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## Trends in micronutrient laboratory testing in Switzerland: a 7-year retrospective analysis of healthcare claims data

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**Abstract:** Background: Micronutrient laboratory tests (MLT) are increasing in many healthcare systems. This study assessed time trends of annual MLT incidence in the Swiss population and examined the frequency of specific MLT, defined as the number of yearly tests performed in individual persons. Methods: For annual time trends, we used a longitudinal design with a seven-year observation period (2012-2018) and for yearly testing frequency we used a cross-sectional design (2018 only). The database consisted of nationwide insurance claims from adult persons. Results: Persons with MLT compared to persons without were older (mean age 57.1 years vs 48.6 years) and to a higher proportion female (65.1% vs 45.5%). Between 2012 and 2018, we included 6.7 million person years and found an increase in the proportion of persons receiving any MLT from 24.5% to 35.0%. Tests with strongest absolute increase during the observation period were vitamin D (from 7.4% of persons to 20.4%), vitamin B12 (from 9.0% to 17.6%) and ferritin (from 17.4% to 26.6%). In 2018, vitamin D and vitamin B12 tests were performed more than once in 4.5% and 3.3% of the population, respectively. Conclusion: We found that the Swiss population undergoes MLT with high and increasing frequency. Testing for vitamin D, vitamin B12 and ferritin is very common and of questionable appropriateness.

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# Trends in Micronutrient Laboratory Testing in Switzerland: A 7-Year Retrospective Analysis of Healthcare Claims Data

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**Background:** Micronutrient laboratory tests (MLT) are increasing in many healthcare systems. This study assessed time trends of annual MLT incidence in the Swiss population and examined the frequency of specific MLT, defined as the number of yearly tests performed in individual persons.

**Methods:** For annual time trends, we used a longitudinal design with a seven-year observation period (2012–2018) and for yearly testing frequency we used a cross-sectional design (2018 only). The database consisted of nationwide insurance claims from adult persons.

**Results:** Persons with MLT compared to persons without were older (mean age 57.1 years vs 48.6 years) and to a higher proportion female (65.1% vs 45.5%). Between 2012 and 2018, we included 6.7 million person years and found an increase in the proportion of persons receiving any MLT from 24.5% to 35.0%. Tests with strongest absolute increase during the observation period were vitamin D (from 7.4% of persons to 20.4%), vitamin B12 (from 9.0% to 17.6%) and ferritin (from 17.4% to 26.6%). In 2018, vitamin D and vitamin B12 tests were performed more than once in 4.5% and 3.3% of the population, respectively.

**Conclusion:** We found that the Swiss population undergoes MLT with high and increasing frequency. Testing for vitamin D, vitamin B12 and ferritin is very common and of questionable appropriateness.

**Keywords:** laboratory testing, micronutrient, claims data, trend

## Introduction

Laboratory testing plays a key role in the treatment of patients and is essential for clinical decision-making. A high proportion of physicians' decisions rely on laboratory testing results in clinical practice.<sup>1</sup> However, in the last decades, laboratory testing significantly increased in nearly all industrialized countries; as data from several countries such as Canada, UK, and Sweden reflect. Questions have been raised on whether all these tests were appropriate and had consequences for clinical decision-making.<sup>2–4</sup> While increases in specific laboratory tests can be understood before the background of demographic changes, an increase in micronutrient laboratory testing (MLT) is difficult to understand especially in developed countries. However, studies on a comprehensive set of micronutrient tests are very scarce and only a few studies focusing on a specific micronutrient test such as vitamin D exist.<sup>3–6</sup> For example, increased testing for vitamin D has been observed in several countries, and even though guidelines do not advocate or even discourage screening for vitamin D deficiency.<sup>5–10</sup>

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In Switzerland, a recent database analysis found increasing MLT use in general practice but comprehensive population-based studies are still lacking.<sup>11</sup> Such insights, however, are necessary to advance the understanding of potential overuse of MLT. Therefore, the aim of this study, was to assess population-based time trends, incidence and frequency of MLT in Switzerland.

