RESEARCH ARTICLE

Multicenter, cross-sectional study of the costs of illness and cost-driving factors in adult patients with epilepsy

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Abstract

Objective: This study was undertaken to quantify epilepsy-related costs of illness (COI) in Germany and identify cost-driving factors.

Methods: COI were calculated among adults with epilepsy of different etiologies and severities. Multiple regression analysis was applied to determine any epilepsy-related and sociodemographic factors that serve as cost-driving factors.

Results: In total, 486 patients were included, with a mean age of 40.5 ± 15.5 years (range = 18–83 years, 58.2% women). Mean 3-month COI were estimated at €4911, €2782, and €2598 for focal, genetic generalized, and unclassified epilepsy, respectively. The mean COI for patients with drug-refractory epilepsy (DRE; €7850) were higher than those for patients with non-DRE (€4720), patients with occasional seizures (€3596), or patients with seizures in remission for >1 year (€2409). Identified cost-driving factors for total COI included relevant disability (unstandardized regression coefficient b = €2218), poorer education (b = €2114), living alone (b = €2612), DRE (b = €1831), and frequent seizures (b = €2385). Younger age groups of 18–24 years (b = −€2945) and 25–34 years (b = −€1418) were found to have lower overall expenditures. A relevant disability (b = €441), DRE (b = €1253), frequent seizures (b = €735), and the need for specialized day-care (b = €749) were associated with higher direct COI, and poorer education (b = €1969), living alone (b = €2612), the presence of a relevant disability (b = €1809), DRE (b = €1831), and frequent seizures (b = €2385) were associated with higher indirect COI.

Significance: This analysis provides up-to-date COI data for use in further health economics analyses, highlighting the high economic impacts associated with disease severity, disability, and disease-related loss of productivity among adult patients with epilepsy. The identified cost drivers could be used as therapeutic and socioeconomic targets for future cost-containment strategies.
1 | INTRODUCTION

In modern health systems, which are subject to increasing economization measures, cost-recovery pressures, and profit motives, the evaluation of illness-specific costs, referred to as the costs of illness (COI), is of central importance.\(^1\) Chronic illnesses and diseases associated with disabilities are of particular interest, because they typically involve long-term expenses for both medical and social care, and determining the profitability of both established and new diagnostic and therapeutic measures can guide treatment decisions.\(^2\) Health economics and outcome research (HEOR) has emerged as a scientific discipline that aims to provide reliable scientific databases for the use of scientists and health care decision-makers worldwide.\(^3\)

Epilepsy is a common, chronic, neurological disorder characterized clinically by the occurrence of recurrent seizures of various semiologies. Aside from a few variants with a self-limiting course, which typically present during childhood and adolescence, most epileptic disorders have a chronic course and are sometimes associated with the development of epileptic encephalopathies or mental or physical disabilities.\(^4,5\) Epilepsy represents a major burden to patients, their families, and health care systems.\(^6\)–\(^10\) The influence of statutory cost-containment policies on direct epilepsy-specific COI has been demonstrated for the German health care system\(^11,12\); however, the introduction of new antiseizure medications (ASMs) and other novel therapeutic or diagnostic interventions can be challenging due to the presence of economically motivated obstacles and controversies.\(^13\)

The primary aim of this study was to determine the COI among adult patients with different epilepsy etiologies, severities, and disease courses. The secondary aim was to identify epilepsy-related cost-driving factors to provide therapeutic and socioeconomic targets for future cost-containment strategies.

2 | MATERIALS AND METHODS

2.1 | Study setting, patients, and design

This analysis was based on data collected during the Epi2020 study, a large, multicenter study focusing on different health care aspects of patients with epilepsy in Germany. Epi2020 enrolled adult patients with epilepsy between October 2020 and December 2020 at four different epilepsy centers: Frankfurt am Main, Greifswald, Marburg, and Münster. All study sites offer specialized inpatient and outpatient care for patients with epilepsy, epileptic encephalopathies, or syndromes associated with epilepsy. Specialized epilepsy centers, such as those where this study was conducted, play a central role in the care of children, adolescents, and adult patients with epilepsy in Germany. Currently, there are 50 centers certified by the German chapter of the International League Against Epilepsy (ILAE) (Deutsche Gesellschaft für Epileptologie e.V., Berlin, Germany), with different focuses in terms of methods (e.g., epilepsy surgery) and age groups (e.g., children and adolescents). In Germany, primary care for epilepsy patients is provided by general practitioners and neurologists in private practice. Patients with unclear, drug-refractory, or potentially surgically treatable epilepsy are usually referred to one of the specialized epilepsy centers. In addition, women who desire to have children are often referred to centers for counseling, as well as pregnant patients for regular monitoring during pregnancy. Although the Epilepsy Center Frankfurt Rhine-Main has a primarily urban catchment area, the epilepsy centers in Greifswald, Marburg, and Münster provide care as the only neurologic departments in their cities and surrounding rural areas, with care for populations of more than half a million each.\(^14\) Due to its representative population structure, the area around Marburg was used earlier for a population-based estimate of the incidence of status epilepticus in Germany.\(^14\) All four hospitals provide the
full range of neurologic care, with expertise in epileptology and intensive care medicine. The study was approved by the ethics committee of Goethe University Frankfurt (reference 19-440) and was registered with the German Clinical Trials Register (DRKS00022024; Universal Trial Number: U1111-1252-5331).

All adult patients (≥18 years old) with confirmed epilepsy diagnoses were eligible for study inclusion. Written consent provided by the patient was mandatory before study enrollment. Patients or, in cases associated with intellectual or physical disabilities, their caretakers were asked to complete a standardized questionnaire designed to systematically record direct and indirect cost components, in addition to sociodemographic and other disease-related information. The cost-assessment questionnaire used in Epi2020 has been validated and established for use in previous HEOR studies.12,15 For each COI item, the respondents were asked whether the costs were incurred during epilepsy treatment, and only epilepsy-associated costs were used for cost calculations.

