JPHSR Journal of Pharmaceutical Health Services Research

Journal of Pharmaceutical Health Services Research, 2021, Vol 12, 343–349
doi:10.1093/jphsr/rmab025
Research Paper
Advance Access publication 27 May 2021

OXFORD

Research Paper

Personalized medicine drugs and the burden of disease in Germany

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Received February 16, 2021; Accepted April 20, 2021.

Abstract

Objectives This study aimed to assess the burden attributable to diseases with subtypes that are indications for the personalized medicine (PM) drugs approved in Germany.
Methods A secondary analysis of a PM drug database and Global Burden of Disease (GBD) Study 2019 data was conducted. Indications of the PM drugs approved in Germany for biomarker-targeted therapy were matched with disease burden causes to quantify the portion of the disease burden attributable to causes that, in some instances, may be treated with PM drugs.
Results Between 1995 and 2020, the number of PM drugs approved in Germany rose from 0 to 83. Accordingly, the portion of the disease burden due to causes of disease with subtypes that are PM drug indications has risen. Indications for use of the 83 PM drugs approved in Germany by the end of 2020 related to 39 of 369 GBD causes, to which 7825 disability-adjusted life years (DALYs) or 24.3% of the total burden of 32 162 DALYs per 100 000 population in Germany were attributed. Twenty years earlier, in 2000, 5 PM drugs related to 2 GBD causes, to which 978 DALYs (3.1%) of a total burden of 31 878 DALYs per 100 000 population were attributed. Considering the median frequency of biomarkers that can change pharmacological treatment resulted in estimating that not more than 3.0% (interquartile range: 1.1–7.3) of the current German disease burden is affected by personalized pharmacotherapy.
Conclusions Mapping PM drug indications to disease burden causes allowed to quantify the disease burden within and outside the domain of personalized pharmacotherapy in Germany.

Keywords: burden of disease; Germany; personalized medicine; precision medicine; public health

Introduction

Since the human genome project identified and mapped the genes of the human genome, hope and potential to improve the health of individuals and populations have been attributed to personalized medicine (PM).[1] PM can enable early diagnosis, more precise treatment and better targeted prevention.[1–3] However, which currently practiced PM approaches are effective and cost-effective is debated.[3]

At present, what is typically referred to as PM primarily offers targeted drug therapy for a relatively small number of diseases.[4, 5] The idea underlying targeting is that the efficacy of some drugs can be improved and/or side effects reduced through preselecting patients suitable for a certain drug based on a biomarker test that precedes drug application. While some patients benefit significantly from a personalized application of some drugs, others do not, or additional benefits are small while the additional cost of a PM drug might be high.[6–11]

Due to potentially high costs and broad variation in benefits, the relationship between PM and health on the population level is debated.[12–14] Related to a lack of quantitative data, debates about the contribution of PM drugs towards population health improvement have largely evolved around qualitative arguments. The number of published economic evaluations of genomic testing as part of PM applications has been found to be small[15, 16] and, to my knowledge, no study to date has attempted to quantify the potential for population health impact of all PM drugs available in a healthcare system.

This study links data from the Global Burden of Disease (GBD) Study 2019 and data on PM drugs.[17, 18] First, the development of PM drugs and their application areas are described for Germany. Secondly, the national burden of disease in Germany attributable to GBD causes, which include one or more diseases that are treated, in some instances, with a PM drug, is identified and compared to the total national disease burden.

Methods

Definition of Personalized medicine drugs

There is no universal definition of PM drugs (cp.[17, 19]). The German Association of Research-based Pharmaceutical Companies (Verband Forschender Arzneimittelhersteller; vfa) classifies drugs for which a biomarker pretest is required or recommended in official drug information, usually the package leaflet or specialist information, as PM drugs. If drug information refers to genetic characteristics that have been found to influence the efficacy or safety of the drug without requiring or recommending a biomarker pretest, then a drug is not considered PM. Examples for the latter group of drugs are clopidogrel, simvastatin and other statins. This study follows the vfa definition of PM drugs.