## Methods

### Design and Setting

We performed a retrospective population-based study incorporating both a longitudinal and a cross-sectional design using electronic healthcare claims database from one of the largest health insurance companies in Switzerland (Helsana Group). The database contained nationwide data, including pharmacy, medical and health services records, from about 1.2 million mandatorily insured persons across all cantons (~15% of the Swiss population). We considered all healthcare invoices submitted to Helsana Group for reimbursement and extracted, deidentified and anonymized persons' data from the Helsana data warehouse for analysis. As already shown in previous analysis, Helsana claims data are a representative sample from the Swiss general population.<sup>12,13</sup> Every Swiss resident is obligated to be enrolled in a basic health insurance, which is provided by health insurers on private market, but regulated by federal authorities. The basic health insurance is obligated to offer basic health insurance to every Swiss resident and to guarantee medical treatment. We included anonymized claims data records from 2012 to 2018 containing information on sociodemographic characteristics and laboratory testing of mandatorily insured persons  $\geq 18$  years of age. For the longitudinal design, we analyzed claims data per person and year (2012–2018), and for the cross-sectional design, we included claims data per person in the most recent year, 2018. The analyzed data of this study are available from the Helsana Group but restrictions exist for the availability of these data that were used under license for the current study. Data are therefore not publicly accessible but can be obtained from the authors by reasoned request and with permission from Helsana.

### Laboratory Tests

A sample of MLT was selected from the list of analyses (AL) from the Federal Office of Public Health.<sup>14</sup> The AL contains all laboratory tests covered by the mandatory health insurance in Switzerland. The selected laboratory

tests were categorized into a vitamin domain (including vitamin D, folic acid, homocysteine, methylmalonic acid, holotranscobalamin, vitamin B12/cyanocobalamin, and other vitamins), a mineral domain (including magnesium and calcium) and a trace elements domain (including iron, ferritin, transferrin, and other trace elements). A detailed list of included MLT and categories is shown in [Supplementary Table S1](#). Tests were aggregated when they measured closely related metabolites (eg different forms of vitamin D).

### Objectives

To determine trends in MLT by measuring absolute annual changes in proportions of persons receiving any or specific MLT during the total observation period (longitudinal design).

To determine incidence of specific MLT stratified by age groups.

To determine frequency of MLT by counting the number of MLTs ordered in individual persons in 2018 (cross-sectional design).

### Statistical Analysis

Using data from 2012 to 2018 (longitudinal), we assessed trends in MLT over seven years by calculating the incidence of laboratory testing per year as the proportions of persons receiving MLT (any, by domain and by individual test) in the total sample. Multiple tests of the same MLT were thereby considered as one test in this analysis. To calculate the absolute annual changes in testing for MLT over the years (2012–2018), a linear regression model was computed using year as continuous variable. Estimates were reported as coefficients including 95% confidence intervals (95%-CI). Statistical significance was set at the 0.05 level. In addition, we report relative changes over the total seven-year observation period, which were calculated by dividing the proportion of persons with the given test in 2012 by those with the test in 2018.

To calculate incidence by age groups we used the data from 2018 exclusively (cross-sectional) and stratified the population in those aged 18–44, 45–64 and  $\geq 65$ .

To assess frequency of MLT in individual persons we also used data from 2018, counted the number of individual tests per person and reported proportions of persons receiving no test, one test, two tests, or more than two tests.

We report data using descriptive statistics and use group comparison tests. Categorical variables were presented as absolute numbers of persons and percentages, continuous data as mean value including standard deviation. The

Pearson's chi-squared test was used to test categorical variables for independency. Differences regarding to continuous variables such as age (in years) were analyzed with a nonparametric analysis of variance (Kruskal–Wallis test for >2-groups-comparisons). Statistical significance was set at the 0.05 level. All analyses were performed using the statistical program R version 3.6.1 (R Development Core Team 2019).