2.2 Cost assessment

Cost calculations were based on current national and international recommendations and followed a well-established and validated, bottom-up approach from the perspective of the statutory health insurance (Gesetzliche Krankenversicherungen).16-18 Direct costs, such as expenditures for hospitalization, outpatient treatment, rehabilitation, medication, therapeutic measures, and medical auxiliaries, were assessed using a validated questionnaire describing the 3-month period immediately before study entry. Drug costs were obtained from the drug prescription report (Arzteverordnungsreport 2020),19 and costs for inpatient care (hospitalization and rehabilitation) were calculated using the current version of the German Diagnosis Related Groups (www.g-drg.de). The costs of outpatient medical consultations, therapies, and diagnostics were calculated using currently valid national benchmarks (Einheitlicher Bewertungsmaßstab, www.kbv.de).20 Costs for medical auxiliaries were derived from provider price lists for cases in which the costs could not be indicated by the patients. Indirect costs, such as expenditures caused by loss of productivity due to unemployment or disease-related reductions in work hours, days off due to seizures, or epilepsy-related early retirement, were evaluated using the human capital approach for patients younger than 67 years, which corresponds to the retirement age in Germany. According to the German Federal Statistical Office (DeSTATIS, www.destatis.de), the mean gross income in 2020 was €47 700 per year, equaling €3975 per month or €131 per calendar day. The productivity loss attributed to epilepsy was equated as the monetary equivalent of time not worked by patients with epilepsy before reaching the retirement age of 67 years.15,21,22 Methodically, indirect COI due to premature epilepsy-related death and intangible costs could not be assessed.

2.3 Epilepsy severity and seizure frequency

All epilepsy diagnoses and medical and seizure terminology used in this study were derived from the latest definitions established by the ILAE.4,5,23,24 Patients with uncertain epilepsy diagnoses were excluded from the data analysis to increase the data quality and reliability. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)25 guidelines were closely followed during study planning, study conduct, and data analysis.

Epilepsy severity was graduated according to established prognostic categories that have been used in previous health economics evaluations.26-28 Newly diagnosed epilepsy (NDE) cases were defined as patients with new onset, unprovoked seizures who were presented for the initiation or completion of a diagnostic workup and were diagnosed with epilepsy as a result. Epilepsy in remission (seizures in remission) cases were defined as patients with complete seizure control for ≥12 months at the time of study entry. Patients with persistent seizures who did not require treatment changes were defined as occasional seizure cases. Patients with ongoing seizures were defined as non-drug-refractory epilepsy or drug-refractory epilepsy (DRE) cases, depending on the expected response to ASMs as judged by the treating physician. Seizure frequency was calculated according to the patients' reports for overall seizure frequency and was not divided according to individual seizure semiology.

2.4 Data entry and statistical analysis

Statistical comparisons were performed using appropriate tests in SPSS (IBM Corporation) or GraphPad Prism 9 (GraphPad Software). Univariate analysis was performed using the Kruskal–Wallis test. Based on the level of measurement, only multiple regression analysis (MRA) using dichotomously dummy-coded variables was found to be suitable for multivariate data exploration. All variables from the univariate analysis, regardless of their significance levels, were included in the MRA, except for the employment situation in the indirect and total COI analyses, as this variable was the basis for the calculation of these values. No adjustments for multiple testing were
made due to the MRA used for the final interpretation of data. The unstandardized regression coefficient (b) was used to illustrate the dynamics of COI for those variables significantly contributing to the MRA. In this context, b indicates the increases or decreases of COI in Euros when the respective predictor was present (e.g., disability). Probability values < .05 were considered significant. Costs have been rounded to full Euro amounts, in keeping with typical convention, and are displayed as the mean, median, minimum, maximum, and 95% confidence interval, which was calculated using the bias-corrected accelerated bootstrapping method, assuming a right-skewed distribution. Sociodemographic data are presented as the mean ± SD, median, minimum, and maximum for continuous variables or as the number and percentage for categorical variables. Figures were created with GraphPad Prism 9 and Pixelmator Pro (Pixelmator Team).

3 | RESULTS

3.1 | Study population

Overall, health economics data were obtained from 486 adult patients enrolled in the present study, with a mean age of 40.5 ± 15.5 years (range = 18–83 years), 58.2% of whom were women (n = 283). Relevant disease-specific and sociodemographic data for the study population are presented in Table 1.

3.2 | Epilepsy-related COI

COI were calculated and stratified for different epilepsy syndromes and according to disease severity and seizure frequency. The average overall COI, without consideration for epilepsy type, severity, or seizure frequency, were calculated as €4203 ± €5473 (median = €1237), ranging from a minimum of €0 to a maximum of €21 667 over a 3-month period. Direct cost components accounted for 32.3% of the total COI, whereas indirect cost components represented 67.7%, with mean expenditures of €1358 ± €1690 (median = €728, range = €0–€13 158) and €2845 ± €4931 (median = €0, range = €0–€11 925), respectively. The proportions of direct and indirect costs and detailed data regarding cost components are presented in Figure 1.

The total COI and potential cost drivers are presented in Table 2, with direct and indirect disease-related expenditures presented in Tables 3 and 4, respectively. No significant differences in direct (p = .798), indirect (p = .213), or total costs (p = .234) were identified between patients recruited at different centers.

| TABLE 1 Sociodemographic and disease-related factors for the study population (N = 486) |
|---------------------------------|-----------------|
| Factor                         | Value           |
| Sex, % (n)                     |                 |
| Female                         | 58.2 (283)      |
| Male                           | 41.8 (203)      |
| Age, years                     |                 |
| Mean ± SD                      | 40.5 ± 15.5     |
| Median                         | 38.0            |
| Range                          | 18–83           |
| Epilepsy onset, years          |                 |
| Mean ± SD                      | 24.0 ± 16.2     |
| Median                         | 20.0            |
| Range                          | 0–79            |
| Epilepsy duration, years       |                 |
| Mean ± SD                      | 16.1 ± 15.1     |
| Median                         | 12.0            |
| Range                          | 0–71            |
| Epilepsy severity, % (n)       |                 |
| NDE                            | 1.9 (9)         |
| SR                             | 40.1 (195)      |
| OS                             | 16.3 (79)       |
| NDRE                           | 21.4 (104)      |
| DRE                            | 20.4 (99)       |
| Therapy regimen, % (n)         |                 |
| 0 ASM                          | 4.5 (22)        |
| 1 ASM                          | 40.5 (197)      |
| 2 ASMs                         | 35.4 (172)      |
| ≥3 ASMs                        | 19.5 (95)       |

Abbreviations: ASM, antiseizure medication; DRE, drug-refractory epilepsy; NDE, newly diagnosed epilepsy; NDRE, non-drug-refractory epilepsy; OS, occasional seizures; SR, seizures in remission.

