremental treatment costs for anticancer drugs in Germany at launch (as
the dependent variable) and months gained in progression-free or overall
survival before and after the introduction of AMNOG (captured by main
effects and an interaction term) and the year of drug launch (as independent
variables).

For products launched in the AMNOG period (i.e., those launched in
2011 or later), we also modeled the relationship between incremental
treatment costs after price negotiations (as the dependent variable) and
months gained in progression-free or overall survival and the year of
drug launch (as independent variables).

Because each of our dependent variables had a right-skewed
distribution, we estimated Poisson regressions with robust standard
errors, which have been noted to be superior to log-linear regressions in
such settings (48-50). However, Poisson regression requires dependent
variables to be greater or equal to zero. We therefore dropped one
observation with negative incremental treatment costs after negotiation
(in this unique case, the treatment costs associated with the new product
were lower than the costs of the comparator therapy). Given our small
sample size, we included control variables sequentially and separately,
following Howard et al. (2015) (6). All analyses were performed using
Stata/SE 15.1. Estimating equations used in the regressions are presented
in the Appendix.

To ensure the robustness of our findings, we performed four
separate sensitivity analyses. First, we re-estimated each model used a
log-linear ordinary least squares regressions instead of Poisson
regressions (Appendix). Second, to determine the impact of extreme values
in our sample, we excluded outliers, defined as observations with

incremental treatment costs per month gained in progression-free or overall survival at launch and/or after negotiation that were larger than the median plus 2.5 times the median deviation value (N=3 for costs at launch [inotuzumab, histamine dihydrochloride, panitumumab], and N=1 for costs after negotiation [inotuzumab ozogamicin]) (51). Third, we used data of months gained in overall survival only (N=27 for costs at launch, and N=21 for costs after negotiation) and without data from the year 2011 (N=4 [eribulin, cabazitaxel, ipilimumab, abiraterone]) to account for possible bias from transitional regulations that were in place through the end of July 2011 (50). Fourth, to assess how the process of negotiating mixed prices might have impacted our results, we included a binary variable that indicated whether the Federal Joint Committee had defined more than one patient subgroup and assessed those patient subgroups differently.

Limitations

Our analyses were subject to several limitations, including our reliance on aggregated and averaged data to estimate how much German payers spent on anticancer products. Because we compared the highest level of benefit reported in EMA authorization reports with negotiated prices that weighted different added benefits – when present – by the sizes of the patient populations to which they applied, we likely underestimated how much German payers spent on a life year gained in products with an added benefit.

Our sample size was also modest, which prevented us from including all potentially relevant control variables simultaneously in regression analyses and limited our ability to detect associations between variables. Given this limitation, we could only include the year of launch as a linear time trend in our regression models. Future analyses of larger samples might include the year of launch as a set of

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independent dummy variables to obtain greater flexibility in accounting for differences over time.

Concerning treatment costs, we were unable to account for confidential supplemental rebates that may have been agreed upon between manufacturers and individual statutory health insurance companies. We also did not factor costs incidental to the use of therapies, such as inpatient or outpatient care and treatment of side effects. Even though data on these costs are available for products assessed through the AMNOG process, the same information is not available for products launched before 2011, nor is it the case that comparators used in the EMA's evaluations were the same as those used in the AMNOG process

We additionally relied on data on progression-free survival, a surrogate measure, in cases in which data on overall survival data were not available. Even though the correlation between progression-free survival and overall survival has been found to be low or modest in some cases (53), it is, in the absence of overall survival data, the only available measure that can be used by manufacturers and payers to set or negotiate product prices (6).

Finally, our sample was not representative of drugs for rare ("orphan") cancers, which are treated differently than other products in the AMNOG process.

Results

Our final sample included 57 anticancer drugs, 14 of which launched in the pre-AMNOG period, and 43 of which launched in the AMNOG period. The average incremental treatment costs at launch were $51,127 over the entire sample. These costs were smaller (p=0.02) in the pre-AMNOG period (mean $29,417) than in the AMNOG period (mean $58,195) but were not

significantly different (p=0.20) from incremental treatment costs based on negotiated prices in the AMNOG period ($43,953).

The average additional overall or progression-free survival gain of anticancer drugs launched in Germany between 2002 and 2017 was 6.4 months, with a minimum of 0.2 months, a maximum of 49.1 months (the median value was 3.5 months with an interquartile range of 2.4-5.8 months). The average baseline overall or progression-free survival for the sample was 10.2 months (with a median of 9.1 months and an interquartile range of 5.0-14.5 months); gains were stable over the period of observation (Exhibit 2).