Data sources

Data about the number of PM drugs approved in Germany are collected by vfa.[17] The database is open access and updated on an ongoing basis. Data include active substance names, main drug indication(s), pretest characteristics and the date since the drug use is personalized, that is, since when the use of the substance in combination with a biomarker pretest was first required or recommended (cp.[4, 20]). Additionally, the European Medical Agency (EMA) website[21] and further sources were used to obtain the date when a drug was first approved in Germany. By the end of 2020, a total of 83 active substances were considered PM drugs. Three of these had more than one personalized application (Crizotinib, Entrectinib, Imatinib).

National disease burden estimates were obtained by extracting data for Germany from the GBD Study, which contains standardized global health data since 1990. The GBD 2019 Study assessed health loss from 369 diseases and injuries for 204 countries and territories.[18] All GBD data are freely available. Data (per 100 000 population) on disability-adjusted life years (DALYs), years of life lost due to premature death (YLL) and years lived with disability (YLD) were extracted through the GBD 2019 results tool for the years from 1995 to 2019.[22]

Data analysis

The development of the number of PM drugs approved in Germany, their application areas, and the dates of their approval and personalization were described. Indications of PM drugs were matched with causes of morbidity and mortality at the lowest level of aggregation assessed by the GBD Study (level 3 and level 4 causes; see Supplementary Material, Table S1). Indications of PM drugs were linked with GBD causes by, first, mapping PM drug indications to ICD-10 codes and, then, matching these ICD-10 codes with those documented for GBD causes.[23] The disease burden in Germany due to causes that were or potentially could have been treated, at least in some, possibly rare, instances, with a personalized drug was identified, quantified and compared over a period of 25 years to the total disease burden. Disease burden and PM drug-indications were aggregated into 22 major cause groups, corresponding to commonly reported GBD level 2 causes. As the GBD Study 2019 provides disease burden data until 2019, the same disease burden for 2020 as in 2019 was assumed. All analysis was performed in Stata 15.1 SE.

Results

Personalized medicine drugs

The number of PM drugs approved in Germany through the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte; BfArM) or the EMA was 83 by the end 2020. Use of a pretest was mandatory for 74 substances and recommended for 9 substances. Application areas of these PM drugs were oncology (73.6%), followed by metabolic disorders (10.3%), immunology (4.6%), epilepsy, HIV, musculoskeletal disorders (each 2.3%), haematology, cardiology, ophthalmology and psychiatry (each 1.1%). In oncology, the area in which most biomarker targeted drugs were developed, treatment with PM drugs was available for subtypes of the following cancers: breast cancer (since 1996), stomach cancer (since 2000), leukaemias (since 2001), bowel cancer (since 2007), lung cancer (since 2009), thyroid cancer (since 2012), lymphoma (since 2012), melanoma (since 2013), ovarian cancer (since 2014), brain cancer (since 2019) and pancreatic cancer (since 2020). The development of the number of PM drugs in Germany and their application areas are shown in Figure 1.

Disease burden

According to the GBD Study 2019, the life expectancy in Germany was 81.2 years in 2019. It has steadily risen from 76.9 years since 1995. The 2019 national disease burden in Germany was 27.3 million disability-adjusted life years (DALYs) or 32 162 DALYs per 100 000 population. Almost equal amounts of the total disease burden were caused by years of life lost due to premature death (YLLs; 17 448 or 54.3%) and by years lived with disability (YLDs; 14 714 or 45.7%). The composition of this disease burden is summarized in Table 1.

Three major cause groups accounted for almost 50% of Germany's disease burden in 2019: neoplasms, cardiovascular diseases and musculoskeletal disorders. Neoplasms (99.0% cancers) and cardiovascular diseases were the two leading causes of premature deaths and years live with disability. Neoplasms and cardiovascular diseases accounted each for more than 6000 DALYs per 100 000 population or 38.3% of the total disease burden. Since 2003, neoplasms have taken over cardiovascular diseases as the number one cause of the disease burden in Germany. The third largest share of 9.8% of the disease burden in 2019 Germany was attributed to musculoskeletal disorders (80.2% lower back, neck pain or osteoarthritis).