3.3 | Cost-driving factors

3.3.1 | Univariate analysis

The univariate analysis revealed sex, age, level of education, employment status, marital status, presence of a relevant disability, epilepsy etiology, epilepsy severity, seizure frequency, and ASM regimen as factors significantly associated with increased total COI (Table 2). Sex, age, employment situation, marital status, the presence of a relevant disability, epilepsy etiology, epilepsy severity, seizure frequency, and the number of ASMs being used were significant cost-driving factors for direct COI (Table 3). Age, education, employment situation, presence of a relevant disability, epilepsy etiology, epilepsy severity, seizure frequency, and the number of ASMs being used were also identified as significant factors associated with indirect
COI (Table 4). The cost distributions for age, epilepsy severity, and seizure frequency are shown in Figure 2.

3.3.2 | Multivariate analysis

The MRA revealed a model with a significantly improved ability to predict epilepsy-specific total costs relative to any univariate analysis \((p < .001)\), with an overall model fit of \(R^2 = .306\). The younger age groups of 18–24 years \((b = −€2945, p < .001)\) and 25–34 years \((b = −€1418, p = .032)\) were associated with significantly lower total COI. Less education \((≤10\text{ years}, b = €2114, p = .003)\), living alone \((b = €2702, p < .001)\), the presence of a relevant disability \((b = €2219, p < .001)\), DRE \((b = €3150, p < .001)\), and experiencing weekly seizures \((b = €3144, p < .001)\) were associated with significantly higher total COI. The MRA also revealed a model with a significantly improved ability to predict epilepsy-specific direct costs relative to any univariate analysis \((p < .001)\), with an overall model fit of \(R^2 = .194\). The presence of a relevant disability \((b = €441, p = .013)\), DRE \((b = €1253, p < .001)\), experiencing weekly seizures \((b = €735, p = .014)\), and the need for specialized daycare \((b = €749, p = .039)\) remained significant variables associated with higher direct costs. All other tested variables remained nonsignificant within the model \((p ≥ .05)\). Finally, the MRA revealed a model with a significantly improved ability to predict epilepsy-specific indirect costs relative to any univariate analysis \((p < .001)\), with an overall model fit of \(R^2 = .241\). The younger age groups of 18–24 years \((b = −€3169, p < .001)\) and 25–34 years \((b = −€1434, p = .021)\) were associated with significantly lower indirect costs, whereas the age group of 55–64 years was associated with higher indirect COI \((b = €1626, p = .035)\). Less education \((≤10\text{ years}, b = €1969, p = .004)\), living alone \((b = €2612, p < .001)\), the presence of a relevant disability \((b = €1809, p < .001)\), DRE \((b = €1831, p = .037)\), and experiencing weekly seizures \((b = €2385, p = .005)\) were associated with significantly higher indirect COI.

4 | DISCUSSION

In increasingly economically oriented health care systems, the accurate evaluations of COI and cost-driving factors represent central aspects that guide the implementation of cost-containment measures. This prospective, multicenter study provided detailed COI data for 486 patients with different epilepsy etiologies and severities, and MRA was used to identify potential cost-driving factors that could serve as future targets for cost-containment approaches.

Disease-specific direct, indirect, and overall COI varied significantly between different patient groups (Tables 2–4). In particular, the differences in cost-driving factors according to age groups, disease severity, and seizure frequency were striking (Figure 1). Many other factors found to be significant in the univariate analysis for higher or lower overall, direct, or indirect COI failed to remain significant in the multivariate analysis. For these variables (e.g., patient sex), it can be assumed that they are not independent
### Table 2: Impacts of sociodemographic and disease-specific factors on total costs of illness in adult patients with epilepsy (in 2020 Euros, N = 486)

| Factor                        | (%) n | Mean ± SD | Median | Minimum | Maximum | 95% confidence interval | p   |
|-------------------------------|-------|-----------|--------|---------|---------|-------------------------|-----|
| Sociodemographic aspects      |       |           |        |         |         |                         |     |
| Age, years                    |       |           |        |         |         |                         |     |
| 18–24                         | 17.7 (86) | 2473 ± 3862 | 986    | 0       | 15 498  | 1732–3251               | <.001c |
| 25–34                         | 25.3 (123) | 3539 ± 4897 | 1347   | 0       | 18 015  | 2710–4473               |     |
| 35–44                         | 21.8 (106) | 4737 ± 5765 | 1675   | 46      | 18 733  | 3729–5853               |     |
| 45–54                         | 13.9 (67)  | 5597 ± 6363 | 1754   | 0       | 21 667  | 4195–7071               |     |
| 55–64                         | 13.0 (63)  | 7789 ± 6152 | 12 053 | 19      | 16 630  | 6316–9269               |     |
| ≥65                           | 8.4 (41)   | 653 ± 802  | 341    | 0       | 3241    | 427–892                 |     |
| Level of education            |       |           |        |         |         |                         |     |
| None                          | 4.7 (23)   | 5728 ± 5406 | 3840  | 0       | 16 805  | 3746–7916               | <.001c |
| ≤10 years                     | 17.5 (85)  | 5857 ± 6236 | 2712   | 0       | 21 667  | 4622–7178               |     |
| 11 years                      | 32.3 (157) | 4403 ± 5595 | 1459   | 25      | 18 252  | 3535–5387               |     |
| 13 years                      | 41.6 (202) | 2983 ± 4650 | 864    | 0       | 21 572  | 2417–3521               |     |
| n.a.                          | 3.9 (19)    | 6272 ± 6293 | 2771   | 0       | 16 423  | 3395–9078               |     |
| Marital status                |       |           |        |         |         |                         |     |
| Permanent relationship        | 55.3 (269) | 3727 ± 5133 | 1077   | 0       | 21 572  | 3052–4455               | .002c |
| Divorced                      | 4.7 (23)    | 7297 ± 5914 | 6724   | 166     | 14 593  | 4596–7911               |     |
| Single, living with others    | 16.5 (80)   | 4738 ± 6256 | 1323   | 0       | 21 667  | 3365–6339               |     |
| Single, living alone          | 19.8 (96)   | 4464 ± 5374 | 1666   | 0       | 18 252  | 3463–5462               |     |
| Widowed                       | 1.9 (9)     | 2854 ± 5263 | 103    | 25      | 12 317  | 103–6127                |     |
| n.a.                          | 1.9 (9)     | 4326 ± 6235 | 1143   | 523     | 16 423  | 916–8554                |     |
| Relevant disability           |       |           |        |         |         |                         |     |
| Yes                           | 58.2 (283) | 5742 ± 6060 | 2438   | 0       | 21 667  | 4984–6453               | <.001c |
| No                            | 41.2 (200) | 2008 ± 3522 | 452    | 0       | 15 498  | 1545–2526               |     |
| Epilepsy-related aspects      |       |           |        |         |         |                         |     |
| Epilepsy syndrome             |       |           |        |         |         |                         |     |
| Focal epilepsy                | 67.7 (329) | 4911 ± 5836 | 1639   | 0       | 21 667  | 4344–5565               | <.001c |
| Temporal lobe epilepsy        | 32.1 (156) | 5085 ± 5695 | 2005   | 0       | 21 667  | 4193–6021               |     |
| Frontal lobe epilepsy         | 8.0 (39)    | 3692 ± 5372 | 1077   | 30      | 18 252  | 2407–5698               |     |
| Idiopathic generalized epilepsy | 21.2 (103) | 2782 ± 4331 | 599    | 0       | 14 421  | 2067–3639               |     |
| Juvenile myoclonic epilepsy   | 8.4 (41)    | 2692 ± 4260 | 636    | 0       | 14 421  | 1519–4032               |     |
| Juvenile absence epilepsy     | 1.9 (9)     | 2974 ± 4363 | 1065   | 46      | 12 424  | 679–5848                |     |
| Unclassified epilepsy         | 11.1 (54)   | 2598 ± 4189 | 660    | 0       | 14 065  | 1612–3657               |     |

