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An American in Berlin: Insights on Drug Assessment and Pricing under AMNOG

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Overview

- The AMNOG system has achieved considerable success in evidence-based drug assessment and price moderation, with lower administrative burdens, fewer patient access barriers, and less social animosity than in the US
- What are the structural and cultural factors that contribute to its comparative success?
- Which challenges face AMNOG?
- How does the AMNOG structure and focus align with policies directed at innovation and support for jobs and exports?

A Note of Methods and Sources

- Support from the Commonwealth Fund and German Managed Care Association (BMC)
- Collaboration with Patricia Ex, Dimi Panteli
- Advisory board: Amelung, Busse, Knieps, Greiner, Koster-Steinebach, Muhlbacher
- Five Berlin site visits 2018-19
- Innumerable meetings, interviews, discussions
- Feedback on presentations, issue briefs, blogs
- Econometric study of net prices in DE and US for 80 physician-administered drugs, 2004-18

Assessment of Clinical Benefit

- Factors supporting the social legitimacy of GBA assessments
- Contrast with the US system
- Challenges facing GBA assessments

The Legitimacy of Benefit Assessment

- Clinical benefit assessment is difficult due to the multi-dimensional, rapidly changing, and always incomplete scientific evidence and patient values
- It is further complicated by being associated with policies on insurance coverage, pricing, and utilization management, which arouse fears in manufacturers, physicians, and patients
- The GBA process seems to have achieved (perhaps grudging) acceptance as evidence-based and patient-centric, rather than merely as a tool to help GKV-SV negotiate low prices
- This is a difficult feat, not to be taken for granted
- Which factors support social legitimacy?

Success Factors in Benefit Assessment: Structure

- Highly formalized process for each new assessment, with reliance on IQWiG (which is not cost-focused) as well as GBA internal staff
- Transparency of IQWiG methods, GBA hearings, documents, final assessments
- Repeated game: participants gain mutual familiarity (and trust?) across multiple drug assessments
- Implicit oversight by the Ministry of Health, to retain connection to political perspectives and imperatives, and to balance the legitimacy of GBA as self-governing body with the legitimacy of government as democratically elected body

Success Factors in Benefit Assessment: Participation

- Participation by manufacturers through early consultations, dossier preparation, public hearings
- Participation by patient advocates and organizations, with insights into patient experience of disease and treatment
- Participation by physician associations, to ensure GBA does not abrogate professional authority over treatment for individual patients
- Participation by Sickness Funds, with insights into patterns of utilization and spending among their enrollees

Contrast with the United States

- In the US, HTA has never achieved social legitimacy. It has been demonized by pharmaceutical firms, (some) patient advocacy organizations, and (many) politicians as a violation of individual patients rights and an obstacle to innovation
  - Governmental HTA bodies have been attacked, weakened, or dismantled altogether
- This leaves to the assessment task to each individual payer
- In turn, this leads to high administrative costs, lack of transparency, and social stress
  - Each payer must decide which drugs to include or exclude from coverage, and when to require prior authorization and step therapy from physicians
  - Physicians must comply with different coverage and utilization restrictions from each payer
- This de-centralized process further undermines the legitimacy of HTA, without offering a solution

Challenges to the DE Structure of Incremental Benefit Assessment

- Accelerated authorization by EMA
- Continuous emergence of new evidence

Accelerated Authorization by EMA

- EMA is following FDA in accelerating authorization of new drugs based on incomplete evidence, including biomarker endpoints, small populations, single arm studies, without an active comparator, etc.
- GBA thus must assess incremental benefit with ever less evidence, with the result that it mandates from manufacturers evidence not required by EMA
- Does this make GBA the more effective gatekeeper, or does it lead mostly to delays for (re)assessment and undermine the goal of accelerated access?
- Does it undermine the EU-wide market authorization standardization embodied in EMA
- Does it undermine the proposed HTA standardization?

Continuous Emergence of New Evidence

- New evidence is continually emerging from follow-on clinical studies in Germany and elsewhere, often required by regulatory and HTA agencies
- The quality and applicability of real world evidence (insurer claims, electronic medical records, patient registries, patient surveys) also is growing rapidly, and typically emerges after the GBA has finished its assessment
- The digital revolution is generating ‘digital biomarkers’, evidence generated by patients themselves through activity trackers, sensors, cell phones. These data are especially relevant for conditions needing continuous monitoring and/or having subjective endpoints (psychiatry, neurology)
- How can these new forms of evidence be integrated with the highly formalized (one-time) GBA assessment process?