Disease burden with indications for personalized medicine drugs

The 94 indications of the 83 PM drugs approved in Germany at end of 2020 related to 39 causes of the 369 causes of disease distinguished by the GBD Study 2019. The 39 causes that contained

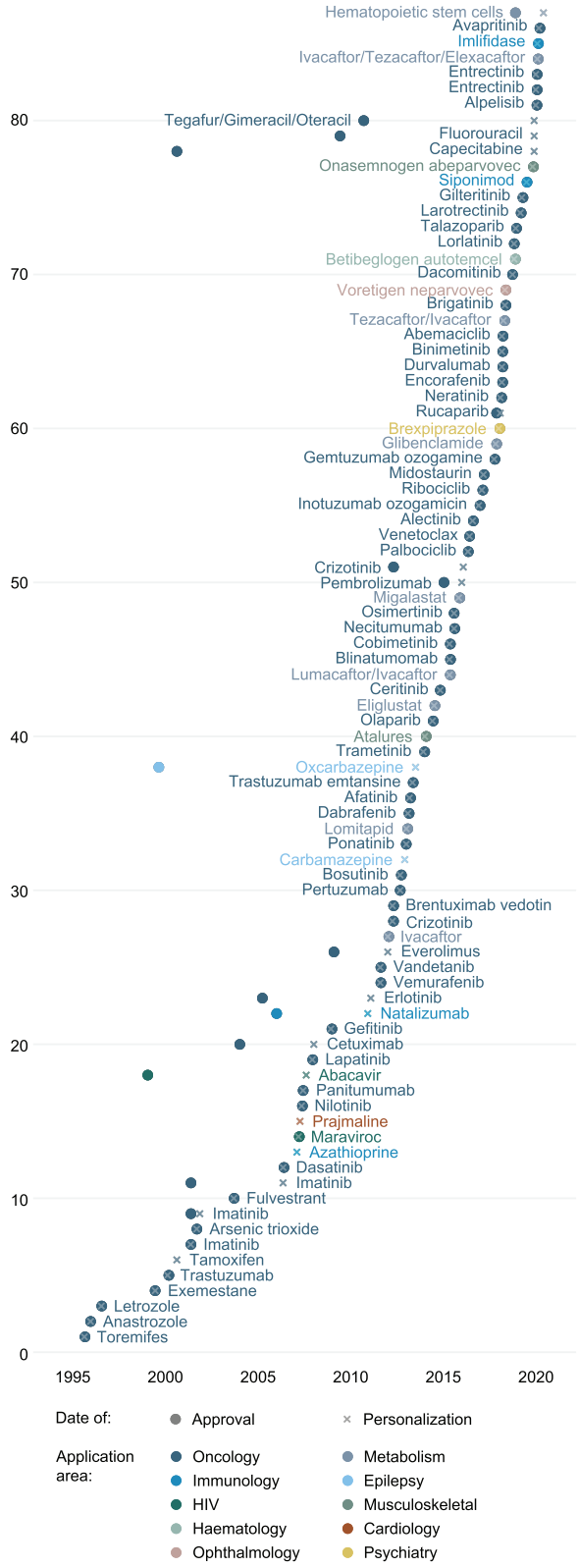

Figure 1 PMs in Germany from 1995 to 2020. *Data sources*: vfa[17] and EMA.[21]

Table 1 Disease burden and PMs in Germany in 2019–20

Rank	Cause of death or injury	Per 100 000 population			PM drugs
		DALYs	YLLs	YLDs	
1	Neoplasms	6262	5921	341	64
2	Cardiovascular diseases	6041	5392	649	1
3	Musculoskeletal disorders	3155	36	3120	1
4	Neurological disorders	2333	975	1358	7
5	Mental disorders	2075	2	2073	1
6	Other NCDs	2069	370	1699	11
7	Diabetes and kidney diseases	1857	829	1029	1
8	Unintentional injuries	1476	419	1058	
9	Chronic respiratory diseases	1433	786	647	
10	Digestive diseases	1302	1033	268	1
11	Sense organ diseases	741		741	1
12	Skin and subcutaneous diseases	712	34	678	1
13	Substance use disorders	699	317	381	
14	Self-harm and interpersonal violence	543	490	53	
15	Respiratory infections and TB	481	380	101	
16	Transport injuries	329	222	107	
17	Maternal and neonatal disorders	266	117	149	3
18	Enteric infections	158	60	98	
19	Nutritional deficiencies	143	10	133	
20	Other infectious diseases	52	35	16	
21	HIV/AIDS and STIs	34	20	14	2
22	NTDs and malaria	2	0.4	1.6	
23	All causes	32 162	17 448	14 714	94