(Continues)
cost-driving factors for COI in the underlying study population. The mean disease-related expenditures for focal epilepsy were calculated at €1536 over 3 months, corresponding to €6144 per year, €512 per month, and €17 per day. COI of €1044, €4176, €358, and €11 were calculated for genetic generalized epilepsies per quarter, year, month, and day, respectively. These amounts were comparable to the mean annual expenditures of €9256 reported in a recent study examining epilepsy-related COI in Austria, the range of €31–€3703 ($40–$4748) reported by a global analysis of the burden of epilepsy in 2006. The observed increase in recent costs appears to be associated with rising per capita income, inflation, and the rising costs of health care.9,11,12

In line with the present findings, several studies from the USA and Europe identified the lack of seizure freedom associated with recurrent seizures, hospitalization, and seizure-related unemployment and productivity losses as the main cost-driving factors underlying

### Table 2 (Continued)

| Factor                        | (%) n | Mean ± SD | Median | Minimum | Maximum | 95% confidence interval\(a\) | \(p^b\) |
|-------------------------------|-------|-----------|--------|---------|---------|-----------------------------|-------|
| **Epilepsy severity**         |       |           |        |         |         |                             |       |
| Newly diagnosed epilepsy      | 1.9 (9)| 2546 ± 2243| 1847   | 71      | 7231    | 1200–4096                   | <.001\(c\) |
| Seizures in remission         | 40.1 (195)| 2409 ± 4369| 399    | 0       | 14 928  | 1770–3038                   |       |
| Occasional seizures           | 16.3 (79) | 3569 ± 5160| 1178   | 30      | 18 733  | 2538–4881                   |       |
| Non-drug-refractory epilepsy  | 21.4 (104)| 4720 ± 5461| 1769   | 0       | 21 667  | 3761–5783                   |       |
| Drug-refractory epilepsy      | 20.4 (99) | 7850 ± 6065| 5726   | 0       | 21 572  | 6587–9103                   |       |
| **Epilepsy duration**         |       |           |        |         |         |                             |       |
| ≤2 years                      | 18.7 (91) | 3761 ± 4911| 1347   | 0       | 16 630  | 2820–4776                   | .080  |
| 3–10 years                    | 22.4 (109)| 3659 ± 5511| 799    | 0       | 21 667  | 2723–4678                   |       |
| ≥10 years                     | 53.9 (262)| 4428 ± 5552| 1425   | 0       | 21 572  | 3817–5067                   |       |
| n.a.                          | 4.9 (24)  | 5898 ± 6247| 2906   | 0       | 18 015  | 3411–8628                   |       |
| **Epilepsy onset**            |       |           |        |         |         |                             |       |
| <18 years of age              | 29.2 (142)| 3679 ± 5112| 1073   | 19      | 16 805  | 2848–4522                   | .278  |
| ≥18 years of age              | 64.6 (314)| 4454 ± 5592| 1483   | 0       | 21 667  | 3843–5057                   |       |
| n.a.                          | 6.2 (30)  | 4050 ± 5852| 988    | 0       | 18 015  | 1959–6032                   |       |
| **Seizure frequency**         |       |           |        |         |         |                             |       |
| ≥1 seizure per day            | 4.3 (21)  | 6183 ± 5730| 3472   | 0       | 18 252  | 3754–8935                   | <.001\(c\) |
| ≥1 seizure per week           | 10.1 (49)| 8481 ± 5997| 8625   | 0       | 21 572  | 6769–10 182                 |       |
| ≥1 seizure per month          | 17.7 (86) | 5105 ± 5528| 2384   | 46      | 18 015  | 3977–6314                   |       |
| ≥1 seizure per 6 months       | 9.3 (45)  | 5273 ± 6031| 2472   | 185     | 21 667  | 3605–6992                   |       |
| ≥1 seizure per 12 months      | 10.7 (52) | 3512 ± 4939| 1161   | 30      | 16 870  | 2301–4873                   |       |
| Seizure-free for              |       |           |        |         |         |                             |       |
| ≥12 months                    | 40.7 (198)| 2274 ± 4257| 405    | 0       | 16 630  | 1685–2881                   |       |
| **Therapy regimen**           |       |           |        |         |         |                             |       |
| No ASM                        | 4.5 (22)  | 3118 ± 5016| 308    | 0       | 14 593  | 1179–5523                   | <.001\(c\) |
| 1 ASM                         | 40.5 (197)| 2309 ± 4198| 425    | 19      | 21 572  | 1768–2945                   |       |
| 2 ASMs                        | 35.4 (172)| 4745 ± 5581| 1795   | 74      | 21 667  | 3927–3991                   |       |
| ≥3 ASMs                       | 19.5 (95) | 7401 ± 6070| 4995   | 218     | 18 252  | 6252–8568                   |       |

Abbreviations: ASM, antiseizure medication; n.a., not available.