## Results

### Trends in MLT (Longitudinal)

During the seven-year observation period, we included 6.7 million person years. Population sizes by year ranged between 906,230 (in 2017) and 997,761 (in 2012). In 2012, the proportion of persons receiving any MLT was 24.5% and the absolute annual change was +1.8% (95% CI = 1.5% to 2.1%; relative seven-year increase by a factor of 1.4). We observed annual increases of proportions of persons receiving any MLT across all MLT domains, the strongest increase appeared in vitamin testing with +2.2% (95% CI = +2.0% to +2.4%; relative seven-year increase by a factor of 2.0). For trends in overall and domain specific MLT see [Table 1](#).

We found statistically significant annual increases in percent of the population tested in every individual MLT ([Table 2](#)). The largest annual increases we found in proportions of persons tested for vitamin D (+2.2%; 95% CI = 2.0% to 2.5%), vitamin B12 (+1.5%; 95% CI = 1.4% to 1.6%) and ferritin (+1.5%; 95% CI = 1.4% to 1.7%). [Figures 1](#) and [2](#) show trends in MLT on the level of individual tests.

### Sociodemographic Characteristics (Cross-Sectional)

From the year 2018, we included 934,685 adult persons, 52.4% women with mean age 51.5 years (SD 19.7; results not shown). Overall, about 35% of the persons had at least one MLT in 2018. Considerable differences appeared when comparing persons receiving micronutrient testing with those who did not: Patients with MLT were older (mean age 57.1 years vs 48.6 years), and to a higher proportion of female gender (65.1% vs 45.5%; [Table 3](#)). Differences in language regions were small.

Concerning MLT by age groups, we found that persons  $\geq 65$  years old had the highest testing incidence consistently across all specific MLT. The highest incidence in this group we noted in testing for ferritin (34.1%), vitamin D (29.7%) and vitamin B12 (26.8%). Conversely, persons 18–44 years old had the lowest testing incidences, but the ranks in the distribution were similarly distributed with ferritin in first place (22.0%), vitamin D second (13.2%) and vitamin B12 third (11.3%). [Table 4](#) shows testing incidences in 2018 by age groups.

### Frequency of MLT

Our data comprised 1.29 million MLT in 2018. Most frequently ordered MLT were ferritin (0.30 million), vitamin D (0.21 million) and vitamin B12 (0.18 million). In terms of testing frequency, ferritin was in first place being performed in 26.6% of persons (19.4% performed once; 7.3% performed twice or more) followed by vitamin

**Table 1** Proportions of Persons with MLT by Years 2012–2018

Variables	Year							Absolute Annual Change [95%-CI]
	2012	2013	2014	2015	2016	2017	2018	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
Total	997,761 (100.0%)	988,564 (100.0%)	978,171 (100.0%)	981,735 (100.0%)	956,119 (100.0%)	906,230 (100.0%)	934,685 (100.0%)	
Persons with $\geq 1$ test for MLT	244,926 (24.5%)	265,719 (26.9%)	284,553 (29.1%)	300,770 (30.6%)	313,897 (32.8%)	311,166 (34.3%)	327,320 (35.0%)	1.8% (1.5–2.1%)
Persons with $\geq 1$ vitamin test	134,931 (13.5%)	158,715 (16.1%)	180,220 (18.4%)	201,539 (20.5%)	221,974 (23.2%)	228,942 (25.3%)	246,820 (26.4%)	2.2% (2.0–2.4%)
Persons with $\geq 1$ mineral test	109,005 (10.9%)	118,731 (12.0%)	129,601 (13.2%)	137,743 (14.0%)	145,410 (15.2%)	145,420 (16.0%)	153,393 (16.4%)	1.0% (1.0–1.0%)
Persons with $\geq 1$ trace element test	179,403 (18.0%)	195,912 (19.8%)	211,491 (21.6%)	226,085 (23.0%)	236,407 (24.7%)	235,578 (26.0%)	251,372 (26.9%)	1.5% (1.3–1.7%)