DALYs, disability-adjusted life years; YLLs, years of life lost due to premature death; YLDs, years lived with disability; NCDs, non-communicable diseases; TB, tuberculosis; NTDs, neglected tropical diseases. *Data sources*: GBD 2019 Study,[18] vfa.[17]

diseases subtypes that might be treated with PM drugs belonged to 12 major cause groups (Supplementary Material, Table S1). The cause group 'neoplasms', for instance, included the disease burden of 41 specific cancer types (5974 DALYs), other malignant neoplasms (229 DALYs) and other neoplasms (59 DALYs). Cancer subtypes in 18 of the 42 cancer groups distinguished by the GBD Study may be treated, in some instances, with one of the 60 PM drugs approved for oncology in Germany. In comparison, PM drugs were available for 15 cancer subtypes in 2010, for 5 in 2000 and for 2 in 1996 when the first two PM drugs (toremifene, anastrozole) were approved for estrogen receptor-positive breast cancer treatment.

Figure 2 shows the development of the disease burden in Germany in 5-year intervals from 1995 to 2020 for 22 major causes of disease. For each cause group, the portion of the disease burden without and with indications for the PM drugs that were available in Germany in the respective year is indicated. The first 10 PM drugs approved in Germany between 1996 and 2006 were all in the area of oncology. PM drugs became subsequently approved in additional areas: for HIV treatment, immunology, cardiology since 2007; for epilepsy since 2013; for musculoskeletal disorders since 2014; for ophthalmology and psychiatry since 2018.

In total, the disease burden due to causes which, in some instances, can currently be treated with PM drugs is 7825 DALYs per 100 000 population compared with a burden of disease of 32 162 DALYs per 100 000 population (24.3%). Fifteen years earlier, the disease burden in the application areas of the 9 PM drugs available in 2005 was 2521 DALYs compared with a total disease burden of 31 338 DALYs (8.0%; Table 2).

Comparing the disease burden with and without indications for PM drugs implies that at least 75% — and probably a lot more — of the disease burden in Germany in 2020 was due to diseases that were outside of the domain of PM drugs. For 25 of 83 PM drugs, the frequency of disease subtypes that might receive different treatments due to personalized drug use has been reported (12.5%, interquartile range: 4.5–30; Supplementary Material, Table S2). Multiplying the 2020 disease burden share with PM drug indications with this frequency results in estimating a share of 978 DALYs (352–1248 or 3.0% [1.1–7.3] of the total burden) per 100 000 population that may have been caused by disease subtypes that were potentially treated differently due to availability of personalized drugs.

Discussion

Applications of PM, defined as targeted drug use based on a biomarker test, are increasing in Germany and elsewhere.[4, 19, 24] Some see potential for PM drugs to improve health outcomes, lower healthcare costs and reduce drug-development costs and time.[25] Others point to successes and setbacks of personalized pharmacotherapy.[3, 26] Again others argue that PM has to become broader than PM drugs, including, for instance, personalized approaches to disease prevention, to become relevant for population health improvement.[27–29]

Due to a lack of quantitative data, debates about the possible contribution of PM to public health are largely built on qualitative arguments. The following quotes illustrate:

> *Research undertaken in the name of precision medicine [or personalized medicine] may well open new vistas of science, and precision medicine itself may ultimately make critical contributions to a narrow set of conditions that are primarily genetically determined. But the challenge we face to improve population health does not involve the frontiers of science*