Exhibit 2 approximately here

Comparing newly-launched anticancer drugs' incremental treatment costs (a) at launch and (b) after negotiation against their associated overall or progression-free survival months gained does not suggest an association in the pre-AMNOG period. By contrast, incremental treatment costs were positively associated with overall or progression-free survival months gained in the AMNOG period, with incremental treatment costs based on negotiated prices consistently lower than incremental treatment costs at launch (Exhibit 3). The average difference between incremental treatment costs at launch versus after negotiation in the AMNOG period was $14,242, representing a relative decrease in incremental treatment costs over the period of benefit assessment and negotiation of 24.5%.

Exhibit 3 approximately here

We estimated average incremental treatment costs of $16,041 per overall or progression-free survival life-month gained at launch in the pre-AMNOG period, and $15,263 per overall or progression-free survival

life-month gained in the AMNOG period, which decreased to $11,476 per overall or progression-free survival life-month gained after negotiation. Neither AMNOG period average was significantly different from the pre-AMNOG period average (p=0.92 and p=0.50, respectively).

Because the estimates of cost per overall or progression-free survival month gained were strongly influenced by one outlier – the acute lymphoblastic leukemia treatment inotuzumab – we excluded it in the subsequent estimation exercises. Differentiating by added benefit status in the AMNOG period revealed average additional treatment costs at launch of $12,267 per overall or progression-free life-month gained for products without an added benefit (N=8), which decreased to $6,994 after negotiation. Given that negotiated prices for products without an added benefit result in treatment costs equivalent to the treatment costs of the current standard of care (25), we estimated that pharmaceutical manufacturers in Germany received an average of $6,994 per overall or progression-free life-month gained for already-established anticancer drugs during this period.

For products that were assessed to have added benefit (N=34), median additional treatment costs were $11,191 per overall or progression-free survival month gained at launch and decreased to $8,690 after negotiation. An additional overall or progression-free survival life-month gained for products with added benefit was therefore reimbursed at an average of $1,696 (i.e., $20,352 per overall or progression-free survival year gained during the AMNOG period).

The estimates are also based on net wholesale prices. However, actual spending by the SHIs is at least 19% higher in practice due to value-added tax. This implies an extrapolated $24,219 per additional year gained in overall or progression-free survival for products found to have added benefit.

Importantly, these estimates are based on the assumptions that the comparator costs for products with and without added benefit were comparable to one another and that the EMA and Federal Joint Committee had the same assessment for products with an added benefit (both of these assumptions were confirmed via T-tests with data collected from the Federal Joint Committee's website: $p=0.23$ and $p=0.26$, respectively; see the Appendix for additional detail).

Regression Results

The regression estimates presented in Exhibit 4 suggest that incremental treatment costs at the time of drug launch were not associated with a greater number of overall or progression-free survival months gained in the pre-AMNOG or AMNOG period. While implementation of AMNOG did not appear to have affected average incremental treatment costs, treatment costs increased by an average of 10.6% per year over the full period of observation (Exhibit 4).

After price negotiation, however, incremental treatment cost increases were positively associated with additional overall or progression-free survival months gained. In the AMNOG period, an additional overall or progression-free survival month gained was associated with an average increase in incremental treatment costs of 3%. However, there was no additional association detected between incremental treatment cost after negotiation and the year of launch (Exhibit 4). These results suggest that higher prices were more closely associated with more beneficial drugs in the AMNOG period, without evidence of a time trend in negotiated prices in that period.

Exhibit 4 approximately here

The results of both base case models were largely robust to the inclusion of control variables described above. Re-estimating regression

models without outliers, with overall survival data only, without products launched in 2011, or by using a log-linear ordinary least squares specifications yielded highly similar results, but rendered the coefficient on year insignificant in most models in which incremental treatment cost at launch was the dependent variable. In the sensitivity analysis that included a variable indicating that multiple patient subgroups had been defined and assigned different added benefits showed that for such products, treatment costs after negotiation decreased by 65.3%. This negative coefficient can be explained by the common practice of negotiating mixed prices for such products, as supported by the additional models presented in the Appendix.

Discussion

We found that the AMNOG system helped push Germany towards drug prices more closely aligned with clinical benefits. In the AMNOG period, there was a significant association between overall or progression-free survival and incremental treatment costs after negotiation, suggesting that the process was successful in tying prices to clinical benefit in a way that did not exist before.

Manufacturers might have responded by strategically offsetting anticipated future discounts resulting from negotiations by increasing launch prices. We did not observe such behavior, though our sample size was admittedly modest.

Among drugs in our sample, price negotiations decreased incremental treatment costs by an average of 24.5%. Additionally, price negotiations seem to offset a positive time trend in launch prices (6), though sensitivity analyses suggest that this time trend was driven by a small number of outliers with exceptionally high prices.