**Table 2** Temporal Changes of MLT

Variables	Absolute Annual Change (95%-CI)	Proportion of Persons Tested in 2012	Relative Seven-Year Change
Vitamin D	+2.2% (2.0–2.5%)	7.40%	2.8
Vitamin B12	+1.5% (1.4–1.6%)	9.00%	2.0
Ferritin	+1.5% (1.4–1.7%)	17.40%	1.5
Folic acid	+1.0% (1.0–1.1%)	5.40%	2.1
Holotranscobalamin	+0.9% (0.8–0.9%)	2.90%	2.8
Calcium	+0.9% (0.8–0.9%)	10.50%	1.5
Magnesium	+0.3% (0.3–0.4%)	2.20%	1.9
Iron	+0.3% (0.3–0.4%)	4.00%	1.5
Transferrin	+0.3% (0.3–0.3%)	1.70%	2.1
Other trace elements	+0.2% (0.2–0.2%)	0.70%	2.4
Homocysteine	+0.1% (0.1–0.1%)	0.40%	1.7
Other vitamins	+0.1% (0.1–0.1%)	0.50%	2.4
Methylmalonic acid	+0.0% (–0.01–0.03%)	0.01%	10.0

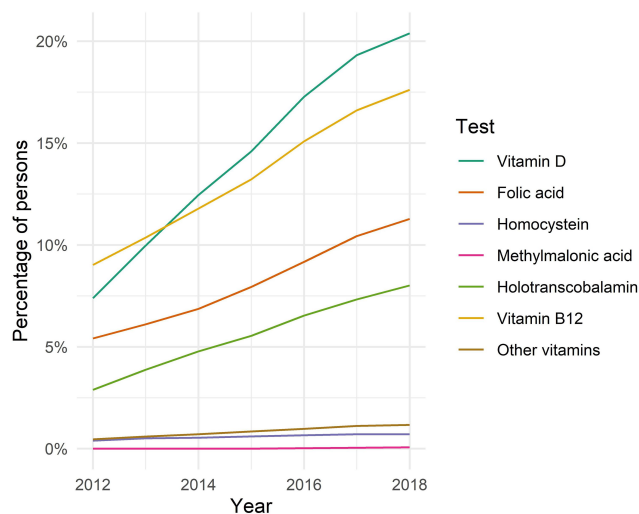
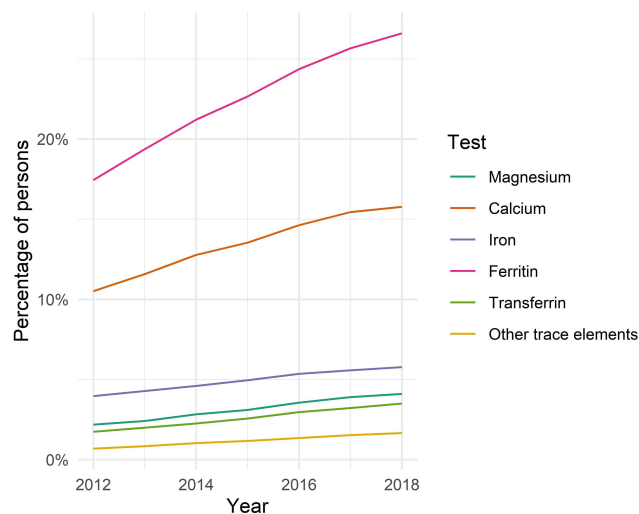
D 20.4% (15.9% performed once; 4.5% performed twice or more) and vitamin B12 17.6 (14.3% performed once; 3.3% performed twice or more). Table 5 shows more detail about the number MLT by individual test.