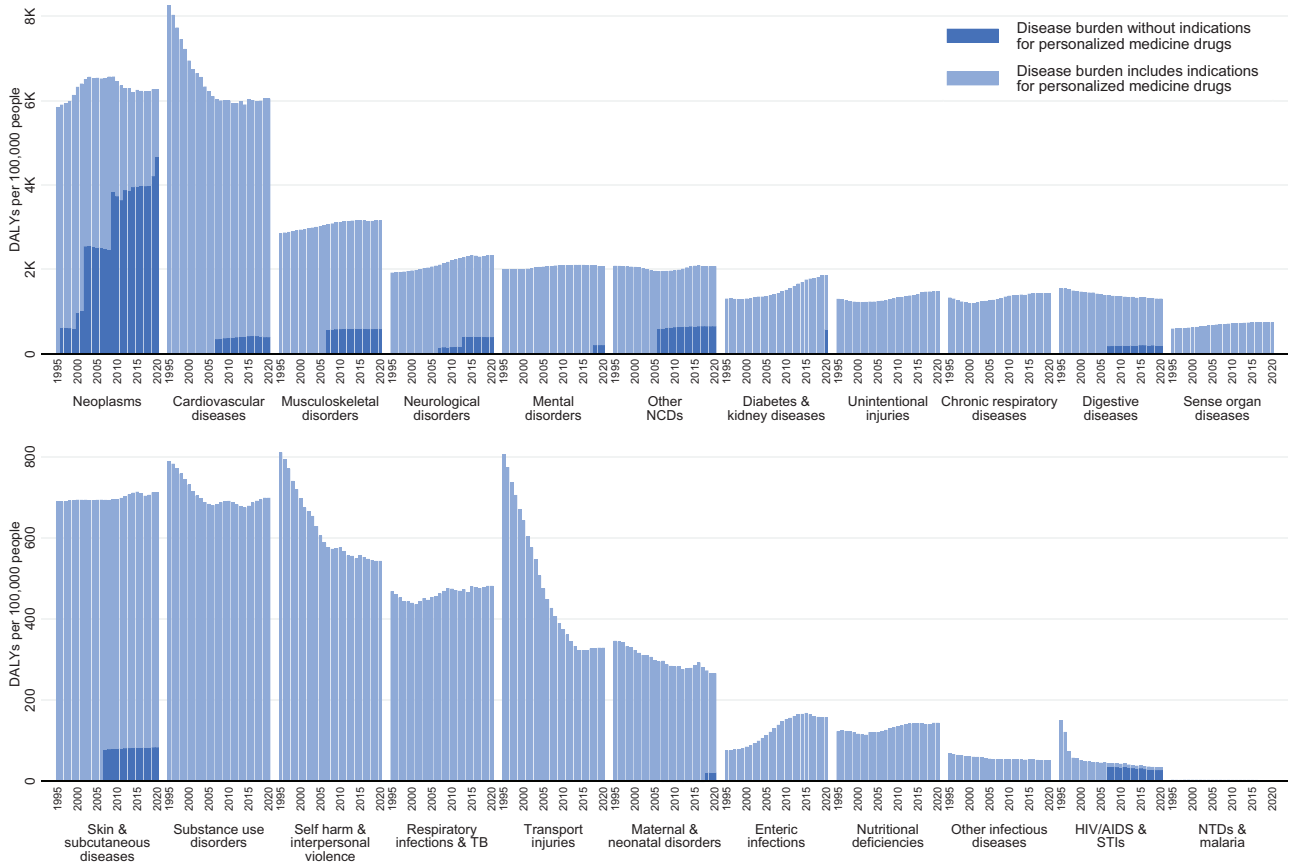

Figure 2 Disease burden with and without indications for personalized medicine drugs in Germany from 1995 to 2020, by major causes. Disease burden for the year 2020 is a prediction, assuming no change from the previous year. *Data sources*: GBD 2019 Study,[18] vfa.[17]

Table 2 Disease burden with and without indications for personalized medicine drugs in Germany from 1995 to 2020