Our results imply that many of the goals associated with the implementation of AMNOG were fulfilled for anticancer drugs. Most importantly, the pricing of anticancer drugs became increasingly aligned with treatment benefit. These results are particularly reassuring in the context of prior research showing that AMNOG did not lead manufacturers to withdraw clinically important medications from the German market (50), suggesting that the change in pricing did not affect patient access in clinically meaningful ways.

The estimate of a median cost of $1,696 per additional overall or progression-free survival month gained for anticancer drugs with added benefit includes some products with mixed prices and is not adjusted for quality of life. As such, a direct comparison to other countries' willingness-to-pay thresholds, usually measured in $/quality-adjusted life-year (QALY) (a life-year gained in full health), is difficult. Nonetheless, as a benchmark, we note that England's willingness-to-pay threshold for one QALY in end-of-life treatments (primarily cancer therapies) equals approximately $63,595 (£50,000) (54), which is higher than our (most likely underestimated) estimate of $24,219 if extrapolated out to a year and accounting for value-added tax.

Summary statistics suggest that treatment costs associated with new drugs kept increasing beyond the introduction of AMNOG. However, comparing the growth in overall health care spending versus pharmaceutical-specific spending before and after the introduction of AMNOG presents a different picture. In the seven years before AMNOG, 2004-2010, standardized health care spending grew by 23.7%, while spending growth for pharmaceuticals was much more rapid, increasing by 32.3% over the same period. In the seven years with AMNOG, (2011-2017), standardized overall health care spending and pharmaceutical spending grew at similar rates, by 26.9% and 26.0%, respectively (55). Further

research should examine the extent to which the implementation of AMNOG has affected the uptake of pharmaceutical products, prescribing rates, and patient outcomes.

The introduction of pricing at a level more closely aligned with treatment benefits may not necessarily be associated with a decrease in spending. As Claxton (2007) has argued, value-based pricing "would lead to higher prices for some products and involve a reallocation of revenue from products which are less valuable to those products which are more valuable" (56). Prices that are more closely aligned with treatment benefits will incentivize manufacturers to produce innovative pharmaceuticals with high value and might therefore – in the long run – increase overall pharmaceutical spending levels and growth, albeit for more clinically important products with better patient outcomes (56).

Our findings are relevant for other countries facing increasing prescription drug prices. In the US, cancer drug prices are set at whatever the pharmaceutical manufacturer decides the market will bear, and are not systematically negotiated by the government in connection with a product's clinical benefit. Currently, US policymakers are discussing a number of ways to reform US drug pricing, with different approaches being proposed to change the way Medicare pays for medications through its Part B and Part D programs. Individually, states are also considering new options for determining how to provide expensive but important new medications through the Medicaid program (57). The AMNOG experience suggests a model for what might happen if policymakers in other countries are successful in introducing a drug price negotiation system in which prices are more closely linked to clinical benefit. This study also shows that the negotiation process led to further reductions in cancer drug prices and that these appear to have offset time trends in drug price increases that were not correlated with clinical benefit.

Another feature of the AMNOG process is that price negotiation occurs after a drug has already entered the market, and thus does not excessively delay patient access immediately after launch.

Yet, in the absence of further policy changes, application of an AMNOG-like system of evidence-based price negotiations in the US would likely not lead to the same changes in oncology drug prices as observed in Germany. For example, cancer drugs remain a protected drug class for the Medicare Part D outpatient drug insurance program, which covers patients over age 65. Since Part D programs must include all drugs in protected classes in their formularies, manufacturers may feel less pressure to bring their prices in line with clinical benefit. Further, many states have similar rules limiting the flexibility of private insurers to exclude cancer drugs from coverage under certain conditions (60). Additionally, in Germany the SHIs jointly negotiate prices on behalf of all payers, representing a level of coordination that has no analog in the US, where negotiations between manufacturers and payers are fragmented, secretive, and often intermediated by pharmacy benefit managers(61). Therefore, policymakers in the US would need to revisit coverage rules as well as rules governing how prices are negotiated to effectively implement similar policies.

Conclusion

AMNOG's introduction of benefit assessments followed by price negotiations for newly authorized prescription drugs in Germany led to anticancer drug prices that were more closely aligned with treatment benefit. Other countries, including the US, may consider components of Germany's AMNOG system as a model for addressing certain aspects of drug pricing dilemmas.

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List of exhibits

Exhibit 1: Study sample selection

Source: Authors' analysis.

Exhibit 2: Characteristics of anticancer drugs in study sample

Source: Authors' analysis.

Exhibit 3: Comparison of incremental treatment costs vs. life-months gained

Source: Authors' analysis.

Exhibit 4: Association between life-months gained and treatment costs (1) at launch, and (2) after negotiation: Regression results of base case models

Source: Authors' analysis.