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Inappropriate requests for tumor markers in patients aged 50 years and older: lessons not learned.

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CONFLICTS OF INTEREST

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Author Contribution

VPNJ and EFC contributed to: Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Manuscript preparation, Manuscript editing and Manuscript review.

Abstract:

Tumor marker (TM) requests are common in the clinical practice when screening for neoplasms. **Objectives:** To investigate, within a private health insurance, the ordering frequency and the costs related to inappropriate TM test orders. **Methods:** This study analyzed data regarding TM requests within a private health insurance between 2010 and 2017. Patients included in this analysis were ≥ 50 years old, had available medical records, and had at least 1 TM tested within the study period. Tests were considered inappropriate when TMs were used in screening for neoplasms, ie, when there was no previous diagnosis. We evaluated data regarding age, sex, the ordering physician's medical specialty, and test costs. **Results:** Between 2010 and 2017, 1112 TM tests were performed and increased from 52 to 262 per year. Our sample consisted mostly of women (69.5%) with a mean age of 59.4 (SD, 8.2) years. Most orders were inappropriate (87.8%) and represented 79.4% of all expenses with TM tests.

Cardiology professionals were the medical specialty that requested the most TM tests (23.9%), followed by internal medicine specialists (22.7%) and gynecologists (19.2%).

Conclusion: We observed a high percentage of inappropriate test orders in the study period, resulting in elevated costs. Studies of this nature deserve the attention of health care managers, and interventions should be performed in order to reduce the inappropriate use of TM tests in clinical practice.

Resumo:

A solicitação de marcadores tumorais (MTs) para rastreio de neoplasias na prática clínica tem sido comum. **Objetivos:** investigar no âmbito de um plano de saúde privado a frequência de solicitação e os custos relacionados à solicitação inapropriada de MTs. **Métodos:** utilizou-se a base de dados de um plano de saúde privado entre os anos de 2010 a 2017. Foram incluídos na pesquisa, sujeitos com idade ≥ 50 anos, que apresentavam prontuários médicos acessíveis e que havia realizado a dosagem de algum MTs no período. Considerou-se como “exame inapropriado” quando o MT foi utilizado como rastreio de neoplasia, ou seja, quando não havia o diagnóstico prévio. Foram avaliados os dados referentes à idade, sexo, especialidade do médico solicitante e informações sobre os custos desses exames. **Resultados:** Foram realizados um total 1.112 testes no período, representando um aumento de 52 para 262 exames/ano. A amostra foi composta na maioria pelo sexo feminino (69,5%), com média de idade de $59,4 \pm 8,2$ anos. A maioria das solicitações foram inapropriadas (87,8%). Notou-se que a solicitação desses exames, impactaram cerca de 79,4% dos gastos totais do plano de saúde com MTs. Os cardiologistas foram a especialidade que mais solicitaram MTs em 23,9% das ocasiões, seguidos pelos especialistas em clínica médica (22,7%) e ginecologistas (19,2%). **Conclusão:** Observamos um alto percentual de pedidos de exames inadequados no período do estudo, resultando em custos elevados. Estudos dessa natureza merecem a atenção dos gestores de saúde e intervenções devem ser realizadas a fim de reduzir o uso inadequado de testes de MT na prática clínica.

Introduction

The technological advances of medicine in recent years are undeniable, especially regarding new diagnostic tests and laboratory prognoses. However, along with this development, new technologies have also brought substantial increases in financial costs to health care services, thus burdening patients and governments, particularly in countries with limited financial resources. The inappropriate use of new health care technologies has grown in many countries, and despite attempts by several publications and guidelines to standardize their use, impactful statistics are shown in the literature regarding the excessive use of these technologies.¹ Beyond financial costs, other possible damages are associated with the inappropriate use of diagnostic tests, especially the risk of excessive diagnostic test requests and unnecessary treatments.² The definition of inappropriate or unsuitable test is broad and can be interpreted in many ways. According to Zhi et al. (2013), an inappropriate test is one which is requested without a clear indication of a diagnostic hypothesis for a specific case.³ Additionally, an adequate clinical indication for testing should also consider sensitivity, specificity, and predictive value studies for the diseases it aims to diagnose; these are generally established by guidelines published by governments, institutes, or medical specialties such as the United States Preventive Services Task Force (USPSTF). However, unlike pharmaceutical clinical studies, studies on the sensitivity and specificity of diagnostic tests are not commonly found in the literature.