Year	Number of PM drugs (applications)	GBD level 3 and level 4 causes (neoplasms)	DALYs per 100 000			
			Total	PM not available at the time	PM available for some causes	%
1995			33 335	33 335		
2000	5 (5)	2 (2)	31 878	30 900	978	3.1
2005	9 (10)	8 (7)	31 338	28 817	2521	8
2010	19 (21)	25 (10)	31 601	25 815	5786	18.3
2015	44 (46)	31 (15)	32 043	25 689	6354	19.8
2020	83 (87)	39 (18)	32 162	24 337	7825	24.3

Disease burden for the year 2020 is a prediction, assuming no change from the previous year. *Data sources*: GBD 2019 Study,[18] vfa.[17]

> *and molecular biology. It entails development of the vision and willingness to address certain persistent social realities, and it requires an unstinting focus on the factors that matter most to the production of population health.*[14]

Few cost-effectiveness analyses of PM drugs exist[15, 16] and, to my knowledge, no previous study attempted to quantify how much morbidity and mortality occurs outside the application areas of available PM drugs.

The study at hand mapped the indications of the PM drugs approved in Germany to national disease burden causes. The results of this mapping indicated that at least 75% of the disease burden, and probably much more burden, occurred due to disease causes outside of PM drug application areas. Using the median frequency for the prevalence of biomarkers, in cases in which such data were available, to gauge the portion of treatment decisions that might have changed due to personalized drug use further suggested that less than 3.0% (interquartile range: 1.1–7.3) of the total burden is affected by personalized drug applications (compared to a one-size-fits-all approach).

Pushing towards quantifying how much population health might be within and outside the domain of PM, as this study has done, is subject to limitations. While the principle of personalizing interventions can be applied in various areas of healthcare,[2] the study at hand focused on personalized pharmacotherapy. The study identified the disease burden shares without and with disease causes that are,

in some instances, PM drug indications. Some PM drugs could be matched with disease burden causes more specifically than others. Cancer drugs could be matched more specifically to GBD causes, for instance, than immunosuppressive drugs. The PM drug *lomitapide*, for instance, is approved as a lipid-lowering agent for the treatment of familial hypercholesterolaemia since 2013. It helps reduce the risk of arteriosclerosis and thus reduces the risk of stroke and ischaemic heart disease. As a consequence, a substantial share of the disease burden due to 'other non-communicable diseases' became marked as a disease group with PM drug indications. However, the homozygous form of familial hypercholesterolaemia is rare (occurring 1 in a million births). Population health improvements are thus small despite potential, large benefits for individual patients. For treatment of common cancers in some patients with PM drugs, the discrepancy between the indicated and the actual disease burden in areas of PM drugs application is likely to be less pronounced. Either way, the disease burden without PM drug indications quantified in this study might be too high. On the other hand, the development of the disease burden in the absence of PM drugs is not known. This may raise concern about potentially underestimating the burden with PM drug indications. Estimating the extent to which PM drug-susceptible disease burden is affected by personalized pharmacotherapy in comparison to drug use without genetic targeting is, however, outside the scope of this study. Finally the evaluated, available biomarker prevalences might fail to approximate how often drug treatment decisions change due to all personalized drug use.

Conclusion

Genetic information is increasingly used to diagnose and treat diseases by subtypes. At the same time, PM drug development and applications may bind resources in areas where a comparatively small portion of the disease burden occurs. This study assessed the portion of the disease burden with PM drug indications in Germany and compared it against the total disease burden.

Mapping PM drug indications to disease burden causes suggested that at least three quarters of the current morbidity and mortality in Germany occurred outside the areas of application of the 83 PM drugs approved by the end of 2020. About 3.0% (interquartile range: 1.1–7.3) of the total disease burden may have been caused by disease subtypes that were potentially treated differently due to the use of personalized pharmacotherapy.

Supplementary Material

Supplementary data are available at *Journal of Pharmaceutical Health Services Research* online.

Author Contributions

S.K. conducted all analyses and wrote the manuscript.

Funding

None.

Conflict of Interest

The author declares no conflict of interest.

Availability of Data and Material

All data are available open access.

Code Availability

Available from the author upon request.

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