\(a\)Calculated using the bias-corrected and accelerated method assuming a right-skewed distribution.

\(b\)Probability value by univariate analysis performed using Kruskal–Wallis test.

\(c\)Statistically significant.

\(d\)Subvariables not included in univariate and multivariate analysis.

USA-based analysis, and the range of €31–€3703 ($40–$4748) reported by a global analysis of the burden of epilepsy in 2006.9,30,31 The observed increase in recent costs appears to be associated with rising per capita income, inflation, and the rising costs of health care.11,12

In line with the present findings, several studies from the USA and Europe identified the lack of seizure freedom associated with recurrent seizures, hospitalization, and seizure-related unemployment and productivity losses as the main cost-driving factors underlying
### Table 3: Impacts of sociodemographic and disease-specific factors on direct costs of illness in adult patients with epilepsy (in 2020 Euros, N = 486)

| Factor                        | (%) | n   | Mean ± SD | Median | Minimum | Maximum | 95% confidence interval | p     |
|-------------------------------|-----|-----|-----------|--------|---------|---------|-------------------------|-------|
| **Sociodemographic aspects**  |     |     |           |        |         |         |                         |       |
| Sex                           |     |     |           |        |         |         |                         |       |
| Female                        | 58.2| 283 | 1209 ± 1565 | 653    | 0       | 13 158  | 1043–1403              | .024  |
| Male                          | 41.8| 203 | 1565 ± 1834 | 866    | 0       | 11 854  | 1355–1802              |       |
| Age, years                    |     |     |           |        |         |         |                         |       |
| 18–24                         | 17.7| 86  | 1444 ± 2033 | 716    | 0       | 13 158  | 1732–3251              | .008  |
| 25–34                         | 25.3| 123 | 1412 ± 1745 | 812    | 0       | 11 854  | 1147–1724              |       |
| 35–44                         | 21.8| 106 | 1323 ± 1444 | 736    | 46      | 6834    | 1067–1614              |       |
| 45–54                         | 13.9| 67  | 1667 ± 2033 | 915    | 0       | 9742    | 1272–2140              |       |
| 55–64                         | 13.0| 63  | 1321 ± 1372 | 668    | 0       | 5335    | 1016–1631              |       |
| ≥65                           | 8.4 | 41  | 654 ± 802  | 341    | 0       | 3241    | 427–892                |       |
| Level of education            |     |     |           |        |         |         |                         |       |
| None                          | 4.7 | 23  | 2039 ± 1835 | 1561   | 0       | 7052    | 1376–2814              | .055  |
| ≤10 years                     | 17.5| 85  | 1495 ± 1910 | 665    | 0       | 9742    | 1112–1893              |       |
| 11 years                      | 32.3| 157 | 1235 ± 1213 | 812    | 25      | 6834    | 1048–1453              |       |
| 13 years                      | 41.6| 202 | 1271 ± 1854 | 651    | 0       | 13 158  | 1060–1513              |       |
| n.a.                          | 3.9 | 19  | 1853 ± 1869 | 1473   | 0       | 6178    | 3395–9078              |       |
| Employment status             |     |     |           |        |         |         |                         |       |
| Employed                      | 50.8| 247 | 1209 ± 1510 | 706    | 0       | 11 854  | 1030–1409              | <.001 |
| Unemployed                    | 6.2 | 30  | 2202 ± 2381 | 1135   | 90      | 9742    | 1451–3108              |       |
| Parental leave                | 4.5 | 22  | 1183 ± 1032 | 689    | 49      | 3414    | 777–1648               |       |
| In training                   | 8.8 | 45  | 1343 ± 2285 | 541    | 27      | 13 158  | 785–2044               |       |
| Early retirement              | 16.0| 78  | 1491 ± 1312 | 948    | 0       | 6327    | 1219–1783              |       |
| Retirement                    | 7.8 | 38  | 688 ± 997   | 240    | 0       | 4155    | 405–981                |       |
| Need for specialized daycare  | 5.8 | 28  | 2466 ± 2498 | 1849   | 0       | 9647    | 1697–3554              |       |
| Marital status                |     |     |           |        |         |         |                         |       |
| Permanent relationship        | 55.3| 269 | 1247 ± 1591 | 636    | 0       | 11 854  | 1072–1449              | <.001 |
| Divorced                      | 4.7 | 23  | 1594 ± 1604 | 1007   | 166     | 6724    | 1053–2281              |       |
| Single, living with others    | 16.5| 80  | 1523 ± 2217 | 648    | 0       | 13 158  | 1077–2074              |       |
| Single, living alone          | 19.8| 96  | 1562 ± 1523 | 1135   | 0       | 7052    | 1282–1870              |       |
| Widowed                       | 1.9 | 9   | 204 ± 309   | 79     | 0       | 971     | 55–432                 |       |
| n.a.                          | 1.9 | 9   | 1571 ± 1445 | 999    | 0       | 4662    | 784–2537               |       |
| Relevant disability           |     |     |           |        |         |         |                         |       |
| Yes                           | 58.2| 283 | 1614 ± 1710 | 999    | 0       | 9742    | 1408–1810              | <.001 |
| No                            | 41.2| 200 | 995 ± 1603  | 369    | 0       | 13 158  | 802–1234               |       |
| Epilepsy syndrome             |     |     |           |        |         |         |                         |       |
| Focal epilepsy                | 67.7| 329 | 1536 ± 1774 | 971    | 0       | 13 158  | 1380–1709              | <.001 |
| Temporal lobe epilepsyb       | 32.1| 156 | 1719 ± 2018 | 1211   | 0       | 13 158  | 1420–2024              |       |
| Frontal lobe epilepsyb        | 8.0 | 39  | 1125 ± 1213 | 648    | 30      | 6327    | 784–1552               |       |
| Factor                                      | (%) | n    | Mean ± SD | Median | Minimum | Maximum | 95% confidence interval | p^a |
|----------------------------------------------|-----|------|-----------|--------|---------|---------|-------------------------|-----|
| Idiopathic generalized epilepsy             | 21.2| 103  | 1044 ± 1524 | 440    | 0       | 7934    | 792–1327               |     |
| Juvenile myoclonic epilepsy^b                | 8.4 | 41   | 1161 ± 1714 | 546    | 0       | 7934    | 715–1648               |     |
| Juvenile absence epilepsy^b                  | 1.9 | 9    | 1605 ± 2458 | 499    | 46      | 7734    | 472–3313               |     |
| Unclassified epilepsy                        | 11.1| 54   | 868 ± 1243  | 424    | 0       | 7052    | 588–1173               |     |