## Discussion

In this study, we explored population wide trends in MLT in Switzerland during 2012 to 2018. We found an increase in all individual MLT but especially so in testing for vitamins where the proportion of tested persons doubled within seven years. Most eminently, the population tested for vitamin D tripled and the population tested for vitamin B12 doubled. The population tested for ferritin only increased by a factor of 1.5 but ferritin was the most prevalent test, ordered at least once in every fourth person

in 2018. In addition, we explored incidence of MLT and frequency in 2018 and found that testing was also very common in the young population and that ferritin, vitamin D and vitamin B12 were performed more than once in over 7%, 4% and 3% of the population. Our results show that MLT are performed in a broad segment of the Swiss population and with high frequency in large number of cases.

We found that MLT are performed in an annually increasing proportion of the adult Swiss population: while a quarter of the population received any MLT in 2012, in 2018 already a third received an MLT. Among the individual MLT we observed strongest absolute increases in testing for vitamin D, vitamin B12 and ferritin: Vitamin D testing was performed in 7% of the population in 2012 and in 20% in

**Figure 1** Temporal use of vitamin tests (2012–2018).**Figure 2** Temporal use of mineral and trace elements tests (2012–2018).

**Table 3** Sociodemographic Characteristics of the Study Sample from 2018

Variables	With MLT	Without MLT	P-value
	N (%)	N (%)	
Total	327 320 (100.0%)	607 365 (100.0%)	
Gender			<0.001
Female	213 200 (65.1%)	276 425 (45.5%)	
Male	114 120 (34.9%)	330 940 (54.5%)	
Mean age (±SD)	57.1 (19.5)	48.6 (19.1)	<0.001
Age in groups (years)			<0.001
18–24	20,313 (6.2%)	71,409 (11.8%)	
25–34	34,057 (10.4%)	100,268 (16.5%)	
35–44	40,516 (12.4%)	103,896 (17.1%)	
45–54	48,269 (14.7%)	105,467 (17.4%)	
55–64	52,072 (15.9%)	90,202 (14.9%)	
65–74	57,891 (17.7%)	67,124 (11.1%)	
75–84	50,645 (15.5%)	43,855 (7.2%)	
≥85	23,557 (7.2%)	25,144 (4.1%)	
Language region			<0.001
German	232 671 (71.1%)	463,127 (76.3%)	
French	66,217 (20.2%)	110,063 (18.1%)	
Italian	28,432 (8.7%)	34,175 (5.6%)	

**Table 4** Incidence of MLT by Age Group in 2018

Tests	Age Group (years)		
	18–44	45–64	≥65
	N (%)	N (%)	N (%)
Vitamins (all)	63,341 (17.1%)	77,380 (26.1%)	106,099 (39.6%)
Vitamin D	48,887 (13.2%)	61,948 (20.9%)	79,753 (29.7%)
Folic acid	26,219 (7.1%)	31,637 (10.7%)	47,546 (17.7%)
Homocysteine	1708 (0.5%)	2530 (0.9%)	2427 (0.9%)
Methylmalonic acid	175 (0.0%)	196 (0.1%)	237 (0.1%)
Holotranscobalamin	18,360 (5.0%)	23,363 (7.9%)	33,171 (12.4%)
Vitamin B12	41,880 (11.3%)	50,922 (17.2%)	71,863 (26.8%)
Other vitamins	3967 (1.1%)	4210 (1.4%)	2722 (1.0%)
Minerals (all)	34,343 (9.3%)	49,280 (16.6%)	69,770 (26.0%)
Magnesium	10,055 (2.7%)	13,086 (4.4%)	15,178 (5.7%)
Calcium	32,439 (8.8%)	47,289 (16.0%)	67,681 (25.2%)
Trace elements (all)	82,007 (22.1%)	76,712 (25.9%)	92,653 (34.5%)
Iron	16,166 (4.4%)	17,647 (6.0%)	20,146 (7.5%)
Ferritin	81,316 (22.0%)	75,753 (25.6%)	91,551 (34.1%)
Transferrin	9434 (2.5%)	10,589 (3.6%)	12,673 (4.7%)
Other trace elements	6074 (1.6%)	5845 (2.0%)	3567 (1.3%)