In this context, tumor markers (TMs) have been frequently used in clinical practice as screening tests for people aged 50 years and older.⁴ TMs include various substances such as cell surface antigens, cytoplasmic proteins, enzymes, hormones, oncofetal antigens, receptors, and oncogenes and their products. According to Sharma (2009), the 3 most important characteristics of an ideal TM are high specificity for a certain type of tumor, reasonable lead-time over the clinical diagnosis, and high sensitivity to avoid false-positive results.^{5,6} Unfortunately, these characteristics are relatively hard to come by in clinical practice, which has led to a general recommendation of not ordering TM tests in routine screening procedures in asymptomatic patients.⁷⁻⁹

Considering that the financial costs of health care services have grown significantly in recent years, optimizing expenses is important. Conversely, various

studies have indicated a high percentage of inadequate orders for TM tests. In Greece, Ntaios et al. (2009) identified only 10% of correctly requested TM tests among 10921 tests, notably cancer antigen 125 (CA 125), alpha-fetoprotein (AFP), cancer antigen 19-9 (CA 19-9), cytokeratin 19 fragment (CYFRA 21-1), and neuron-specific enolase (NSE).¹⁰

Studies evaluating the inadequate request of TM tests are scarce in Brazil. This study investigated, within a private health insurance, the ordering frequency and the costs related to inadequate orders of TM tests such as CA 125, carcinoembryonic antigen (CEA), CA 19-9, cancer antigen 15-3 (CA 15-3), cancer antigen 72-4 (CA 72-4), and cancer antigen 27-29 (CA 27-29).

Methods

This retrospective study was performed within a non-profit, private employer-sponsored health insurance. This health insurance is managed by a federal public institution located in Brasília, Federal District, Brazil. Its financial resources are mostly provided by the government, whereas a smaller fraction is funded by the users (approximately 20%). This health insurance covers an annual average of 5979 users, including current or retired employees and their dependents.

The study population consisted of all the individuals who performed complementary blood tests through their health insurance plans between 2010 and 2017. Only active employees (and not those retired or dependents) aged 50 years and older with accessible medical records were included. This age threshold was established in order to select patients who commonly undergo screening tests. The year 2012 was not analyzed due to data inconsistency, since there was a change in the management software that could result in possible methodological bias.

The “inappropriate tests” variable was considered present when no previous neoplasm diagnosis had been performed and at least one of the following TMs were present on the medical records: CA 125, CEA, CA 15-3, CA 72-4, CA 19-9, and CA 27-29; these were grouped under the “TM” variable. The criteria for this classification were established following recommendations by USPSTF¹¹⁻¹³, The Royal Australian College of General Practitioners (RACGP)¹⁴, and the American Society of Clinical Oncology (ASCO)¹⁵.

Other variables analyzed in this study include age (completed years at the time of testing), sex (male/female), the ordering physician's medical specialty, and information on costs (individual test costs and user co-participation) as informed by the insurance manager. Values in *reais* (Brazilian currency, R\$) were converted to US dollars considering the exchange rate in February 2020 (US\$ 1.00 = R\$ 4.06).

It is reasonable to consider that all cancer diagnoses were recorded, since any sick leave, notification, or even early retirement due to cancer are reported on the patients' medical records. The medical records were reviewed by the study's designated physician.

All statistical analyses used SPSS v. 25.0. Descriptive statistics were used in measures of position (mean, median, and standard deviation), and the chi-square test, Fisher's exact test, and binary logistic regression were performed as appropriate.

The study was approved by the Research Ethics Committee of the Medical School of the University of Brasília (CAAE 88696318.9.0000.5558).