Price Determination

- The AMNOG record in moderating prices
- Key features of the price negotiation process
- Contrast with the United States
- Challenges facing price determination in DE

The DE Price Surprise

- The outsider encounters a range of opinion as to whether net prices (after negotiations) in DE are higher, lower, or similar to net prices in other western EU nations, but everyone agrees that prices in DE are lower than in the US
- This is surprising, since the DE culture and drug coverage structure would seem to limit leverage available to GKV-SV
  - Drugs are available for prescription immediately after EMA authorization
  - No prior authorization and only weak retrospective limits on physician prescription choices
  - Very limited cost sharing, not linked to drug price
  - Sickness Funds must pay the price determined by negotiations or arbitration (no positive list)
- How does the DE achieve price moderation? Why do not manufacturers insist on receiving their full list prices?

Incentives for Agreement

- Some features of the DE system make its market and prices attractive to manufacturers, so that they have a strong desire to come to agreement even where their leverage is strong
- A large drug market, prosperous economy, governmental budget surpluses, tight labor market, high visibility
- Immediate reimbursement after EMA authorization, allowing drugs to gain physician and patient acceptance
- Free pricing in first year, allowing for high short-term revenues and creating an anchor for subsequent rebate negotiations in DE and reference pricing in other nations
- Even if net prices are below what manufacturers would prefer, they are high enough to contribute positive contribution margins and help support R&D

Dis-Incentives for Dis-Agreement

- Mandatory arbitration increases uncertainty and risk. Board does not 'split the difference' between final payer and manufacturer offers, but conducts own assessment
- Repeated game: Aggressive price demands for drugs without substitutes could lead to aggressive payer demands for rebates for drugs with substitutes
- Reputational concerns: Pharmaceutical firms must accept the principle of efficiency (Wirtschaftlichkeit) underpinning the entire DE system, and fear political and public relations consequences of being viewed as undermining this
- If the AMNOG process is viewed as failing to deliver price moderation, and if the German economy were to enter a difficult period, there could be pressure for direct ceilings on drug prices, based on formal cost-effectiveness analysis (CEA) and budget impact analysis (BIA)

Contrast with the United States

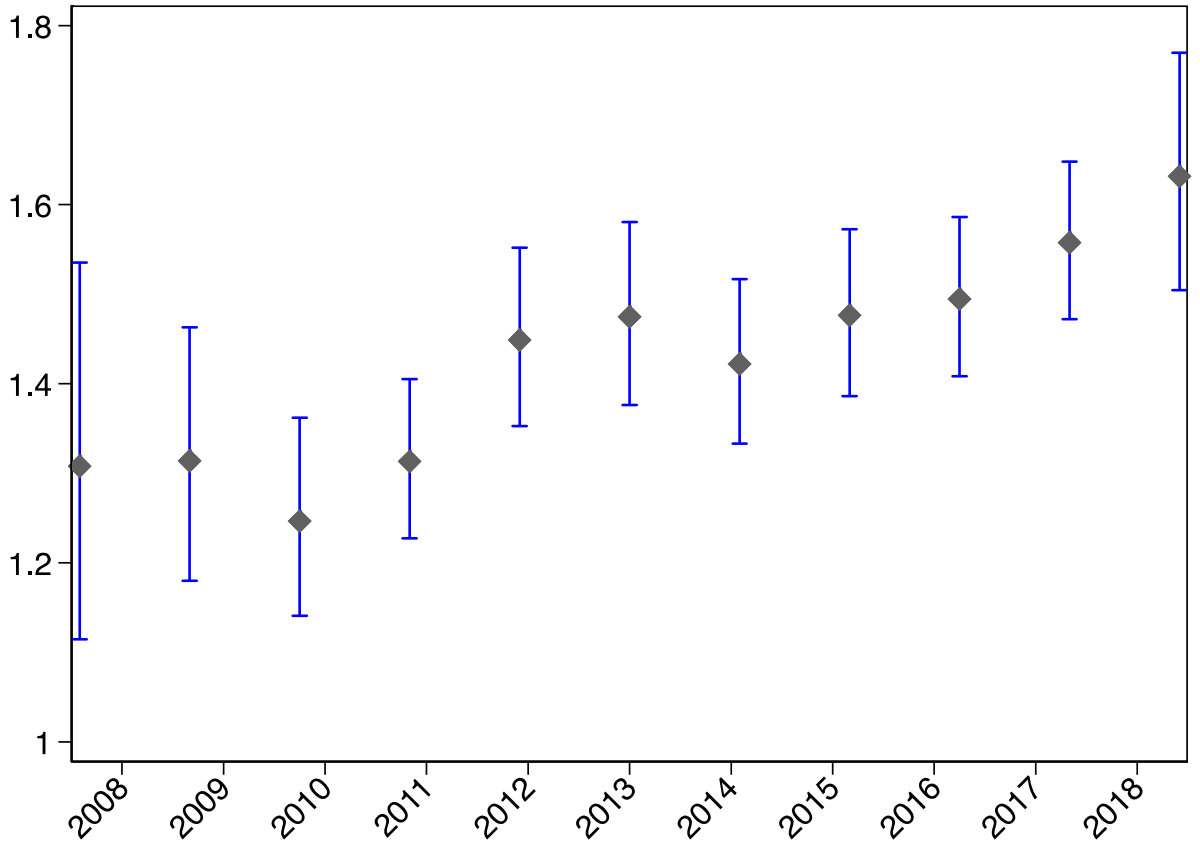
- The ‘innovation race’ has brought multiple therapeutically similar products to many specialty indications, allowing US payers to threaten patient access restrictions for drugs not offering a large (non-transparent) rebate
- To obtain rebates, payers have imposed formulary exclusions, physician prior authorization, patient cost sharing
- These tools have led to substantial reductions in physician prescription and patient access
- This has also generated significant price rebates, reducing margins for manufacturers