2018 and was thereby both frequently performed and subject to a large absolute and relative increase. Regarding testing for vitamin B12, we also found both a high testing frequency and in addition a strong temporal increase. Moreover, ferritin was also among the MLT that were frequently performed and

increasing over time. Together, tests of vitamin D, vitamin B12 and ferritin represent more than half of the MLTs performed but it is noteworthy that significant temporal increases occurred also in every other observed MLT without exception. Several studies so far found that laboratory testing is generally increasing and especially so for vitamin laboratory test.<sup>2–4,11</sup> While this obviously reflects a global phenomenon also occurring in Switzerland, the observation remains still largely unexplained and paradox since we are unaware of a nutritional deficiency crisis in Switzerland, as in all the other countries where this trend has been observed. To find the highest incidence among MLT for ferritin testing is consistent with iron deficiency being the most common nutritional disorder also in industrialized countries.<sup>15,16</sup> However, population based screening for iron deficiency is not recommended by eminent international guidelines such as the US Preventive Services Task Force (USPSTF), not even in the subgroup of pregnant women.<sup>17</sup> Similarly, in the general population, screening for vitamin D deficiency is discouraged by the USPSTF and recommendations for screening for vitamin B12 deficiency are lacking entirely.<sup>10</sup> In contrast, we found that in 2018 at least 27%, 20% and 18% of the entire Swiss population received at least one ferritin, vitamin D or vitamin B12 respectively. Such a high testing coverage resembles a de-facto population based screening which is not supported also by local guidelines and can be criticized at least for low value care or even overtesting. While our data was insufficient to advance the understanding of reasons for the high testing incidence or appropriateness in individual cases, several recent studies suggests that rates of inappropriate laboratory testing has increased considerably especially involving MLT.<sup>2,5,18–20</sup> One possible explanation for the high testing rates could be that physicians have financial incentives for testing in the Swiss healthcare system, which may influence the testing rates.<sup>21</sup>

The finding that the population ≥65 has the highest testing incidence is consistent with expectations since it represents the population segment at highest risk for micronutrient deficiencies.<sup>22,23</sup> There is little external reference available for contrasting these results but a recent study of vitamin D testing incidence in the UK found that vitamin D testing incidence was 1.6% in 2015 which was already questioned of appropriateness.<sup>24</sup> Our results of a testing incidence for vitamin D of 20% is more than ten times higher than that therefore even more questionable for appropriateness, especially in persons 18–44 years old.

**Table 5** Frequency of MLT in 2018

Test	Number of Tests			
	0	1	2	≥3
	N (%)	N (%)	N (%)	N (%)
Ferritin	686,065 (73.4%)	180,923 (19.4%)	46,332 (5.0%)	21,365 (2.3%)
Vitamin D	744,097 (79.6%)	148,388 (15.9%)	32,119 (3.4%)	10,081 (1.1%)
Vitamin B12	770,020 (82.4%)	133,386 (14.3%)	24,667 (2.6%)	6612 (0.7%)
Calcium	787,276 (84.2%)	106,131 (11.4%)	23,694 (2.5%)	17,584 (1.9%)
Folic acid	829,283 (88.7%)	87,727 (9.4%)	13,924 (1.5%)	3751 (0.4%)
Holotranscobalamin	859,791 (92.0%)	64,512 (6.9%)	85 23 (0.9%)	1859 (0.2%)
Iron	880,726 (94.2%)	42,935 (4.6%)	7977 (0.9%)	3047 (0.3%)
Magnesium	896,366 (95.9%)	30,183 (3.2%)	4982 (0.5%)	3154 (0.3%)
Transferrin	901,989 (96.5%)	26,029 (2.8%)	4801 (0.5%)	1866 (0.2%)
Other trace elements	919,199 (98.3%)	9789 (1.0%)	4 097 (0.4%)	1600 (0.2%)
Other vitamins	923,786 (98.8%)	4285 (0.5%)	2726 (0.3%)	3888 (0.4%)
Homocysteine	928,020 (99.3%)	5799 (0.6%)	697 (0.1%)	169 (0.0%)
Methylmalonic acid	934,077 (99.9%)	597 (0.1%)	11 (0.0%)	0 (0.0%)