Results

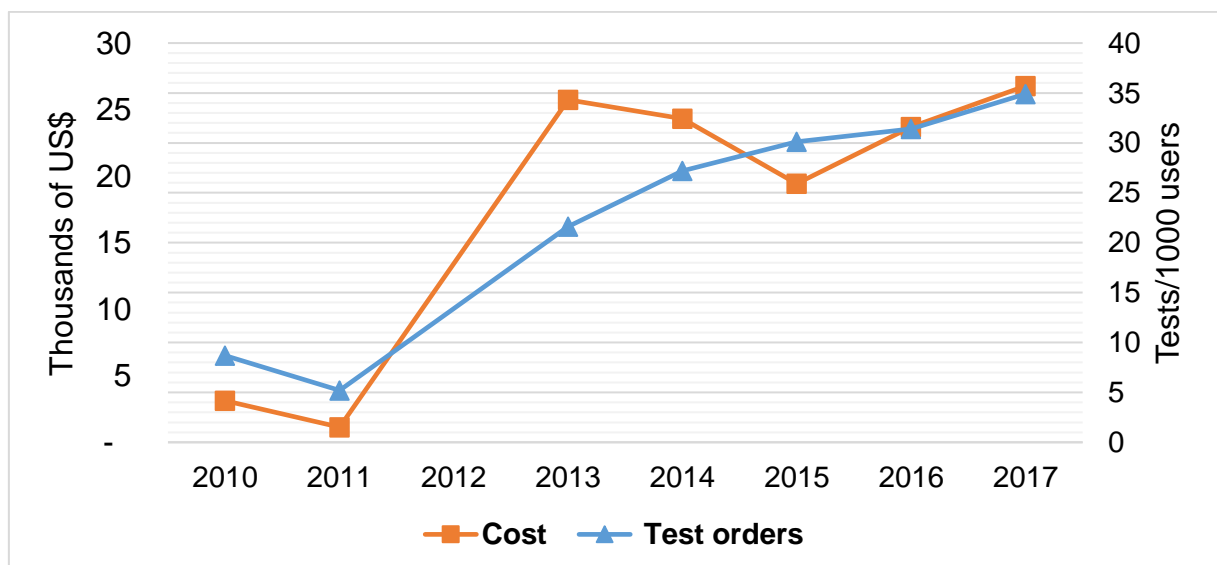
Between 2010 and 2017, 1112 TM tests were ordered, and yearly orders increased from 52 to 262. Our sample consisted mostly of women (69.5%) with a mean age of 59.4 (SD, 8.2) years.

The analysis of medical records showed that 12.2% (n = 136) of tests were appropriately ordered (that is, were ordered after cancer diagnosis) and 87.8% (n = 976) were inappropriately ordered.

Of 136 orders considered appropriate, 80.9% were for female patients, with a mean age of 60.4 (SD, 7.4) years. The odds of adequate test ordering were associated with patient age (odds ratio [OR] = 1.08, 95% [confidence interval] CI: 1.03-1.13) and female patients (OR = 8.37, 95%CI: 4.08-17.17) ($X^2(2) = 43.965$; $p < 0.001$, Nagelkerke $R^2 = 0.273$).

A progressive increase was observed in absolute and per capita numbers of inappropriate test orders over the years, from 48 test orders in 2010 (mean of 8.7 orders per 1000 registered users) to 227 orders in 2017, corresponding to 34.9 orders per 1000 registered users.

Figure 1 – Number of inappropriate tumor marker requests per 1000 health insurance users between 2010 and 2017 and related costs.



The total costs of TM tests in the study period were US\$ 156 452.60. Of these, US\$ 124 222.91 (79.4%) were spent on inappropriate orders, which increased from US\$ 3127.17 in 2010 to US\$ 26 776.83 in 2017. The mean cost of inappropriate

tests was US\$ 16.81 (SD, US\$ 15.58) for the patient and US\$ 110.43 (SD, US\$ 91.16) for the government. Between 2010 and 2017, the mean cost of inappropriate test orders was US\$ 2.90 for every health insurance user (Table 1).

Table 1: Expenses (in US\$) on appropriate and inappropriate test orders between 2010 and 2017.