US/DE Price Ratios for Physician-Administered Drugs

- For physician-administered drugs, net price data are available in the US, because private payers are required to report average revenues net of all negotiated price discounts and rebates (Average Sales Price) to the government for drugs covered under Medicare Part B
- Net price data for Germany are available thru LauerTaxe
- We conducted a difference-in-differences multivariable regression analysis of net price trends in US and DE for 80 physician-administered drugs launched between 2004-2018

- We find that DE improved its performance (lower net prices), compared to the US, after AMNOG in 2011

Ratio of US/DE Net Prices for 80 Physician-Administered Drugs



US data from CMS Part B (ASP); DE data from LauerTaxe.
Calculations by F Berkemeier, C Whaley, JC Robinson

Challenges to DE Structure of Price Determination

- Price changes after initial negotiations
- Precision medicine and ‘orphanization’
- Budget impact and appropriate utilization

Price Changes after Negotiation

- DE retains the pre-AMNOG ban on unilateral price increases after the initial negotiations/arbitration. Drug prices can only change subsequent to new GBA assessment and GKV negotiations, pften when manufacturer seeks new indication
- Principles of pricing based on incremental clinical value would appear to permit price increase with new evidence of efficacy, and price decrease with new evidence of toxicity.
- Market launches of new drugs would seem to require repricing of already approved drugs, as comparator changes
- Could DE adopt a more flexible system of ‘pricing with evidence development’ or would this overwhelm GKV-SV?
- Does the ban on post-launch price increases give incentive for manufacturers to set high list prices (taking into account expected 25% GKV-SV rebate and the ban on increases)?

Precision Medicine and “Orphanization”

- Precision medicine (companion Dx) and the research focus on rare conditions reduce the ability of GBA to conduct comparative assessments and GKV-SV to negotiate prices based on comparative performance
- If almost every drug becomes an orphan drug, without a comparator or competitor, will price discipline erode?
  - Will DE need a cap on price-per-patient (as in UK)?
  - Would this require adoption of QALY methods and conflict with the culture of patient access?
- How will AMNOG deal with ‘one and done’ gene and cell therapies, where the entire treatment is applied in year one even if benefit continues over many years?

Budget Impact and Appropriate Utilization

- Volume of drug use (and hence budget impact) is not explicitly included in the AMNOG process of price determination
  - It became salient after the HCV drug breakthroughs, and will reappear if there are emerge effective treatments for Alzheimer's and other prevalent conditions
- Some other nations interpret HTA has including:
  - comparative clinical effectiveness
  - cost effectiveness
  - budget impact
- But DE only includes the first of the three
- Will AMNOG and GKV-SV explicitly consider budget impact?
- Will Sickness Funds seek to limit use of approved drugs, and obtain supplementary rebates, based on more extensive contracting by regional physician associations with more detailed clinical guidelines for individual physicians?

Alignment of AMNOG with Other Policy Concerns

- Self-governance and legitimacy
- Innovation and industrial policy

Self-Governance and Social Legitimacy

- How does the collaborative (self-governance) structure of AMNOG fit with rising EU concerns for concentration and lack of competition?
- Manufacturers appear to be subject to anti-trust policy but not physicians, hospitals, Sickness Funds
- Is this stable?
- If the German economy comes under stress, will the elected legislators seek to have more direct control over prices and spending, as seen in other major EU nations?
- How to politicians judge whether AMNOG is ‘working’?
- What might be the indirect impact of larger political changes in the EU, including political fragmentation and Brexit, have on the German HTA and pricing framework?

Innovation and the Life Sciences Industry

- Economists argue that prices close to marginal costs of manufacturing and distribution will lead to reductions in risky investments in R&D
  - We see this already in anti-biotics and perhaps in some therapeutic classes with low-priced generic drugs but remaining unmet clinical needs (e.g., cardiovascular)
- If market and political developments continue to squeeze industry margins in the United States, what might be the effect on investments, and then indirectly on prices in other nations?
- How will the AMNOG focus on moderation in drug prices and spending align with governmental concerns for supporting the DE life sciences industry, a major source of jobs and exports?

The Life Sciences Industry

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