**Epilepsy severity**

| Factor                                      | (%) | n    | Mean ± SD | Median | Minimum | Maximum | 95% confidence interval | p^a |
|----------------------------------------------|-----|------|-----------|--------|---------|---------|-------------------------|-----|
| Newly diagnosed epilepsy                     | 1.9 | 9    | 1601 ± 952 | 1792   | 71      | 3425    | 1032–4096              | <.001^c|
| Seizures in remission                       | 40.1| 195  | 681 ± 938  | 310    | 0       | 6311    | 562–806                |     |
| Occasional seizures                         | 16.3| 79   | 1394 ± 1623 | 894    | 30      | 7.334   | 1068–1780              |     |
| Non-drug-refractory epilepsy                | 21.4| 104  | 1454 ± 1747 | 1006   | 0       | 11 854  | 1165–1851              |     |
| Drug-refractory epilepsy                    | 20.4| 99   | 2538 ± 2162 | 2301   | 0       | 13 158  | 2131–2966              |     |

**Epilepsy duration**

| Factor                                      | (%) | n    | Mean ± SD | Median | Minimum | Maximum | 95% confidence interval | p^a |
|----------------------------------------------|-----|------|-----------|--------|---------|---------|-------------------------|-----|
| ≤2 years                                     | 18.7| 91   | 1357 ± 2049 | 741    | 0       | 13 158  | 995–1791               | .398|
| 3–10 years                                   | 22.4| 109  | 1316 ± 1763 | 470    | 0       | 9742    | 1017–1635              |     |
| ≥10 years                                    | 53.9| 262  | 1349 ± 1525 | 744    | 0       | 9647    | 1178–1541              |     |
| n.a.                                         | 4.9 | 24   | 1644 ± 1645 | 1252   | 0       | 6090    | 1027–2362              |     |

**Epilepsy onset**

| Factor                                      | (%) | n    | Mean ± SD | Median | Minimum | Maximum | 95% confidence interval | p^a |
|----------------------------------------------|-----|------|-----------|--------|---------|---------|-------------------------|-----|
| <18 years of age                             | 29.2| 142  | 1303 ± 1510 | 705    | 19      | 7934    | 1069–1555              | .266|
| ≥18 years of age                             | 64.6| 314  | 1394 ± 1758 | 818    | 0       | 13 158  | 1215–1590              |     |
| n.a.                                         | 6.2 | 30   | 1241 ± 1807 | 452    | 0       | 6724    | 680–1861               |     |

**Seizure frequency**

| Factor                                      | (%) | n    | Mean ± SD | Median | Minimum | Maximum | 95% confidence interval | p^a |
|----------------------------------------------|-----|------|-----------|--------|---------|---------|-------------------------|-----|
| ≥1 seizure per day                          | 4.3 | 21   | 2262 ± 1868 | 2173   | 0       | 7052    | 1571–3011              | <.001^c|
| ≥1 seizure per week                         | 10.1| 49   | 2520 ± 2493 | 1959   | 0       | 13 158  | 1916–3249              |     |
| ≥1 seizure per month                        | 17.7| 86   | 1727 ± 1568 | 1341   | 0       | 6724    | 1400–2094              |     |
| ≥1 seizure per 6 months                     | 9.3 | 45   | 1908 ± 2109 | 1081   | 185     | 9742    | 1350–2525              |     |
| ≥1 seizure per 12 months                    | 10.7| 52   | 1261 ± 1374 | 728    | 30      | 6178    | 908–1625               |     |
| Seizure-free for ≥12 months                 | 40.7| 198  | 734 ± 1182  | 323    | 0       | 11 854  | 592–915                |     |

**Therapy regimen**

| Factor                                      | (%) | n    | Mean ± SD | Median | Minimum | Maximum | 95% confidence interval | p^a |
|----------------------------------------------|-----|------|-----------|--------|---------|---------|-------------------------|-----|
| No ASM                                       | 4.5 | 22   | 559 ± 1118 | 46     | 0       | 4602    | 182–1041               | <.001^c|
| 1 ASM                                        | 40.5| 197  | 758 ± 1143 | 340    | 19      | 9647    | 607–914                |     |
| 2 ASMs                                       | 35.4| 172  | 1607 ± 1782 | 977    | 74      | 11 854  | 1364–1903              |     |
| ≥3 ASMs                                      | 19.5| 95   | 2334 ± 1994 | 1779   | 218     | 13 158  | 1977–2757              |     |

Abbreviations: ASM, antiseizure medication; n.a., not available.

^aCalculated using the bias-corrected and accelerated method assuming a right-skewed distribution.

^bProbability value by univariate analysis performed using Kruskal–Wallis test.

^cStatistically significant.

^dSubvariables not included in univariate and multivariate analysis.
### TABLE 4  Impacts of sociodemographic and disease-specific factors on indirect costs of illness in adult patients with epilepsy (in 2020 Euros, \(N=486\))