Year	Appropriate orders			Inappropriate orders		
	No.	Insurance cost	Total cost	No.	Insurance cost	Total cost
2010	4	204.46	265.80	48	2406.32	3127.17
2011	4	204.46	255.59	29	908.81	1136.97
2013	17	5040.52	5762.00	125	22 597.68	25 746.49
2014	22	5635.15	6392.13	163	21 480.95	24 311.31
2015	29	5482.97	6180.53	185	17 008.55	19 425.57
2016	25	5078.47	5799.02	199	20 672.39	23 698.56
2017	35	6548.59	7574.61	227	22 706.55	26 776.83
	136	28 194.62	32 229.69	976	107 781.25	124 222.91

Regarding the medical specialty of ordering physicians, most were cardiologists (23.9%), internal medicine specialists (22.7%), obstetricians and gynecologists (19.2%), and general practitioners (10.14%). Although clinical oncologists were ranked seventh on this list, with only 5.6% of all orders, they presented the most adequate test orders in comparison with other specialties, with a statistically significant association. Data on test orders by medical specialty are shown in Table 2.

Table 2: Association between medical specialties and appropriate TM test orders

Specialty ¹	No. of tests	Appropriate tests n (%)	Inappropriate tests n (%)	p value
Cardiology	266	19 (7.1)	247 (92.9)	0.000
Internal medicine	252	33 (13.1)	219 (86.9)	0.000
Obstetrics/gynecology	213	21 (9.9)	192 (90.1)	0.000
General practice	179	13 (7.3)	166 (92.7)	0.000
Urology	88	4 (4.5)	84 (95.5)	0.000
Endocrinology and metabolism	68	5 (7.4)	63 (92.6)	0.000
Medical oncology	62	47 (75.8)	15 (24.2)	0.000
General surgery	51	9 (17.6)	42 (82.4)	0.000

Gastroenterology	30	0	30 (100)	-
Infectious disease	29	4 (13.8)	25 (86.2)	0.000
Breast surgery	29	8 (27.6)	21 (72.4)	0.016
Gastrointestinal endoscopy	21	0	21 (100)	-
Geriatrics	18	2 (11.1)	16 (88.9)	0.001
Intensive care medicine	18	2 (11.1)	16 (88.9)	0.001
Dietetics	18	0	18 (100)	-
Nephrology	16	0	16 (100)	-
Occupational medicine	15	2 (13.3)	13 (86.7)	0.005
Pediatrics	14	5 (35.7)	9 (64.3)	0.285
Other specialties ²	111	-	-	-

¹ Medical specialty as informed by the respective professional boards: Regional Councils of Medicine of Distrito Federal (CRM-DF), Goiás (CRM-GO), and São Paulo states (CREMESP) in 2018.

² Medical specialties that individually accounted for $\leq 1\%$: orthopedics and traumatology, neurology, proctology, homeopathy, sports medicine, allergy and immunology, acupuncture, dermatology, hematology and hemotherapy, otolaryngology, oncology, vascular surgery, psychiatry, surgical oncology, gastrointestinal surgery, nuclear medicine, neurosurgery, ophthalmology, pulmonology, rheumatology, health care administration, hospital administration, hepatology, traffic medicine; angiology and vascular surgery, anesthesiology, cardiovascular surgery, head and neck surgery, pathology, peroral endoscopy.

Discussion

In this study, performed within a private health insurance, we observed a significant and progressive increase in the number of inappropriate TM test orders without the appropriate cancer diagnosis and in contrast with what is recommended by scientific societies. We observed a substantially high rate of inappropriate requests (85.2%), generating expenses that accounted for 79.4% of all expenses with TM tests.

Brazilian studies on this field are scarce. However, a high frequency of inappropriate test requests was also observed in other countries. In Greece, 90% of TM test orders were inappropriate.¹⁰ In Modena, Italy, a study reported that 62% of patients admitted to an internal medicine unit were ordered at least one TM test.¹⁸ In Padua, less than 40% of 23 059 TM test orders within a university hospital were considered adequate.¹⁹ Another broad Italian study revealed an estimate of more than one request for biomarker testing for every 5 people, which did not correspond to the cancer prevalence in the country.²⁰ In Turkey, inappropriate TM test orders were also impressive: around 90% of 1858 patients were ordered TM tests in benign conditions.²¹ In Canada, studies showed that the rate of inappropriately ordered tests (not only TMs) could reach 20%, leading to unnecessary costs of the order of millions of dollars.^{1,22}