The incidence we calculated disregarded multiple annual tests in individual patients. Therefore, we investigated the frequency of specific tests per person. The MLT with the highest rate of being performed multiple times in individual persons was ferritin. Given the need for monitoring iron levels in patients requiring iron supplementation, a comparably high testing frequency seems understandable. However, the observation that more than seven percent of the entire Swiss population still received two or more ferritin tests in 2018 argues for a very high testing frequency which is possibly related to the easy access and reimbursement of advanced iron supplementation treatments in Switzerland.<sup>25,26</sup> Vitamin D was in second place and vitamin B12 third place of MLT performed with high frequency, being tested twice or more in 4% and 3% of the Swiss population respectively in 2018. Repeated testing of these vitamins within one year is rather inexplicable since once detected, these vitamin deficiencies can usually be safely treated without the need for re-assessment. Therefore, these repeated MLT tests are especially suspect for potential overtesting. Calcium tests were performed twice or more in 4% of the population but since calcium requires closer monitoring in some patients (depending on comorbidities and medications) these repeat tests may be clinically appropriate in many cases.

## Strengths and Limitations

The main strengths of this study are: First, the population-based approach including more than six million person years

and almost one million persons in 2018 (more than 10% of the entire population). Second, the completeness of the data (covering all healthcare invoices from inpatient and outpatient setting). Third, the representativeness of the database.<sup>12,13</sup> Fourth, the comprehensiveness focusing on a large set of MLT rather than a single laboratory test. Limitation of the study includes the potential for under-reporting of claims (approximately 3% according to internal Helsana analyses are underreported and are paid out-of-pocket). Thus, there is a potential underestimation of MLT in our data and actual MLT may be even more frequent than estimated by our study. However, our study still represents MLT paid for within the insurance system and thereby the part that is of greatest public concern. Second, since our data did not include clinical parameters (laboratory values) and diagnoses (eg for osteoporosis or anemia) we were unable to determine the actual appropriateness of MLT.

## Implications for Research

The very high frequency of MLT and the strong temporal trends strongly indicate a need for further investigations since such potentially inappropriate testing may be responsible for substantial avoidable expenditures. Future research should therefore first precisely identify inappropriate use of MLT, and secondly targeted interventions should be tested to reduce inappropriate use of MLT. Among such possible interventions are campaigns such as “choosing wisely” or “smarter medicine” that focus on recommendations on interventions to avoid.<sup>9,27</sup>

## Implications for Practice

For physicians, the results of our study suggest the need for reflecting current use of MLT and possibly reducing unnecessary tests. Guideline authors and opinion leaders could bring up the topic amongst physicians and public campaigns could inform the general population about the actual value and limitations of MLT.

## Conclusion

In conclusion, the present study shows a high incidence and a strong increase in MLT in Switzerland and raises concerns about potential inappropriateness.

## Ethics Statement

All data were retrospective, pre-existing, deidentified and anonymized in compliance with Swiss regulations on privacy law. Since the data used were retrospective, deidentified and anonymized health-related data prior to analysis, this study is not subject to the Swiss Federal Law on human research (Humanforschungsgesetz) and was thus exempted from the local ethics committee approval (ethical committee of the Canton Zurich) and from seeking informed consent of patients.<sup>28</sup>

## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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## Disclosure

DrCarola A Huber is an employee of Helsana Group. Dr Eva Blozik is an employee of Helsana Group and reports grants from Swiss Cancer Research Foundation, Novartis Pharma, Vifor Pharma, and MSD Switzerland, outside the submitted work. Mr Markus Näpflin is an employee of Helsana Group and reports grants from Novartis Pharma Switzerland, MSD, Amgen, and Vifor, outside the submitted work. The authors declare no other conflicts of interest in this work.

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