| Factor                        | (\%) \(n\) | Mean ± SD     | Median | Minimum | Maximum       | 95% confidence interval | \(p^d\) |
|-------------------------------|-------------|---------------|--------|---------|---------------|-------------------------|---------|
| **Sociodemographic aspects**  |             |               |        |         |               |                         |         |
| **Sex**                       |             |               |        |         |               |                         |         |
| Female                        | 58.2 (283)  | 2448 ± 4667   | 0      | 0       | 11 925        | 1989–2895               | .112    |
| Male                          | 41.8 (203)  | 3399 ± 5239   | 0      | 0       | 11 925        | 2751–4094               |         |
| **Age, years**                |             |               |        |         |               |                         |         |
| 18–24                         | 17.7 (86)   | 1029 ± 3063   | 0      | 0       | 11 925        | 478–1634                | <.001c  |
| 25–34                         | 25.3 (123)  | 2127 ± 4332   | 0      | 0       | 11 925        | 1382–2909               |         |
| 35–44                         | 21.8 (106)  | 3414 ± 5293   | 0      | 0       | 11 925        | 2479–4409               |         |
| 45–54                         | 13.9 (67)   | 3930 ± 5542   | 0      | 0       | 11 925        | 2698–5136               |         |
| 55–64                         | 13.0 (63)   | 6468 ± 5846   | 11 925 | 0       | 11 925        | 4957–7942               |         |
| ≥65                           | 8.4 (41)    | 0             | 0      | 0       | 0             | –                       |         |
| **Level of education**        |             |               |        |         |               |                         |         |
| None                          | 4.7 (23)    | 3689 ± 5116   | 523    | 0       | 11 925        | 1864–5823               | <.001c  |
| ≤10 years                     | 17.5 (85)   | 4363 ± 5677   | 0      | 0       | 11 925        | 3261–5564               |         |
| 11 years                      | 32.3 (157)  | 3168 ± 5120   | 0      | 0       | 11 925        | 2384–4070               |         |
| 13 years                      | 41.6 (202)  | 1712 ± 4032   | 0      | 0       | 11 925        | 1195–2207               |         |
| n.a.                          | 3.9 (19)    | 4419 ± 5873   | 0      | 0       | 11 925        | 1912–7045               |         |
| **Marital status**            |             |               |        |         |               |                         |         |
| Permanent relationship        | 55.3 (269)  | 2480 ± 4654   | 0      | 0       | 11 925        | 1896–3123               | .327    |
| Divorced                      | 4.7 (23)    | 5703 ± 6091   | 0      | 0       | 11 925        | 3117–7950               |         |
| Single, living with others    | 16.5 (80)   | 3216 ± 5220   | 0      | 0       | 11 925        | 2133–4404               |         |
| Single, living alone          | 19.8 (96)   | 2902 ± 4975   | 0      | 0       | 11 925        | 1944–3849               |         |
| Widowed                       | 1.9 (9)     | 2650 ± 5258   | 0      | 0       | 11 925        | 0–5963                  |         |
| n.a.                          | 1.9 (9)     | 2755 ± 5156   | 196    | 0       | 11 925        | 78–6109                 |         |
| **Relevant disability**       |             |               |        |         |               |                         | <.001c  |
| Yes                           | 58.2 (283)  | 4128 ± 5532   | 0      | 0       | 11 925        | 3477–4785               |         |
| No                            | 41.2 (200)  | 1013 ± 3113   | 0      | 0       | 11 925        | 598–1486                |         |
| **Epilepsy-related aspects**  |             |               |        |         |               |                         |         |
| **Epilepsy syndrome**         |             |               |        |         |               |                         |         |
| Focal epilepsy                | 67.7 (329)  | 3375 ± 5237   | 0      | 0       | 11 925        | 2834–3980               | .014c   |
| Temporal lobe epilepsy\(a\)  | 32.1 (156)  | 3367 ± 5207   | 0      | 0       | 11 925        | 2561–4231               |         |
| Frontal lobe epilepsy\(a\)   | 8.0 (39)    | 2838 ± 4866   | 0      | 0       | 11 925        | 1416–4386               |         |
| Idiopathic generalized epilepsy| 21.2 (103) | 1738 ± 4087   | 0      | 0       | 11 925        | 1012–2582               |         |
| Juvenile myoclonic epilepsy\(a\) | 8.4 (41)   | 1531 ± 3935   | 0      | 0       | 11 925        | 474–2777                |         |
| Juvenile absence epilepsy\(a\) | 1.9 (9)    | 1369 ± 3961   | 0      | 0       | 11 925        | 0–3980                  |         |
| Unclassified epilepsy         | 11.1 (54)   | 1730 ± 3908   | 0      | 0       | 11 925        | 801–2750                |         |

(Continues)
epilepsy-related COI. Although hospitalization predominantly impacts direct COI, productivity loss due to job loss and unemployment is most likely to affect indirect COI.27,30,32,33 The costs of ASMs were not significant within the model, despite having been identified as a relevant cost component affecting direct COI by patients with epilepsy.27,30,32,33 This outcome is likely attributable to the comparable prices of different ASMs due to statutory cost-containment measures and the correlation between ASM regimens and seizure frequency, treatment response, and epilepsy severity.11 Therefore, among the current study population, ASMs were not identified as an independent variable affecting COI. These findings distinguish epilepsy from other chronic neurological diseases, such as multiple sclerosis (€44 000–€62 700/year) and chronic inflammatory demyelinating polyneuropathy (€11 333 per 3 months), for which expensive disease-modifying drugs have been identified as cost-driving factors of direct COI.34,35 Similar to the findings presented by other studies, epilepsy is increasingly associated with indirect