Regarding medical specialties, we observed that oncologists ordered a larger number of appropriate TM tests compared with other specialists. To the best of our knowledge, to date, no studies have investigated this relationship. Moss et al. (2008), evaluating the knowledge of medical professionals regarding the sensitivity and specificity of CA 125 for ovarian cancer, reported that 54% of general practitioners believed that this marker should not be restricted to disease monitoring, but 40% of these physicians were unable to identify the causes of false-positive results despite believing they were fit to request this type of test.²³ In addition, a study by the same authors showed that general practitioners did not feel confident on how to manage patients with a raised CA 125, even in the presence of a normal ultrasound scan, thus referring these patients for secondary evaluations; this reflects an unfamiliarity of these physicians with the interpretation of TM results.²⁴ Considering our results, test orders by oncologists may have had an enhanced sensitivity and consequent appropriateness since these, even when indicated for screening, were based on other diagnostic clues.

Some studies have attempted to explain the reasons that lead physicians to request inappropriate tests, and these reasons include technical unfamiliarity, pressure by the patient and family members, financial gain, and fear of ethical and legal complaints.^{25,26} One study involving 1768 primary care physicians in the United States identified that one-third of them were unfamiliar and uncertain when requesting and interpreting laboratory results for diagnoses in primary care.²⁷ It is well known that patients usually ask their doctors for tests and referrals to other specialties. Kravitz et al. (2003) reported that 1 in every 5 patients made this type of request.²⁸ Moreover, the patient's family influences half of all medical decisions.²⁹ It seems that oncologists are less influenced by patients when it comes to requesting procedures and tests. Gogineni et al. (2015), studying the demands and requests of patients receiving anticancer treatment, showed that the physician complied with less than 1% of these demands or requests.³⁰

In this context, some studies have proposed strategies and interventions to reduce the number of inappropriately requested tests.^{25,26} Adopting clinical protocols to guide the medical conduct in order to reduce unnecessary or redundant diagnostic tests seems to generate savings of up to 57%.³¹ A study performed within a laboratory of a university hospital in Croatia showed that standardizing minimum intervals for performing tests could lead to a significant reduction (approximately 50%) in TM test

orders, and consequently to a reduction in overall costs.³² Similarly, Torre et al. (2015) indicated that the number of adequately requested TMs increased from 31 to 78% once their utilization protocol was standardized.³³ Educational programs directed at primary care physicians could lead to a reduction of up to 51% in performed tests (TMs or not), saving approximately US\$ 60 000 per year.³⁴ In Northern Ireland, researchers showed that 72% of TM tests were adequately requested, justifying these results by effective audit methods combined with the publication of guidelines.³⁵ Physicians believe that evidence-based practice supported by the use of electronic medical records, structured care programs, and continuous quality monitoring and by the identification of barriers and facilitators of clinical practice guidelines are effective strategies to avoid the unnecessary use of tests.³⁶

Limitations of this study include its retrospective nature, the fact that only one health insurance and not all its users were included in the sample, and the absence of information from year 2012. Grouping all TMs (CA 125, CEA, CA 15-3, CA 72-4, CA 19-9, and CA 27-29) into one category precluded a more thorough analysis. Nevertheless, the strengths of this study include its large sample size, the period evaluated (7 years), and the quality of the medical records and performed tests, in addition to the fact that this is the first Brazilian study on this topic.

Conclusion

In the present study, performed within a private health insurance over 7 years, we observed a high frequency (87.8%) of inappropriate TM test orders. Oncologists were apparently the professionals with the best judgement for ordering these tests. Considering the perspective of a substantial increase in health care costs in the next years, especially in countries such as Brazil, initiatives that aim to reduce the use of unnecessary technologies/tests are of utmost importance. It is possible that audits, physician education programs, well-established protocols, and patient education may contribute to the correct use of these tumor biomarkers.

Conflicts of interest

The authors do not have any financial or non-financial conflicts of interest.

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