### TABLE 4 (Continued)

| Factor                      | (%) | n  | Mean ± SD | Median | Minimum | Maximum | 95% confidence interval | p<sup>d</sup> |
|-----------------------------|-----|----|-----------|--------|---------|---------|-------------------------|-------------|
| **Epilepsy severity**       |     |    |           |        |         |         |                         |             |
| Newly diagnosed epilepsy    | 1.9 | (9) | 944 ± 1995| 0      | 0       | 5619    | 0–2374                  | <.001<sup>c</sup> |
| Seizures in remission       | 40.1| (195)| 1728 ± 4105| 0      | 0       | 11 925  | 1153–2333               | .148        |
| Occasional seizures         | 16.3| (79)| 2175 ± 4570| 0      | 0       | 11 925  | 1201–3368               |             |
| Non-drug-refractory epilepsy| 21.4| (104)| 3267 ± 5085| 0      | 0       | 11 925  | 2320–4264               |             |
| Drug-refractory epilepsy    | 20.4| (99)| 5312 ± 5776| 1307   | 0       | 11 925  | 4135–6529               |             |
| **Epilepsy duration**       |     |    |           |        |         |         |                         |             |
| ≤2 years                    | 18.7| (91)| 2403 ± 4516| 0      | 0       | 11 925  | 1552–3339               | .148        |
| 3–10 years                  | 22.4| (109)| 2343 ± 4599| 0      | 0       | 11 925  | 1540–3207               |             |
| ≥10 years                   | 53.9| (262)| 3079 ± 5126| 0      | 0       | 11 925  | 2505–3684               |             |
| n.a.                        | 4.9 | (24)| 4254 ± 5556| 849    | 0       | 11 925  | 2246–6667               |             |
| **Epilepsy onset**          |     |    |           |        |         |         |                         |             |
| <18 years of age            | 29.2| (142)| 2377 ± 4604| 0      | 0       | 11 925  | 1674–3114               | .526        |
| ≥18 years of age            | 64.6| (314)| 3061 ± 5056| 0      | 0       | 11 925  | 2498–3621               |             |
| n.a.                        | 6.2 | (30)| 2809 ± 5117| 0      | 0       | 11 925  | 988–4549                |             |
| **Seizure frequency**       |     |    |           |        |         |         |                         |             |
| ≥1 seizure per day          | 4.3 | (21)| 3921 ± 5273| 915    | 0       | 11 925  | 1820–6355               | <.001<sup>c</sup> |
| ≥1 seizure per week         | 10.1| (49)| 5961 ± 5622| 3920   | 0       | 11 925  | 4420–7485               |             |
| ≥1 seizure per month        | 17.7| (86)| 3379 ± 5222| 0      | 0       | 11 925  | 2396–4448               |             |
| ≥1 seizure per 6 months     | 9.3 | (45)| 3365 ± 5284| 0      | 0       | 11 925  | 1880–4911               |             |
| ≥1 seizure per 12 months    | 10.7| (52)| 2251 ± 4599| 0      | 0       | 11 925  | 1066–3532               |             |
| Seizure-free for ≥12 months | 40.7| (198)| 1539 ± 3925| 0      | 0       | 11 925  | 1038–2083               |             |
| **Therapy regimen**         |     |    |           |        |         |         |                         |             |
| No ASM                      | 4.5 | (22)| 2558 ± 4824| 0      | 0       | 11 925  | 668–4831                | <.001<sup>c</sup> |
| 1 ASM                       | 40.5| (197)| 1551 ± 3813| 0      | 0       | 11 925  | 1049–2124               |             |
| 2 ASMs                      | 35.4| (172)| 3137 ± 5129| 0      | 0       | 11 925  | 2396–3991               |             |
| ≥3 ASMs                     | 19.5| (95)| 5067 ± 5782| 522    | 0       | 11 925  | 3927–6177               |             |

Abbreviations: ASM, antiseizure medication; n.a., not available.

<sup>a</sup>Calculated using the bias-corrected accelerated method assuming a right-skewed distribution.

<sup>b</sup>Probability value by univariate analysis performed using Kruskal–Wallis test.

<sup>c</sup>Statistically significant.

<sup>d</sup>Subvariables not included in univariate and multivariate analysis.
costs due to productivity loss, including absence from work due to seizures or side effects, unemployment, and early retirement. Because employment situations served as the basis for calculating indirect COI and are, therefore, directly included in total costs, these aspects were excluded from the MRA. Therefore, productivity loss was not identified as a sociodemographic risk factor for high COI in the current analysis due to methodological limitations.

An increase in COI with age and the presence of a relevant disability that affects daily living has also been demonstrated in children, adolescents, and adults with epilepsy or other diseases characterized by epilepsy and epileptic seizures, such as Dravet syndrome or tuberous sclerosis complex. NDE has also been shown to be associated with high care costs, although this finding was not reflected in the available data, which may be due to the low number of NDE cases in the present study population. NDE is usually associated with costs for diagnostic procedures, inpatient admission, and days off work upon presentation with a first seizure.

**FIGURE 2** Mean epilepsy-related total, direct, and indirect costs of illness (from top to bottom, in Euros), according to (A) age, (B) epilepsy severity, and (C) seizure frequency, displayed as bar charts. DRE, drug-refractory epilepsy; NDE, newly diagnosed epilepsy; NDRE, non-drug-refractory epilepsy; OCS, occasional seizures; SR, seizures in remission.
In contrast with the present findings, previous studies did not identify associations between low education levels or marital status and disease-related COI. The finding that both factors were significantly associated with higher COI in the present study may indicate the potential benefits of disease-specific educational and counseling services, which have previously been demonstrated to improve health-related quality of life and patient satisfaction. Different disease-specific and sociodemographic factors were found to have significant influences on epilepsy-specific COI, and these factors may represent ideal targets for the future treatment of epilepsy and cost-containment measures from both medical and economic perspectives.

This study has several methodical limitations that may bias the results and restrict the generalizability of the findings. The study design relied on patients and their caregivers providing complete and truthful information, and post hoc data verification was not possible except for plausibility checks. In this study, COI were recorded retrospectively over a period of 3 months; hence, indirect costs due to epilepsy-related premature death (e.g., due to sudden unexpected death in epilepsy patients) or due to seizure-related trauma (fatal injuries and accidents) could not be assessed. Likewise, intangible costs could not be captured for methodological reasons. The use of mean daily doses to assess drug costs does not allow for the consideration of differences in the drug prices established by different manufacturers, which, although unlikely due to the large sample size, could lead to bias in the estimated ASM costs. Despite the multicenter recruitment of patients, regional characteristics in drug prescriptions or the provision of other medical services could also affect the comparability and generalizability of the data. Moreover, the recording of COI at epilepsy centers may have led to an upward bias of the cost results. In addition, reductions in both elective inpatient and outpatient medical care imposed in response to the SARS-CoV-2 pandemic may also have influenced the data. In line with previous German COI studies, the proportion of female patients in the present study population was higher than in the general population (51% vs. 58%, www.destatis.de). Due to a lack of gender-specific inclusion bias, this seems to be mainly due to a higher willingness of patients to participate in the study and possibly to more female patients being assigned to the centers (e.g., counseling for female patients with the desire to have children). However, the multicenter study design and the close consideration of STROBE guidelines should reduce the potential impacts of these limitations to an acceptable minimum.

In conclusion, epilepsy generates relevant COI, and the levels of direct, indirect, and total costs depend on various sociodemographic and disease-specific factors. Although some of these factors cannot be influenced, disease-specific factors reveal potential intervention targets for further cost containment. In particular, reductions in seizure frequency and adequate therapy for patients with DRE appear to be central factors that should be targeted. Based on the previously reported high demand for and acceptance of specialized epilepsy counseling services in contrast to their very limited availability and uneven distribution among German federal states, the present findings suggest that the timely referral of patients with DRE or high seizure frequency to specialized counseling centers, specialized resident neurologists, or epilepsy centers could be advantageous. Providing specific counseling for patients and family members and access to advanced diagnostics and therapeutic options, these facilities could help to reduce indirect COI and also direct cost components.

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CONFLICT OF INTEREST

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publication and affirm that this report is consistent with those guidelines.

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